

SPEDP 2021

REUNIÃO ANUAL

HYBRID EDITION

PORTO | 11 e 12 DE NOVEMBRO



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COMISSÃO LOCAL E COORDENAÇÃO DO CURSO

DRA. ANA LUÍSA LEITE | CHVNGE

DRA. JOANA FREITAS | CMIN

DRA. MARIA JOANA SANTOS | HB

DRA. SOFIA TEIXEIRA | CHUP

JÚRI DOS TRABALHOS

DRA. FILIPA ESPADA | ULS MATOSINHOS

DRA. JOANA VILAVERDE | CHUP

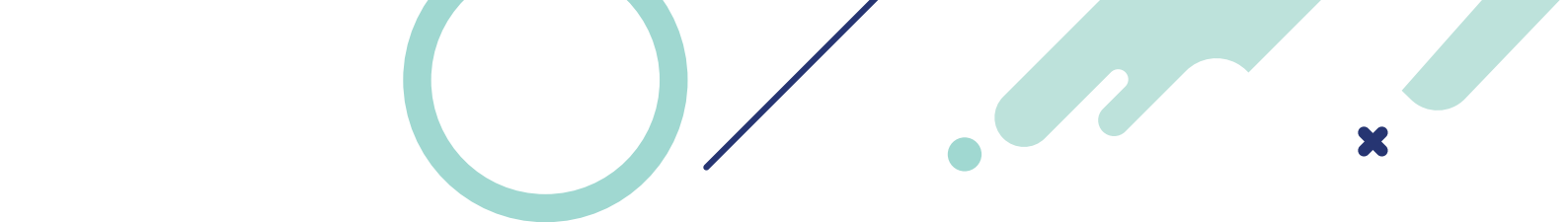
DRA. MARIA JOÃO OLIVEIRA | CMIN

ORGANIZAÇÃO:



Design & Secretariado





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CURSO TEÓRICO-PRÁTICO

DIABETES - TEMPO NO INTERVALO-ALVO

INTRODUÇÃO AO CURSO

- Dra. Sofia Teixeira

O TEMPO NO INTERVALO-ALVO

CASO CLÍNICO 1

Painel de discussão: Dra. Carolina Moreno e Dra. Raquel Coelho

- Dra. Ana Laura Fitas

ESTRATÉGIAS NUTRICIONAIS ÚTEIS PARA AUMENTAR O TEMPO NO INTERVALO-ALVO

CASO CLÍNICO 2

Painel de discussão: Dra. Ana Margarida Monteiro e Dra. Brigida Robalo

- Dra. Nanci Baptista

ESTRATÉGIAS FARMACOLÓGICAS ÚTEIS PARA AUMENTAR O TEMPO NO INTERVALO-ALVO

CASO CLÍNICO 3

Painel de discussão: Prof. Dra. Helena Cardoso e Dra. Joana Campos

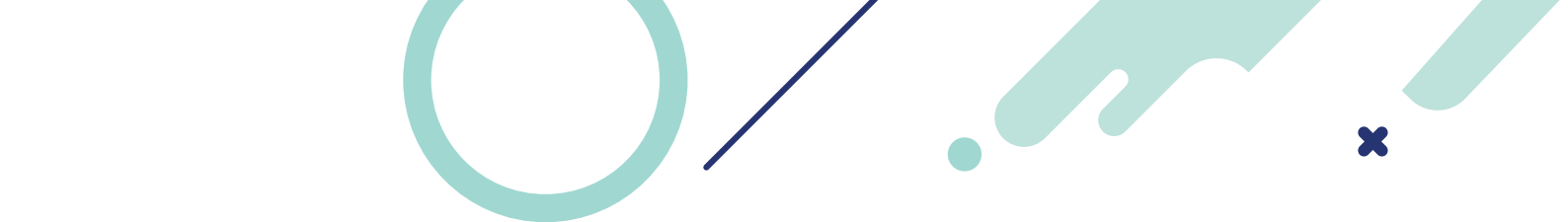
- Dra. Teresa Azevedo

ESTRATÉGIAS TECNOLÓGICAS ÚTEIS PARA AUMENTAR O TEMPO NO INTERVALO-ALVO

CASO CLÍNICO 4

Painel de discussão: Prof. Dra. Cíntia Castro-Correia e Prof. Dr. Miguel Melo

- Dr. Luis Ribeiro
- 



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INTRODUÇÃO AO CURSO

Sofia Teixeira
Endocrinologista - CHUPorto

AGENDA

- Funcionamento do Curso
- Origem do Curso

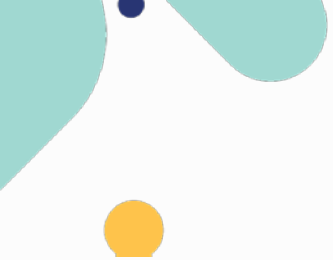
FUNCIONAMENTO DO CURSO

4 sessões

FUNCIONAMENTO DO CURSO

Participação do público

- Televoto + Perguntas ao Moderador
- Manual do Curso
- Avaliação Final



TELEVOTO



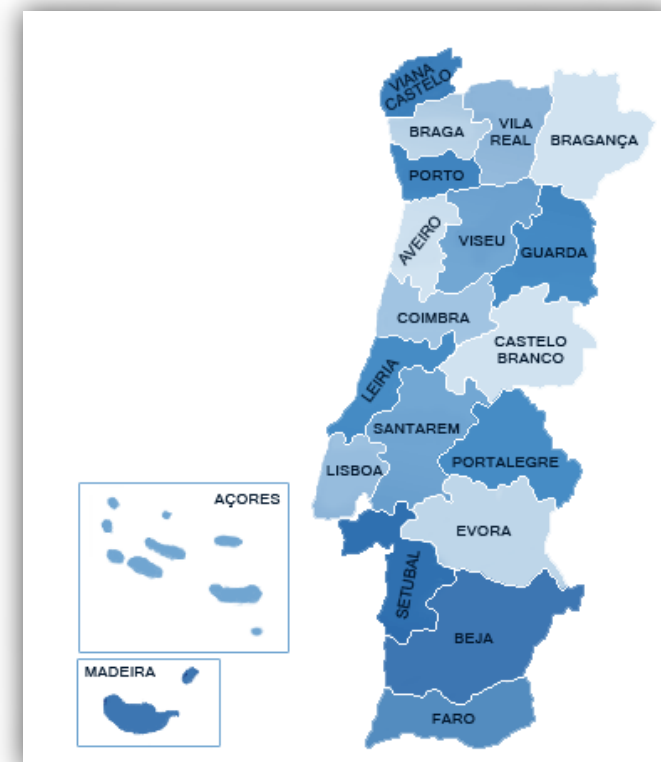
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PERGUNTA 1: Em que fase se encontra?

- a) Pediatra**
- b) Endocrinologista**
- c) Interno de Pediatria**
- d) Interno de Endocrinologia**
- e) Outro**

PERGUNTA 2: Qual é região do país onde trabalha?

- a) Norte
- b) Centro
- c) Sul
- d) Açores
- e) Madeira





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PERGUNTAS AO MODERADOR

CHAT



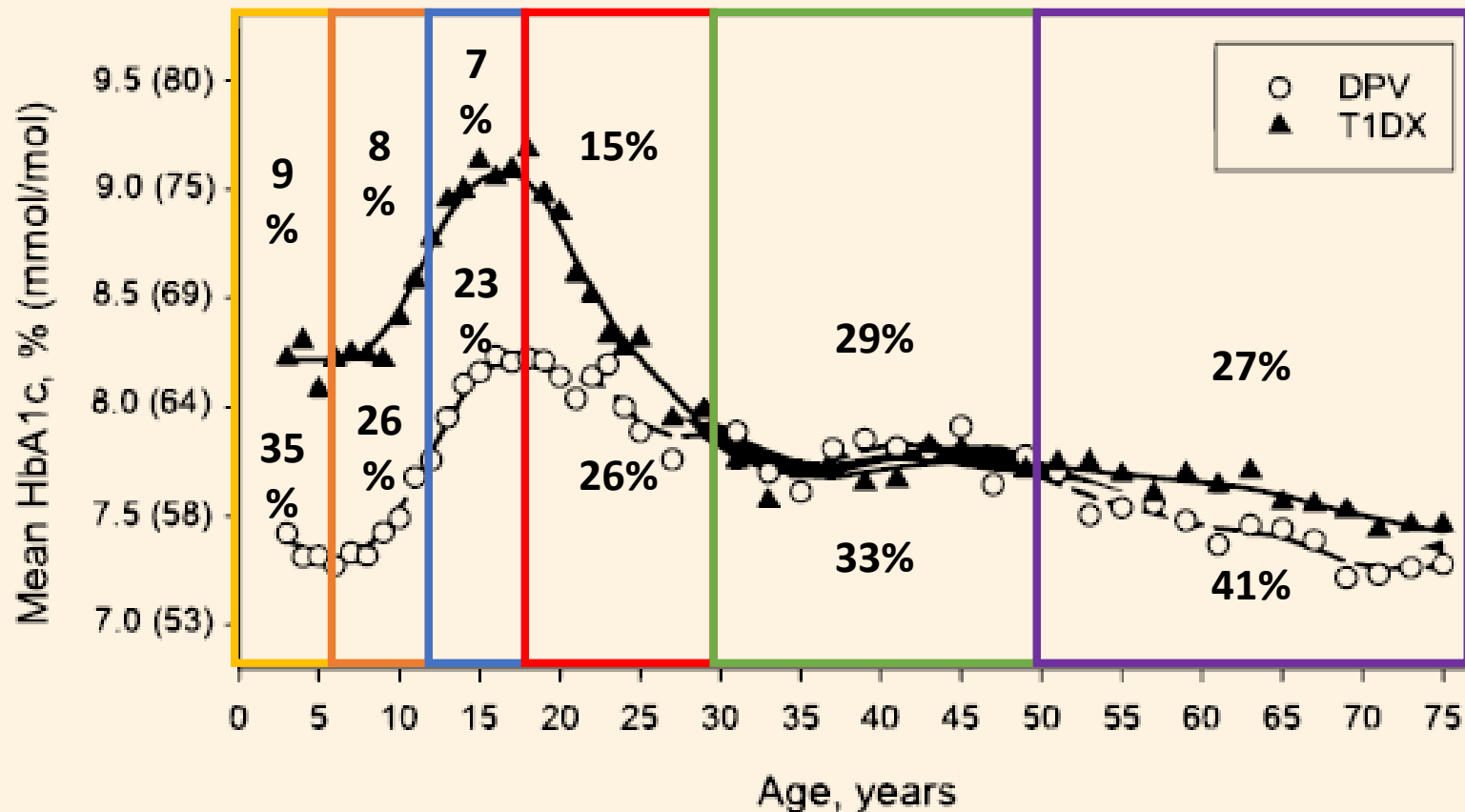
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ORIGEM DO CURSO

HbA1c



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< 6 anos

6 – 12 anos

12 – 18 anos

18 – 30 anos

30 – 50 anos

≥ 50 anos

2015-2016

A hiperglicemia associa-se a disfunção cognitiva

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	Pathophysiological mechanism	Strength of evidence*
Demographic		
Early disease onset (age <47 years) ^{3,25,27,32,43,54,65-67}	Cerebral glucose utilisation is increased in children, <u>the immature CNS could be particularly sensitive to disruption in glucose availability</u>	A
Metabolic		
Hyperglycaemia ^{15-12,33,38,40,41,43,44,54}	Excessive activation of the polyol pathways, accumulation of advanced glycation end products, and increased oxidative stress leading to cell damage or death (apoptosis)	B
Diabetic ketoacidosis (particularly at diagnosis) ^{47-49,68,69}	Changes in cerebral perfusion, ketones, and lactate are elevated, N-acetyl-L-aspartate (a marker of neuronal wellbeing) is decreased, conscious state is impaired, increased risk of cerebral oedema	B
Hypoglycaemia with coma or seizure ^{15,25,70}	Upregulation of GLUT1 and GLUT3 transporters in response to falling brain glucose levels; uncontrolled release of excitatory amino acids, such as glutamate-glutamine triggers a cascade of events leading to impaired consciousness, seizures, coma, and compromised neuronal integrity	C (severe, prolonged, or occurring in the very young child)

*Evidence graded according to American Diabetes Association guidelines.⁷¹ Grade A, clear evidence from well conducted, generalisable, randomised controlled trials that are adequately powered. Grade B, supportive evidence from well conducted cohort studies. Grade C, supportive evidence from poorly controlled or uncontrolled studies.

Table: Known risk factors for brain changes and cognitive deficits in youth with type 1 diabetes

O efeito da **Disglicemia** no cérebro varia em função do estadio de neurodesenvolvimento

A Hiperglicemia associa-se a alterações da **estrutura** e da **função cerebral** das pessoas com DM1

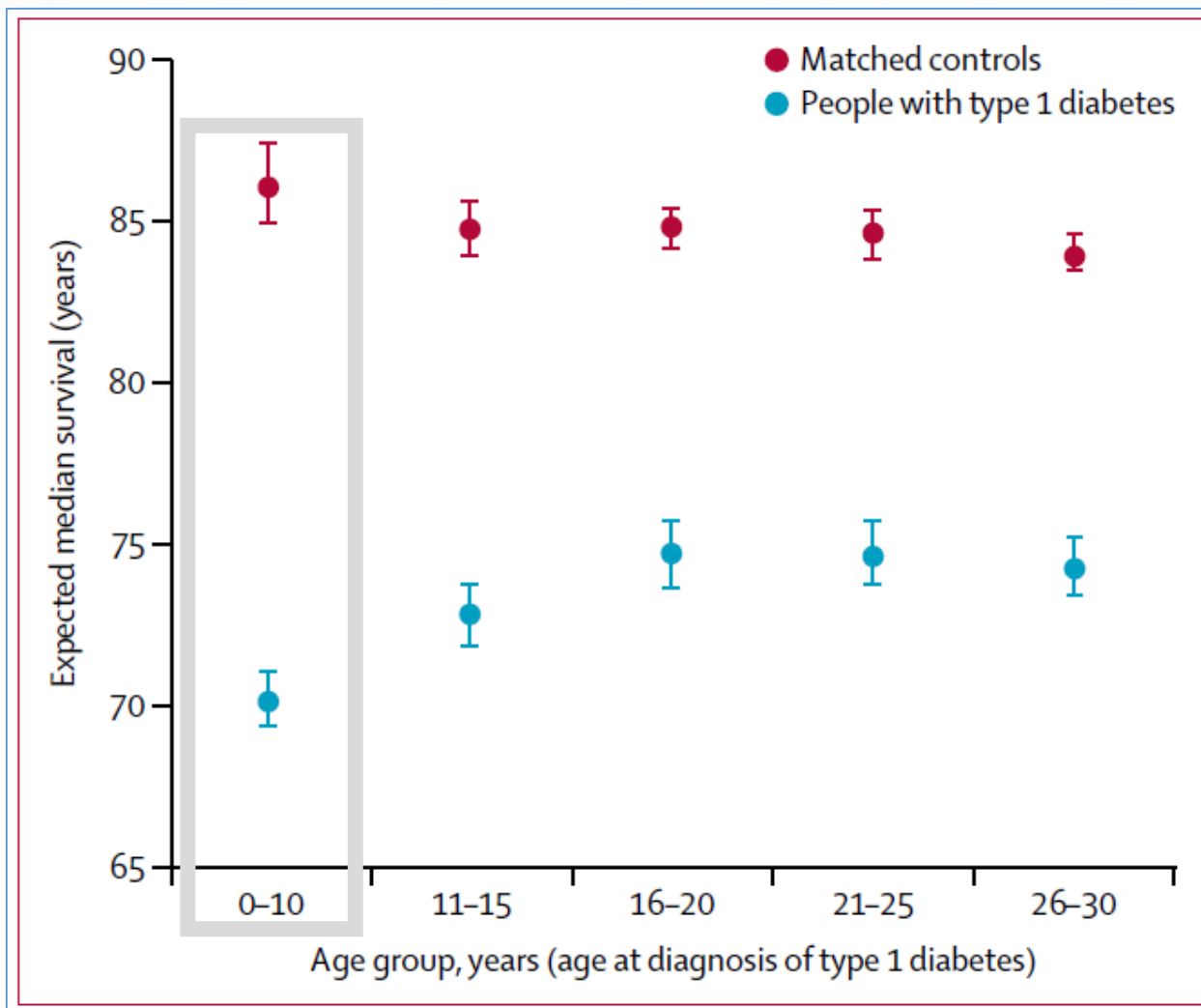
O papel da **Hipoglicemia** nas alterações da estrutura e da função cerebral das pessoas com DM1 é controverso.

A esperança de vida da pessoa com DM1 é menor do que a população sem DM

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A pessoa com DM1 **perde**, em média, **10 a 16 anos** de vida, dependendo da **idade** em que foi feito o **diagnóstico** da diabetes (duração da doença controlada)

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Model 3.*

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)
Time-updated renal disease — no. of events/total no.	6673/197,786	2091/197,786
Reference group (controls)	1.00	1.00
Normoalbuminuria	2.76 (2.33–3.27)	3.64 (2.61–5.06)
Microalbuminuria	4.87 (4.00–5.92)	6.35 (4.41–9.16)
Macroalbuminuria	9.82 (8.11–11.89)	13.10 (9.19–18.67)
Stage 5 chronic kidney disease	28.09 (22.95–34.39)	38.98 (26.90–56.47)
Time-updated eGFR and stage 5 chronic kidney disease — no. of events/total no.	6711/198,632	2108/198,632
Reference group (controls)	1.00	1.00
eGFR		
>120 ml/min	4.41 (3.53–5.50)	4.65 (2.91–7.42)
60 to 120 ml/min	3.24 (2.74–3.84)	4.56 (3.30–6.31)
15 to <60 ml/min	7.64 (6.26–9.32)	10.42 (7.25–14.98)
Stage 5 chronic kidney disease	29.01 (23.68–35.54)	41.32 (28.52–59.86)

**O risco de morte por
doença**

cardiovascular

correlaciona-se com a

HbA1c

(HbA1c = medida de

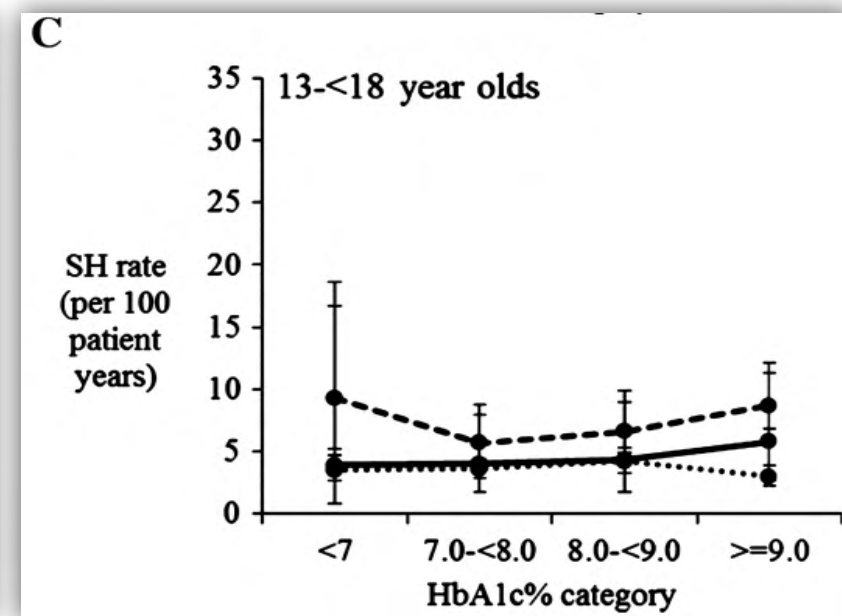
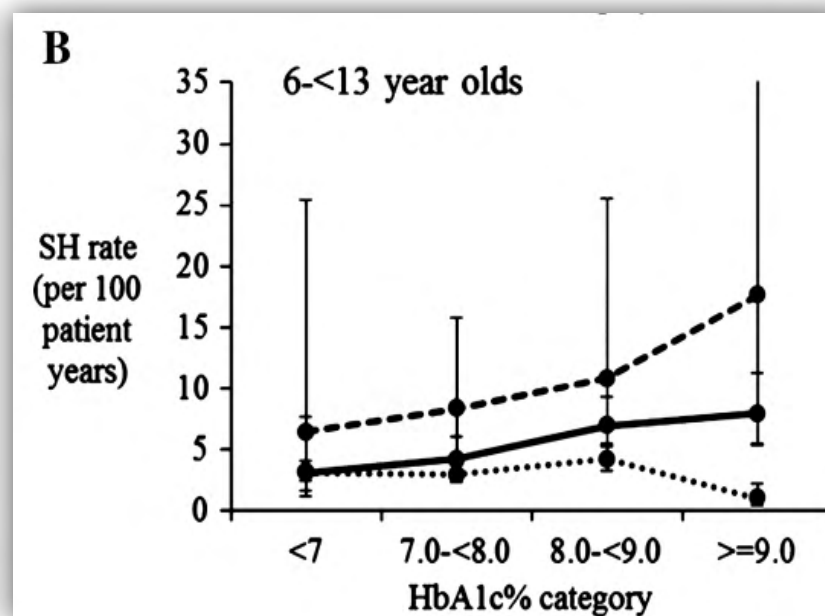
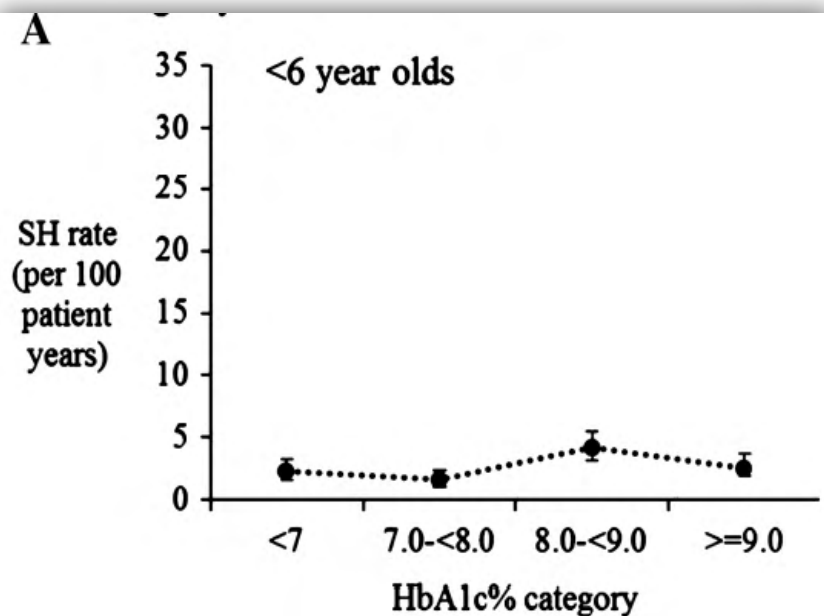
hiperglicemia)

A hipoglicemia grave não se correlaciona com a HbA1c em idade pediátrica

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Registry: ..●.. DPV -●- T1DX —●— WACDD



Aveni Haynes et al. *Pediatr Diabetes*. 2017 Nov;18(7):643-650. doi: 10.1111/pedi.12477. Epub 2016 Nov 23.

Em resumo:

- **Hiperglicemia (e Hipoglicemia?)** associa-se a alterações da **estrutura e da função cerebral** das crianças.
- O risco de **morte por doença cardiovascular e por todas as causas** correlaciona-se com a **HbA1c**.
- A correlação clássica entre a **HbA1c** e risco de **Hipoglicemia Grave** não se observa com as terapias e tecnologias contemporâneas.

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Diabetes Care Volume 40, December 2017



International Consensus on Use of Continuous Glucose Monitoring

Diabetes Care 2017;40:1631–1640 | <https://doi.org/10.2337/dc17-1600>

Table 1—Key metrics for CGM data analysis and reporting

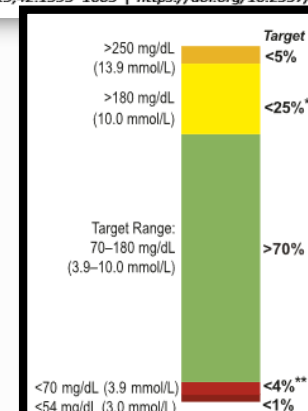
CGM metric	Measures	ATTD consensus
1	Mean glucose Severe hypoglycemia* Percentage of time in hypoglycemic ranges, mg/dL (mmol/L)	√ (calculated) Clinical diagnosis: event requiring assistance (level 3)
2	Clinically significant/very low/immediate action required	<54 (<3.0) (level 2)
3	Alert/low/monitor Percentage of time in target range, mg/dL (mmol/L)	<70–54 (<3.9–3.0) (level 1)
4	Default Secondary Percentage of time in hyperglycemic ranges, mg/dL (mmol/L)	70–180 (3.9–10.0) 70–140 (3.9–7.8)
5	Alert/elevated/monitor	>180 (>10) (level 1)
6	Clinically significant/very elevated/immediate action required Diabetic ketoacidosis*	>250 (>13.9) (level 2) Clinical diagnosis: ketones, acidosis, and usually hyperglycemia (level 3)
7	Glycemic variability Primary glycemic variability Stable Unstable Secondary glycemic variability	CV CV <36% CV ≥36% SD
8	eA1C	√ (calculated)
9	Three time blocks: sleep, wake, 24 h Recommended data sufficiency	12:00 A.M.–6:00 A.M., 6:00 A.M.–12:00 A.M., 12 A.M.–12:00 A.M.
10	Collection period (minimum no. of weeks)	2
11	Percentage of expected CGM readings (minimum percentage)	70–80 (10 of 14 days)
12	Episodes of hypoglycemia/hyperglycemia (minimum no. of minutes) (with beginning and end of episode defined)	15 min
13	Area under the curve	√ (calculated)
14	Risk of hypoglycemia and hyperglycemia	LBGI/HBGI recommended
15	Standardized CGM visualization of data	AGP recommended

Diabetes Care Volume 42, August 2019



Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

Diabetes Care 2019;42:1593–1603 | <https://doi.org/10.2337/dc19-0028>



1921

2017

2019

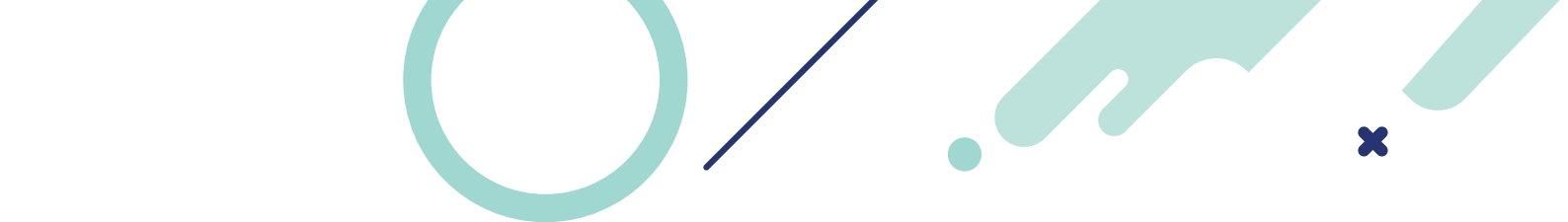


TEMPO NO INTERVALO-ALVO

- DR^a ANA LAURA FITAS

MODERAÇÃO

- DR^a CAROLINA MORENO
- DR^a RAQUEL COELHO



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O TEMPO NO INTERVALO-ALVO

Ana Laura Fitas

Hospital de Dona Estefânia, CHLC
Unidade de Endocrinologia Pediátrica
Responsável: Dra. Lurdes Lopes



CASO CLÍNICO

M., 14 anos

- Diabetes desde os 8 anos
- Perfusão subcutânea contínua de insulina desde os 11 anos
- Autovigilância glicémica: glicémia capilar + sensor de glicose intersticial Freestyle Libre®

Consulta 20.10.2021:

- **HbA1C 6,9%**
- Relatório de *Ambulatory Glucose Profile* [AGP]

CASO CLÍNICO

Relatório do AGP

7 Outubro 2021 - 20 Outubro 2021 (14 Dias)

LibreView

ALVOS E ESTATÍSTICAS DE GLICOSE

7 Outubro 2021 - 20 Outubro 2021

14 Dias

O % que o sensor de tempo está ativo

94%

Intervalos e alvos para

Diabetes tipo 1 ou tipo 2

Intervalos de glicose

Intervalo-alvo 70-180 mg/dL

Abaixo de 70 mg/dL

Abaixo de 54 mg/dL

Acima de 180 mg/dL

Acima de 250 mg/dL

Alvos % de leituras (hora/dia)

Maior que 70% (16h 48min)

Menor que 4% (58min)

Menor que 1% (14min)

Menor que 25% (6h)

Menor que 5% (1h 12min)

Cada aumento de 5% no tempo no intervalo (70-180 mg/dL) é clinicamente benéfico.

Glicose média

172 mg/dL

Indicador de gestão da glicose (GMI)

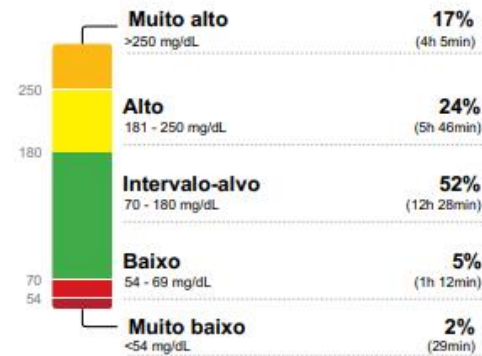
7,4% ou 58 mmol/mol

Variabilidade da glicose

44,0%

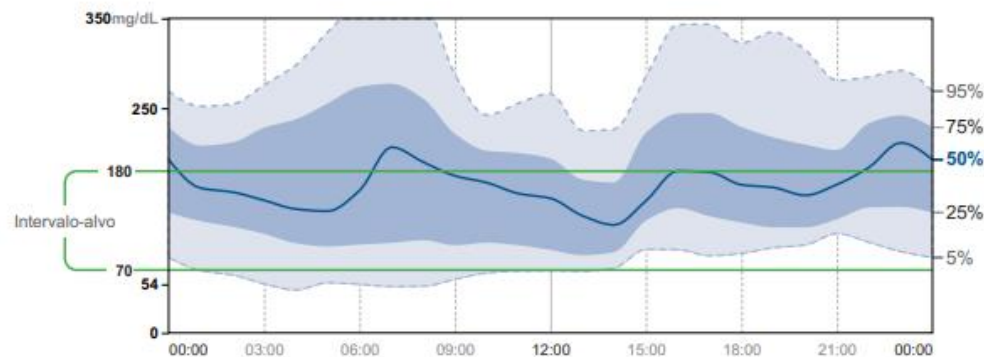
Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

PERÍODO NOS INTERVALOS



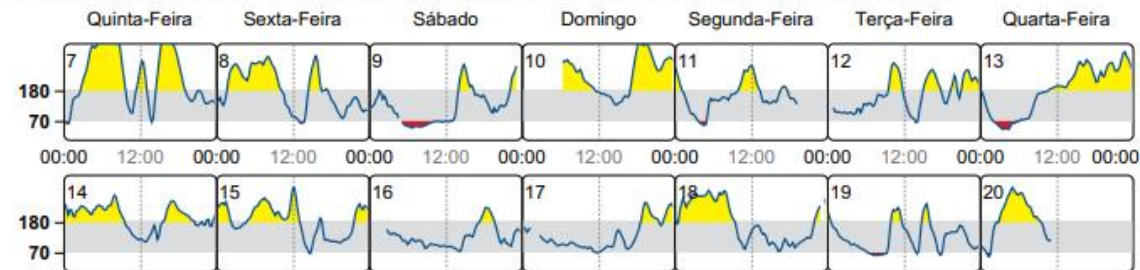
PERFIL DE GLICOSE EM AMBULATÓRIO (AGP)

O AGP é um resumo dos valores de glicose do período de relatório, com a mediana (50%) e outros percentis apresentados como se ocorressem num único dia.



PERFIS DE GLICOSE DIÁRIOS

Cada perfil diário representa um período da meia-noite de um dia até à meia-noite do dia seguinte, com a data apresentada no canto superior esquerdo.



CASO CLÍNICO

Relatório do AGP

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Abaixo de 70 mg/dL	Menor que 4% (58min)
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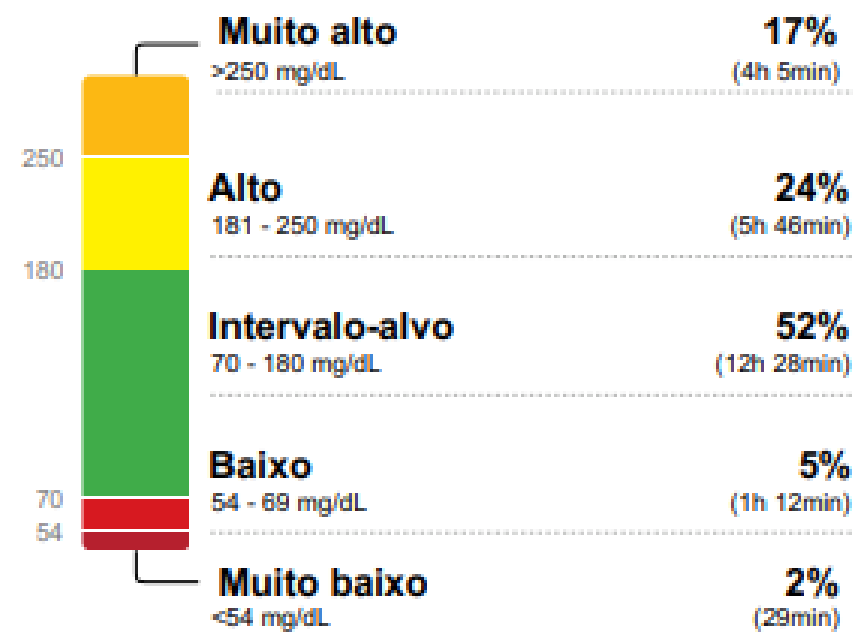
Glicose média 172 mg/dL

Indicador de gestão da glicose (GMI) 7,4% ou 58 mmol/mol

Variabilidade da glicose 44,0%

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

PERÍODO NOS INTERVALOS



Pergunta 1: Em relação ao AGP, qual a opção verdadeira?

1. Não é adequado para interpretação porque o número de dias incluído é insuficiente.
2. Não é adequado para interpretação porque a percentagem de utilização do sensor é demasiado baixa.
3. O tempo no intervalo-alvo está adequado face aos objetivos.
4. O tempo abaixo de alvo está adequado face aos objetivos.
5. O tempo acima de 250mg/dL excede o máximo recomendado.

ALVOS E ESTATÍSTICAS DE GLICOSE

7 Outubro 2021 - 20 Outubro 2021

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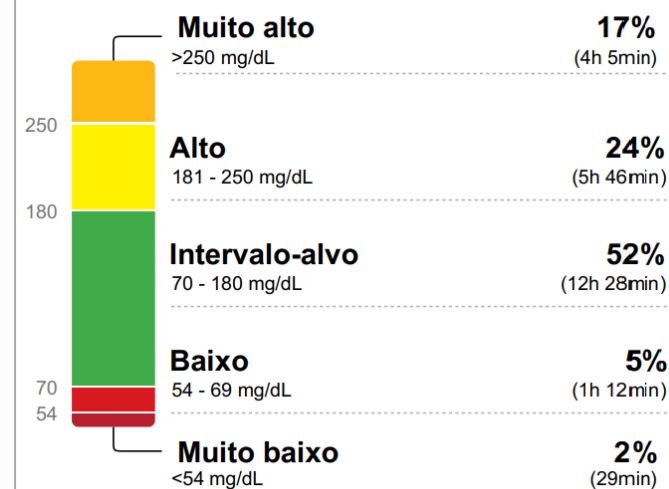
7,4% ou 58 mmol/mol

Variabilidade da glicose

44,0%

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

PERÍODO NOS INTERVALOS



AMBULATORY GLUCOSE PROFILE [AGP]

- Criado em 2013 (Mazze et *al.*), como **modelo para apresentação de dados de monitorização contínua da glicose** [MCG], entretanto desenvolvido e atualizado
- Adotado pela maioria dos *softwares* de dispositivos de MCG comercializados
- Inclui os **dados quantitativos essenciais de MCG e perfil de níveis de glicose** ao longo de **14 dias**
- É atualmente um **componente essencial da tomada de decisões clínicas em diabetes**.

AMBULATORY GLUCOSE PROFILE [AGP]

Caraterísticas essenciais à **utilidade clínica**:

- **Compreensível** pelos clínicos e pelas pessoas com diabetes / famílias → ferramenta de trabalho para **decisões partilhadas**
- Uma **única página** facilita revisão e registo no processo eletrónico
- Permite aos clínicos **identificar rapidamente os dados** quantitativos relevantes
- Facilita a **individualização** das estratégias terapêuticas.

AMBULATORY GLUCOSE PROFILE [AGP]

Para que a sua utilização seja válida é preciso assegurar que os dados são adequados para interpretação.

Premissa básica para análise dos dados da monitorização da glicose intersticial:

Tempo de sensor ativo >70% nos últimos 14 dias

Correlaciona-se fortemente com:

- Glicemia média de 3 meses
- Tempo no alvo
- Métricas de hiperglicemia

PARÂMETROS A AVALIAR NO AGP

Table 2—Standardized CGM metrics for clinical care: 2019

1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
3. Mean glucose	
4. Glucose management indicator (GMI) (75)	
5. Glycemic variability (%CV) target $\leq 36\%$ (90)*	
6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2

Use of Ambulatory Glucose Profile (AGP) for CGM report

CV, coefficient of variation. *Some studies suggest that lower %CV targets ($<33\%$) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas (45,90,91).

Pergunta 1: Em relação ao AGP, qual a opção verdadeira?

1. Não é adequado para interpretação porque o número de dias incluído é insuficiente. **X**
2. Não é adequado para interpretação porque a percentagem de utilização do sensor é demasiado baixa. **X**
3. O tempo no intervalo-alvo está adequado face aos objetivos.
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5. O tempo acima de 250mg/dL excede o máximo recomendado.

x



ALVOS E ESTATÍSTICAS DE GLICOSE

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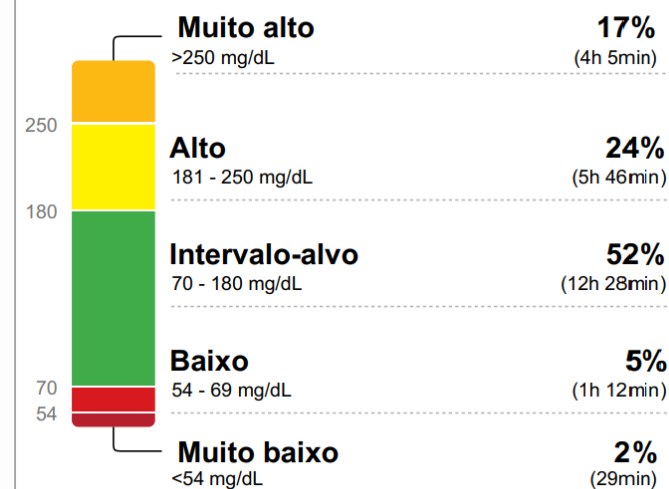
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PERÍODO NOS INTERVALOS



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Cada aumento de 5% no tempo no intervalo (70-180 mg/dL) é clinicamente benéfico.

Glicose média

172 mg/dL

Indicador de gestão da glicose (GMI)

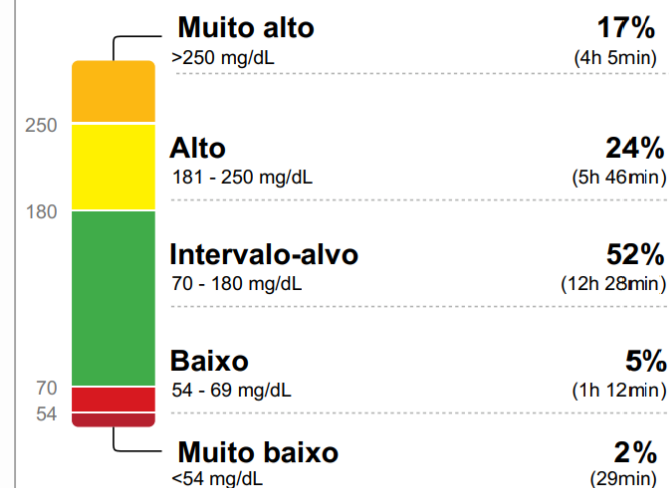
7,4% ou 58 mmol/mol

Variabilidade da glicose

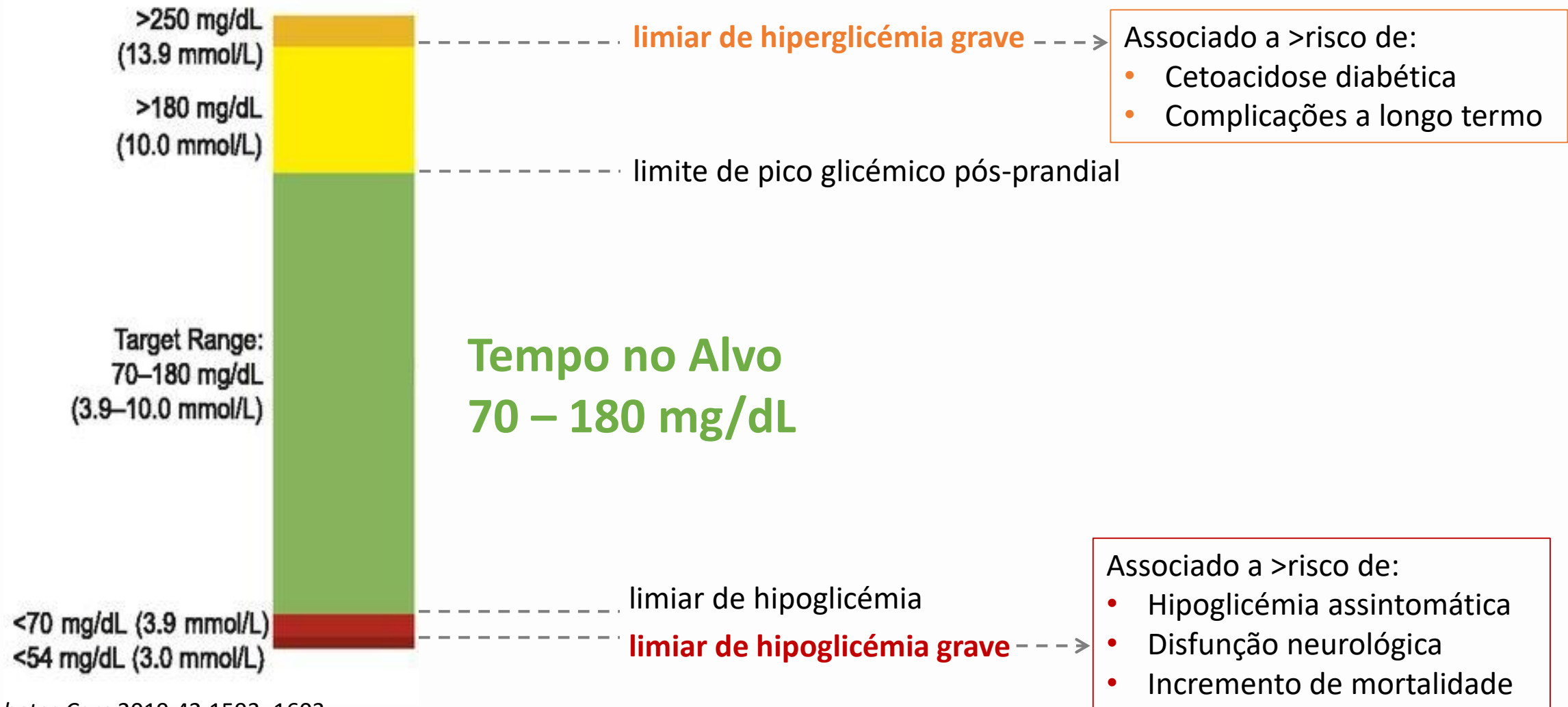
44,0%

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

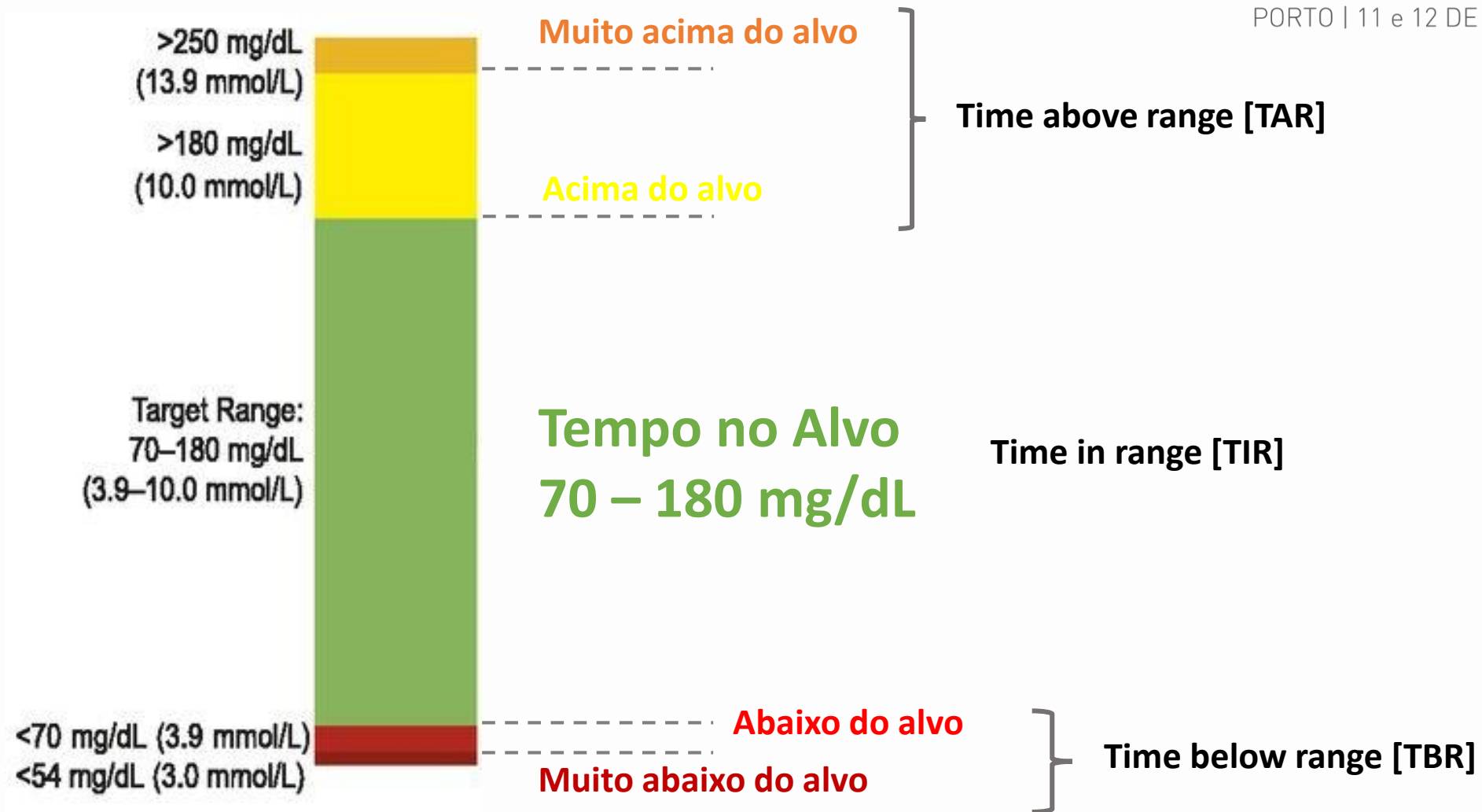
PERÍODO NOS INTERVALOS



TEMPO NO ALVO



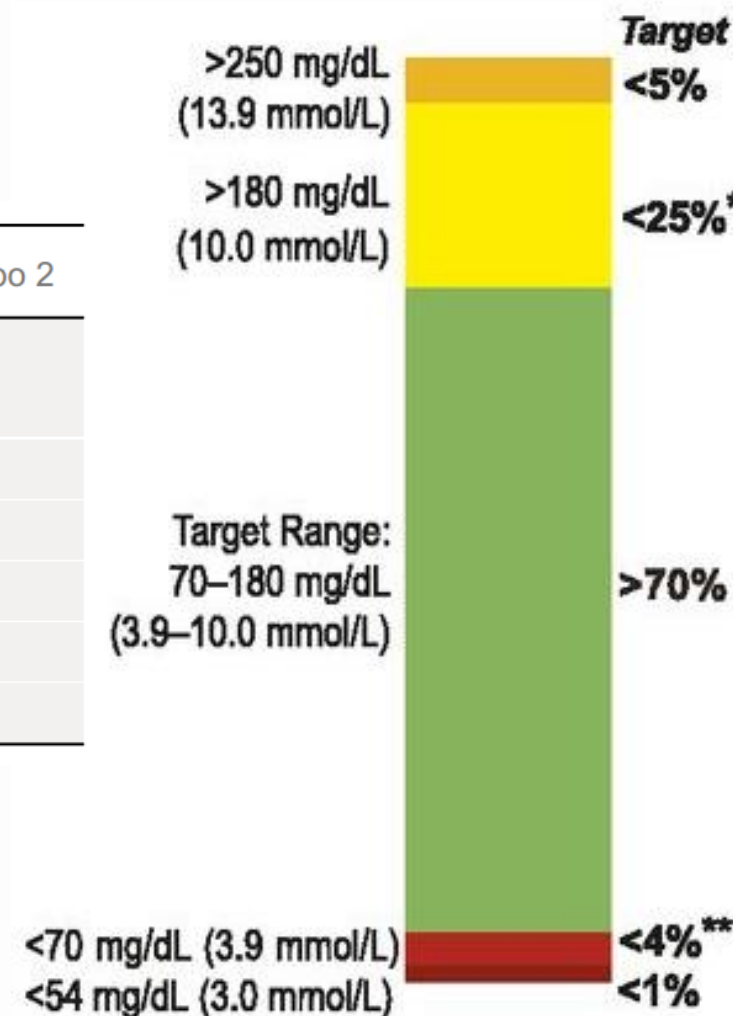
TEMPO NO ALVO



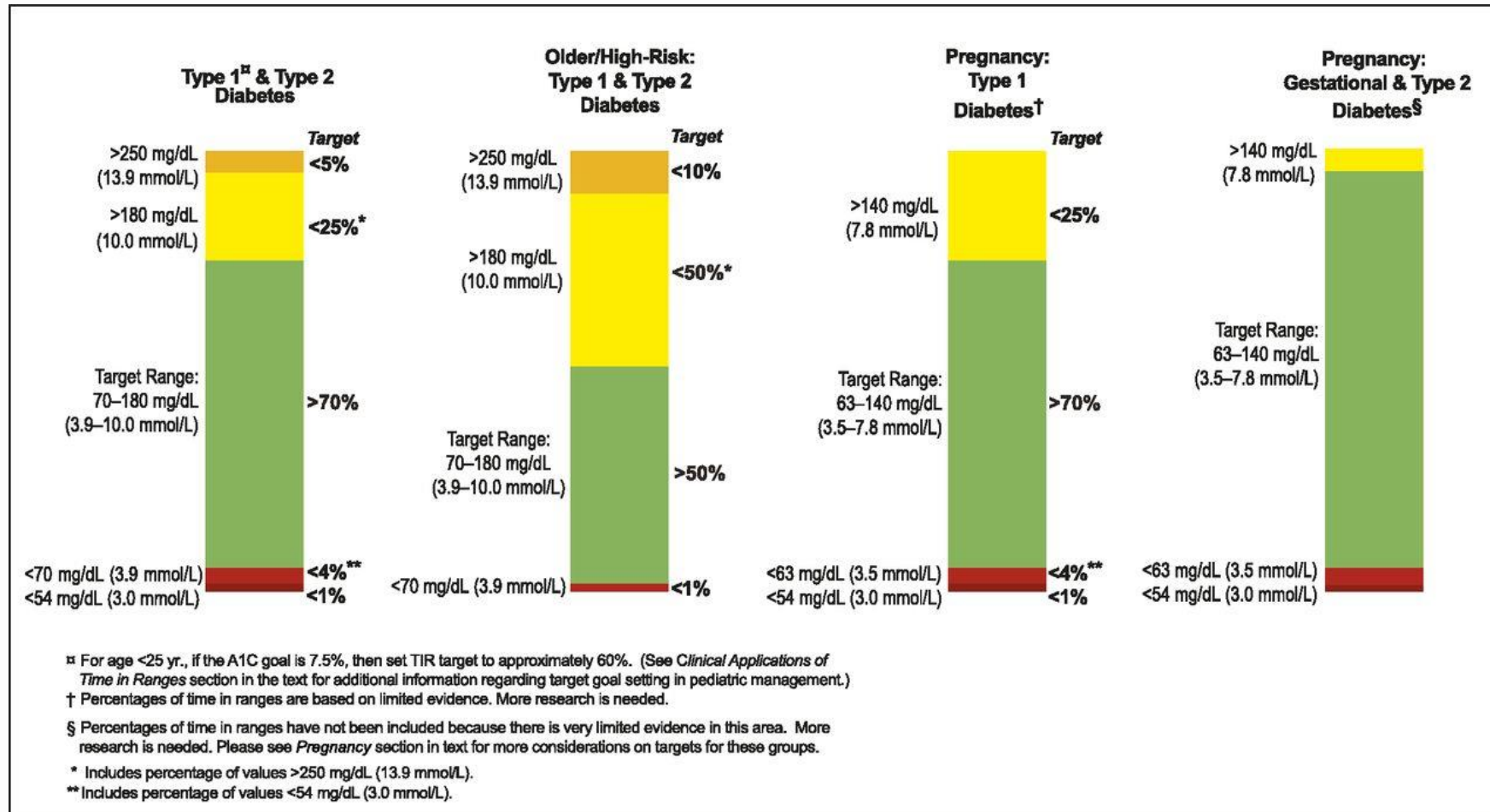
TEMPO NO ALVO

Objetivos

Intervalos e alvos para		Diabetes tipo 1 ou tipo 2
Intervalos de glicose	Alvos % de leituras (hora/dia)	
Intervalo-alvo 70-180 mg/dL	Maior que 70% (16h 48min)	
Abaixo de 70 mg/dL	Menor que 4% (58min)	
Abaixo de 54 mg/dL	Menor que 1% (14min)	
Acima de 180 mg/dL	Menor que 25% (6h)	
Acima de 250 mg/dL	Menor que 5% (1h 12min)	
Cada aumento de 5% no tempo no intervalo (70-180 mg/dL) é clinicamente benéfico.		



TEMPO NO INTERVALO ALVO



Pergunta 1: Em relação ao AGP, qual a opção verdadeira?

1. Não é adequado para interpretação porque o número de dias incluído é insuficiente.
2. Não é adequado para interpretação porque a percentagem de utilização do sensor é demasiado baixa.
3. O tempo no intervalo-alvo está adequado face aos objetivos. **X**
4. O tempo abaixo de alvo está adequado face aos objetivos. **X**
5. O tempo acima de 250mg/dL excede o máximo recomendado. **✓**

ALVOS E ESTATÍSTICAS DE GLICOSE

7 Outubro 2021 - 20 Outubro 2021

14 Dias

O % que o sensor de tempo está ativo

94%

Intervalos e alvos para

Diabetes tipo 1 ou tipo 2

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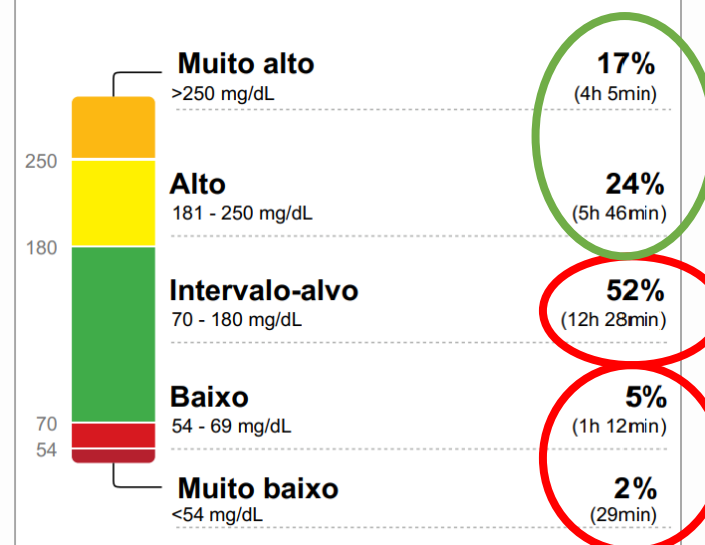
7,4% ou 58 mmol/mol

Variabilidade da glicose

44,0%

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

PERÍODO NOS INTERVALOS



NORMALIDADE GLICÉMICA

Dados de MCG em pessoas sem diabetes – como é a glicémia normal?

10 dias de CGM em 153 crianças (>6 anos) e adultos; HbA1c base 5.1%

Resultados

- Média de glicémia global: 99 mg/dL
- TIR estrito (70-140): 97%
- TAR >140: 2,1% (30 min/dia); TAR >160: 4 min/dia
- TBR <60 e <54: negligível

Dr. Roy Beck , EASD 2018

CASO CLÍNICO

Relatório do AGP

7 Outubro 2021 - 20 Outubro 2021 (14 Dias)

LibreView

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Intervalos e alvos para

Diabetes tipo 1 ou tipo 2

Intervalos de glicose

Intervalo-alvo 70-180 mg/dL

Abaixo de 70 mg/dL

Abaixo de 54 mg/dL

Acima de 180 mg/dL

Acima de 250 mg/dL

Alvos % de leituras (hora/dia)

Maior que 70% (16h 48min)

Menor que 4% (58min)

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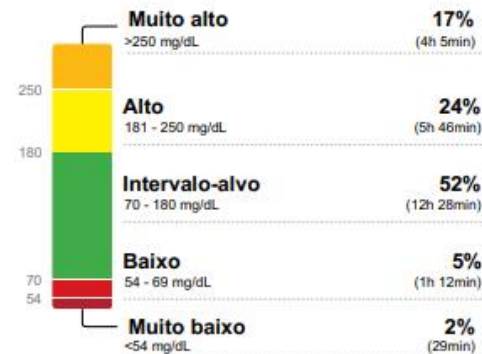
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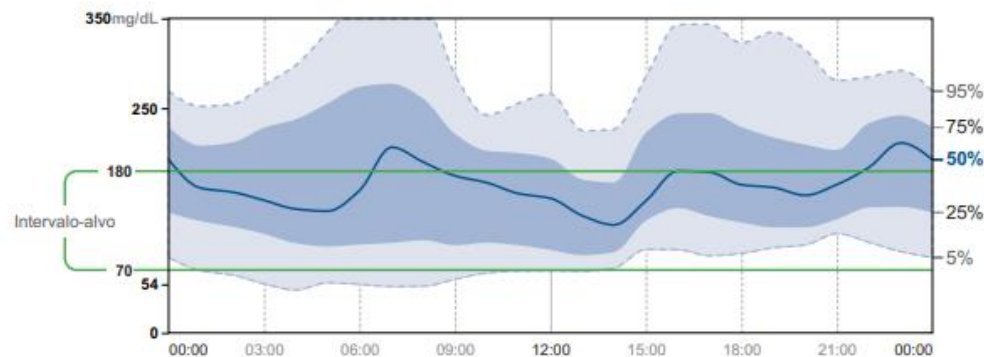
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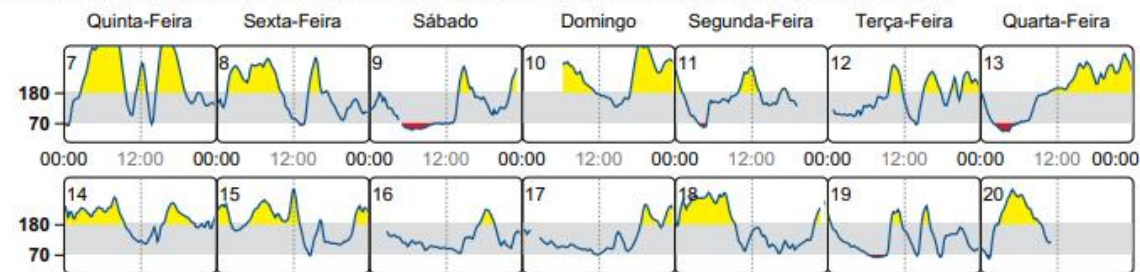
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Cada perfil diário representa um período da meia-noite de um dia até à meia-noite do dia seguinte, com a data apresentada no canto superior esquerdo.



Pergunta 2: Em relação à variabilidade glicêmica, qual a verdadeira?

1. É adequada, porque o indicador “variabilidade da glicose” está normal.
2. É demasiado baixa, porque o indicador “variabilidade da glicose” está abaixo do objetivo.
3. É adequada porque a média de glicose é normal.
4. É excessiva porque o indicador “variabilidade da glicose” está acima do objetivo.
5. É adequada, porque o tempo no alvo está de acordo com os objetivos.

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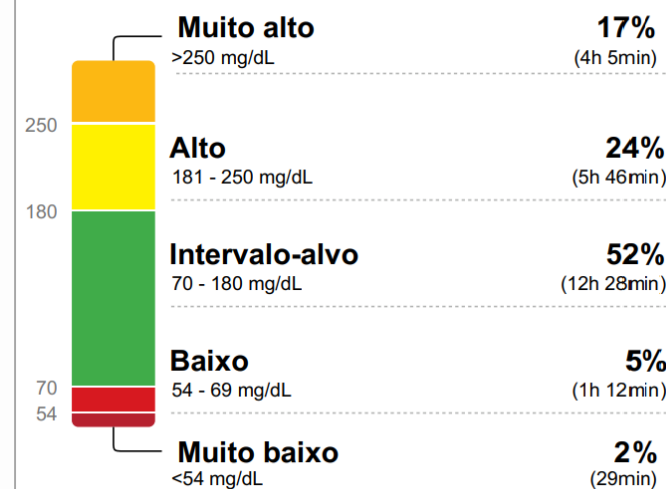
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VARIABILIDADE GLICÉMICA (VG)

Flutuações acentuadas da glicemia → ↑stress oxidativo e inflamação → lesão endotelial

JAMA 2006 295(14):1681-7

Alguma evidência (ainda sob controvérsia) associa o excesso de variabilidade com:

- Aumento de risco cardiovascular ---- *VG como marcador de risco independente para mortalidade CV em doentes com diabetes*
- Deterioração de função cognitiva
- Redução da qualidade de vida

Na prática clínica:

- fator de risco para hipoglicemia
- frustração, episódios sintomáticos

VARIABILIDADE GLICÉMICA

Variabilidade glicêmica (VG) – indicador de hiper- e hipoglicemia que toma em consideração:

- a **amplitude** da excursão glicêmica
(how far out of range a blood glucose measurement is)
- o **tempo** passado em excursão glicêmica
(how long the blood glucose is out of range)

**Média, Desvio padrão e
Coeficiente de variação**

Tempos fora de alvo

VARIABILIDADE GLICÉMICA

- **Glicose média** – média de todas as determinações no período selecionado
- **Desvio padrão / *standard deviation* (SD)** – medida de dispersão dos valores em torno da media
 - Objetivo: SD tão baixo quanto possível
 - Interpretação em função da média de glicose:

Coeficiente de variabilidade (CV) = (SD / média) x 100 (%)

Objetivo: ≤ 36%

ALVOS E ESTATÍSTICAS DE GLICOSE

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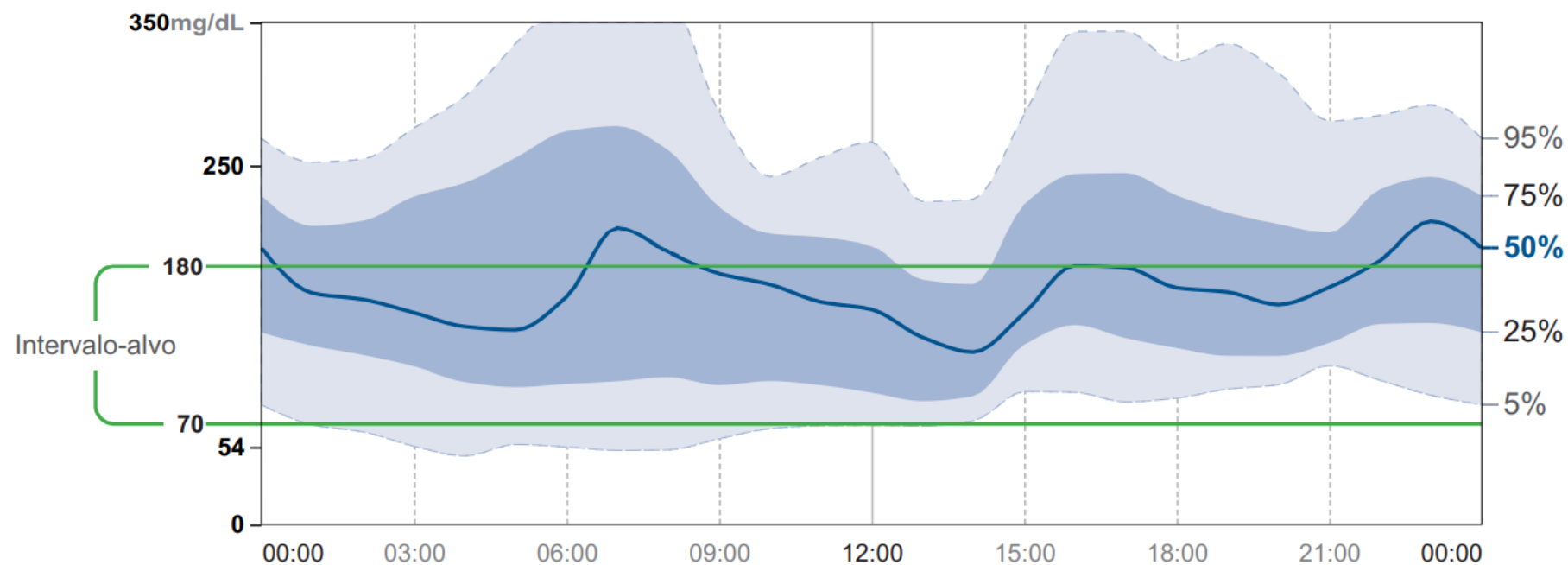
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VARIABILIDADE GLICÊMICA

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Pergunta 2: Em relação à variabilidade glicêmica, qual a verdadeira?

1. É adequada, porque o indicador “variabilidade da glicose” está normal. X
2. É demasiado baixa, porque o indicador “variabilidade da glicose” está abaixo do objetivo. X
3. É adequada porque a média de glicose é normal. X
4. É excessiva porque o indicador “variabilidade da glicose” está acima do objetivo. ✓
5. É adequada, porque o tempo no alvo está de acordo com os objetivos. X

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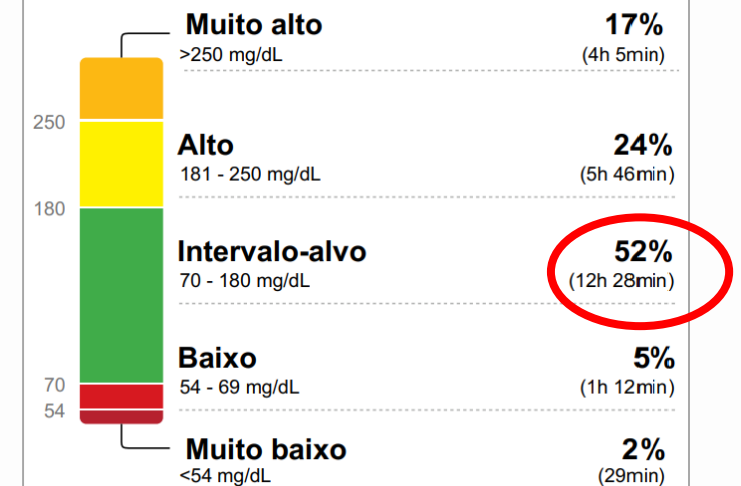
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PERÍODO NOS INTERVALOS



CASO CLÍNICO

M., 14 anos

Consulta 20.10.2021:

- HbA1C 6,9%
- Relatório de **AGP**

Relatório do AGP

7 Outubro 2021 - 20 Outubro 2021 (14 Dias)

LibreView

ALVOS E ESTATÍSTICAS DE GLICOSE

7 Outubro 2021 - 20 Outubro 2021 14 Dias

O % que o sensor de tempo está ativo 94%

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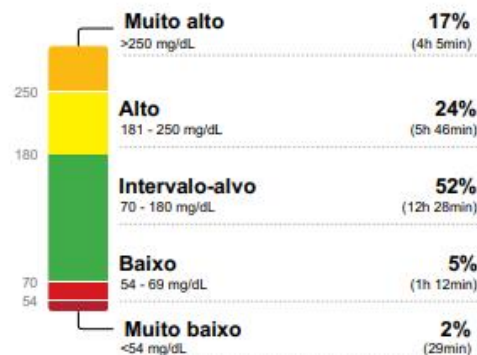
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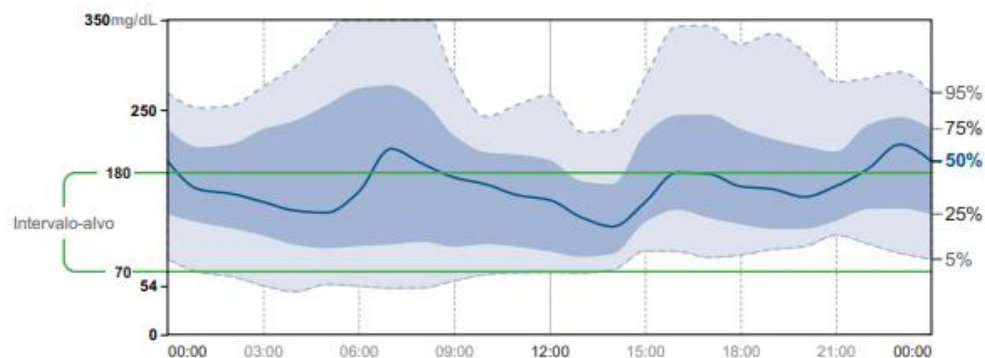
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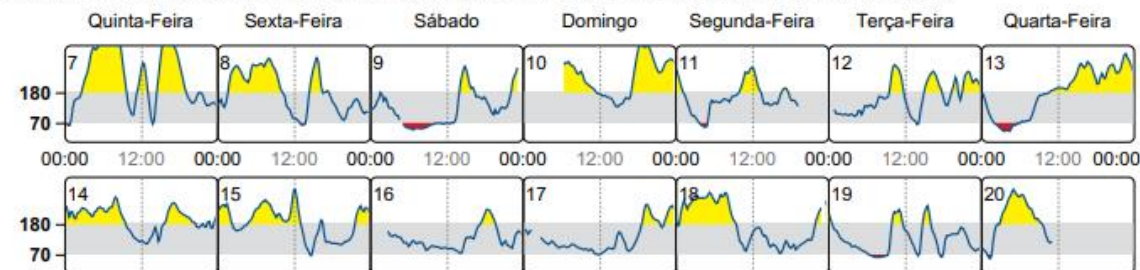
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1. Não podemos valorizar porque é muito diferente da HbA1C.
2. Deve estar correto, o aparelho de HbA1C é que pode não estar calibrado.
3. Não tem interesse porque se baseia apenas nos valores da MCG.
4. Está de acordo com o objetivo.
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ALVOS E ESTATÍSTICAS DE GLICOSE

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GLUCOSE MANAGEMENT INDICATOR [GMI]

INDICADOR DE GESTÃO DA GLICOSE

- Cálculo de aproximação à HbA1C, com base nos valores de glicose medidos pela MCG
- Inicialmente chamado “HbA1C estimada” (eHbA1C)
 - designação confusa, com expectativa de sobreposição com HbA1C medida
 - frustração com valores de eHbA1C e HbA1C não concordantes

GMI vs. HbA1C

- GMI – reflete um período de 14 dias
 - HbA1C – média de 3 meses
- Seriam totalmente concordantes se a média de glicose na MCG fosse constante durante 90 dias
- Haverá sempre cenários clínicos em que GMI e HbA1C não coincidem.*
- Devem avaliar-se ambos os parâmetros como peças individuais de um puzzle complete de avaliação do control glicémico.

TIR e HbA1C

TIR relaciona-se inversamente com a HbA1C

↑ TIR ~ 10% → ↓ HbA1C ~ 0,5 - 0.8%

Table 5—Estimate of A1C for a given TIR level based on type 1 diabetes and type 2 diabetes studies

Beck et al. (26) (n = 545 participants with type 1 diabetes)			Vigersky and McMahon (27) (n = 1,137 participants with type 1 or type 2 diabetes)	
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)	95% CI for predicted A1C values, %	TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)
20%	9.4 (79)	(8.0, 10.7)	20%	10.6 (92)
30%	8.9 (74)	(7.6, 10.2)	30%	9.8 (84)
40%	8.4 (68)	(7.1, 9.7)	40%	9.0 (75)
50%	7.9 (63)	(6.6, 9.2)	50%	8.3 (67)
60%	7.4 (57)	(6.1, 8.8)	60%	7.5 (59)
70%	7.0 (53)	(5.6, 8.3)	70%	6.7 (50)
80%	6.5 (48)	(5.2, 7.8)	80%	5.9 (42)
90%	6.0 (42)	(4.7, 7.3)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

TIR 70% ⇔ HbA1C ~ 7%

TIR 50% ⇔ HbA1C ~ 8%

J Diabetes Sci Technol 2019;13:614–626
Diabetes Technol Ther 2019;21:81–85
Clin Diabetes 2020 Dec;38(5):439-448

HbA1C

- Reflete a glicemia media nos últimos 2-3 meses (8-12 semanas).
- Ainda atualmente reconhecida como o *key surrogate marker* para o desenvolvimento de complicações a longo termo da diabetes tipo 1 e 2 , e foi usada como *endpoint* primário em muitos estudos de MCG.
- É o único marcador validado prospectivamente para avaliação de risco de complicações da diabetes
- Apesar das limitações que se têm vindo a evidenciar,
 - a sua importância na tomada de decisão clínica não deve ser subvalorizada,
 - **A utilidade da HbA1C pode ser ampliada quando interpretada de forma complementar com os dados de MCG.**

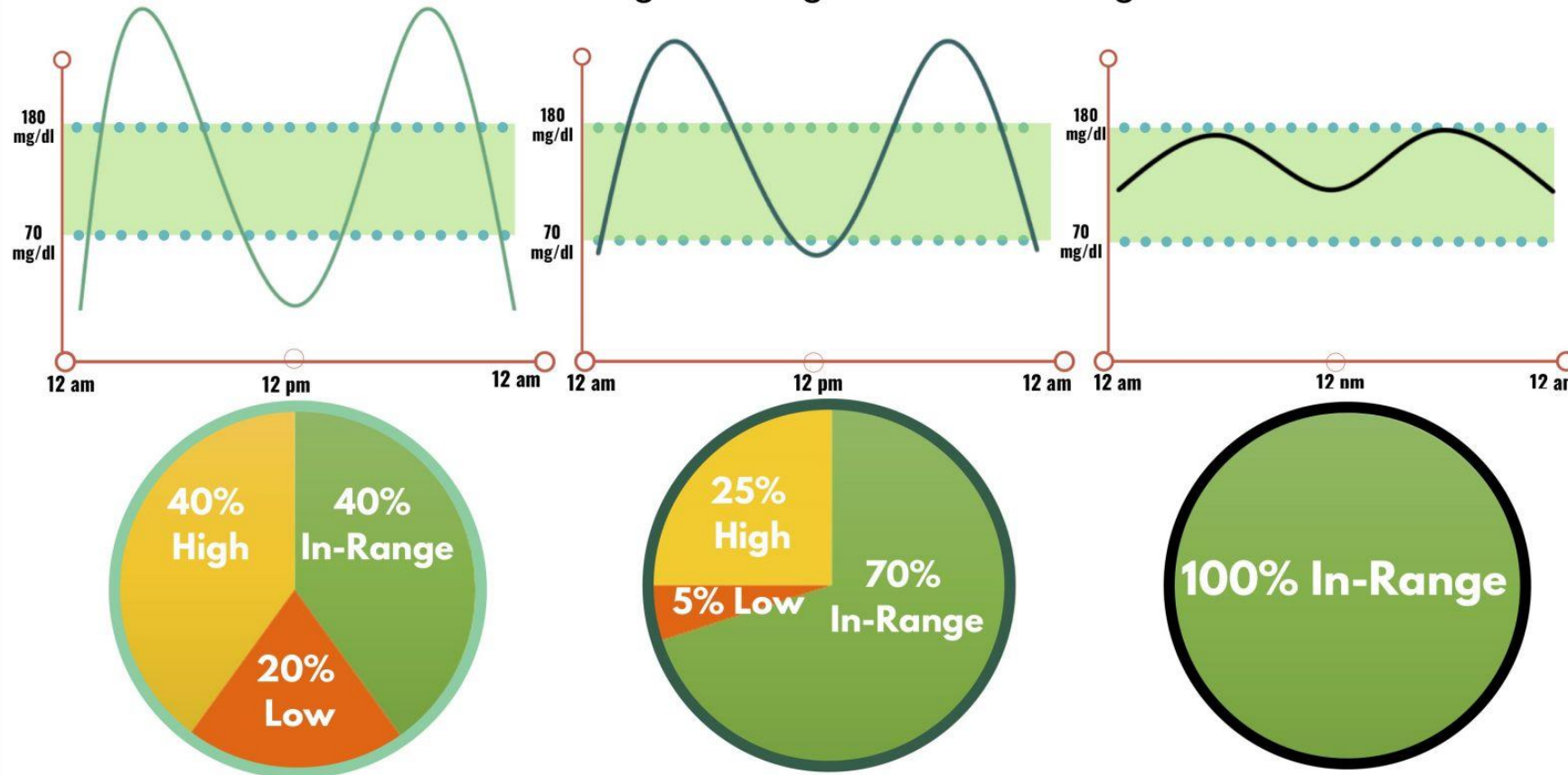
HbA1C – LIMITAÇÕES

- Não fornece informação acerca das excursões glicémicas agudas e complicações agudas de hipo- e hiperglicémia
- Não identifica a magnitude e frequência da variação glicémica intra- e interdiária
- Comorbilidades podem ser fatores de confundimento:
 - anemia
 - hemoglobinopatias
 - ferropénia
 - gravidez

HbA1C – LIMITAÇÕES

THE MANY FACES OF A 7% A1C

(and an average blood glucose of 154 mg/dl)



Pergunta 3: Em relação ao Indicador de gestão da glicose (GMI) qual a verdadeira?

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X

X

X

X



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- Relatório de **AGP**



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SPEDP 2021

REUNIÃO ANUAL

HYBRID EDITION

PORTO | 11 e 12 DE NOVEMBRO

O TEMPO NO INTERVALO-ALVO

Ana Laura Fitas

Hospital de Dona Estefânia, CHLC
Unidade de Endocrinologia Pediátrica
Responsável: Dra. Lurdes Lopes





SPEDP 2021

REUNIÃO ANUAL

HYBRID EDITION

CURSO TEÓRICO-PRÁTICO
DIABETES - TEMPO NO INTERVALO-ALVO

**ESTRATÉGIAS NUTRICIONAIS ÚTEIS PARA AUMENTAR O TEMPO NO
INTERVALO-ALVO**

CASO CLÍNICO 2

Painel de discussão: Dra. Ana Margarida Monteiro e Dra. Brigída Robalo

- Dra. Nanci Baptista



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SPEDP 2021

REUNIÃO ANUAL

HYBRID EDITION

PORTO | 11 e 12 DE NOVEMBRO

**Estratégias nutricionais úteis para aumentar o
tempo no intervalo-alvo**

Nanci Baptista

Sumário

- Contagem de hidratos de carbono
- Índice glicémico e Carga glicémica
- Contagem de proteínas e gorduras
- Aplicação de diferentes tipos de bólus

Caso clínico



17A6M

Peso 62,2 kg

Altura 168 cm

IMC 22kg/m²

Última HbA1C - 7,6%

Diagnóstico: 01/05/2010

PSCI desde: 20/03/2020

Monitorização: *Freestyle Libre*

Dados Bomba:

DDT 55.2U; Basal 17.2U (33 %); Bólus 35U(67%)

Ingestão média HC/dia:185g

Glicemia média 187mg/dl

Monitorização Glicose (últimos 14 dias):

Nº leituras diárias 21

% de dados captados - 86%

Glicemia média 161 mg/dl

Alvos do doente(70-180) Tempo no Alvo 66%; Acima do alvo 32%; Abaixo 2%

HbA1c estimada 7,2 %

Esquema de insulina

Basal

00-03h	0,89 U/H
03-04h	0,87 U/H
04-05h	0,83 U/H
05-07h	0,79 U/H
07-08h	0,76 U/H
08-09h	0,74 U/H
09-10h	0,7 U/H
10-11h	0,67 U/H
11-14h	0,64 U/H
14-22h	0,68 U/H
22-24h	0,72 U/H

Bólus

06-10h	1U	6 gr HC
10-12h	1U	15 gr HC
12-15h	1U	12 gr HC
15-19h	1U	11 gr HC
19-22h	1U	18 gr HC
22-00h	1U	16 gr HC
00-06h	1U	18 gr HC

FSI = 50mg/dl

Diário alimentar – Registo 3 dias

Domingo

PA (9h45)	200ml leite MG + 30 g cereais arroz tufado + 20 g cereais kellogs
MM (10h15)	130 g banana descascada + 35 g flocos de aveia
A (12h25)	Big Mac + batatas médias + 400ml limonada
L (18h00)	52 g pão trigo + 1 pacote leite achocolatado
J (19h45)	2 conchas de sopa + 180 g alheira + 25g pão integral + 90 tangerina

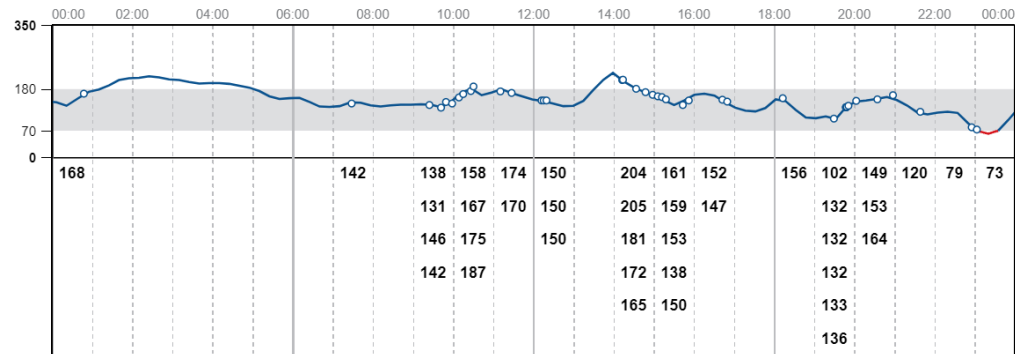
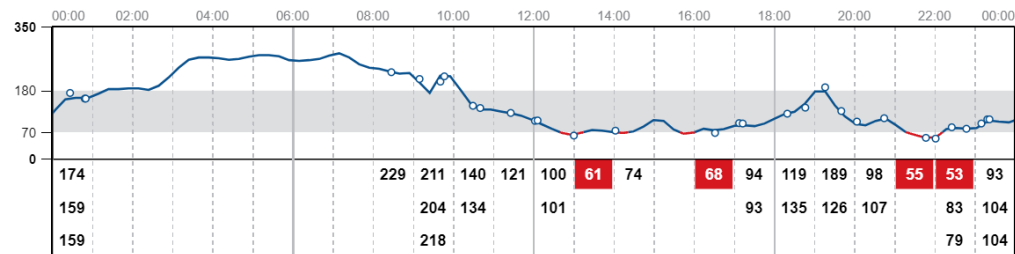
Segunda-feira

PA (9h30)	200ml leite MG + 47 g pão trigo
MM (10h)	1 iogurte straciatella + 1 barrita cereais e mel kellogs
A (12h)	2 conchas de sopa + 3ovos mexidos + 75 g esparguete
L (17h50)	2 barritas cereais e mel kellogs + 200 ml compal pessego
J (20h)	2 conchas de sopa + 180 g alheira + 112 g pera

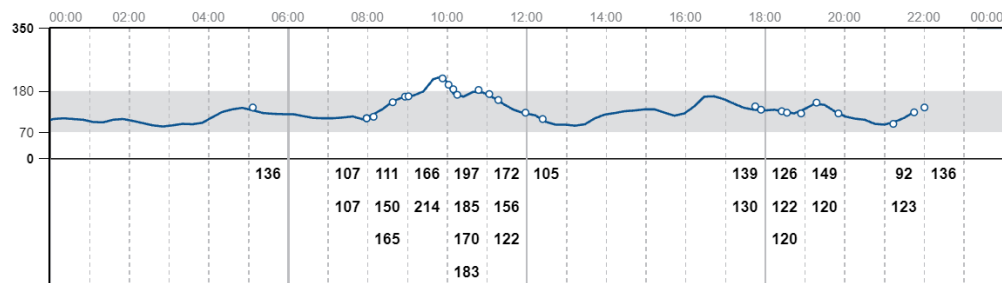
Terça-feira

PA (10h)	90 g banana descascada + 35 g flocos de aveia
A (12h)	2 conchas de sopa + 200 g bacalhau à gomes de sá + 150 g melão c/ casca + 1 biscoito de aveia (9g)
L (16h30)	1 croissant chocolate + 1 pacote leite achocolatado
J (20h)	2 conchas de sopa + 100 g bacalhau à gomes de sá + 160 g maçã

DOM 17 Out

 Glicose mg/dL

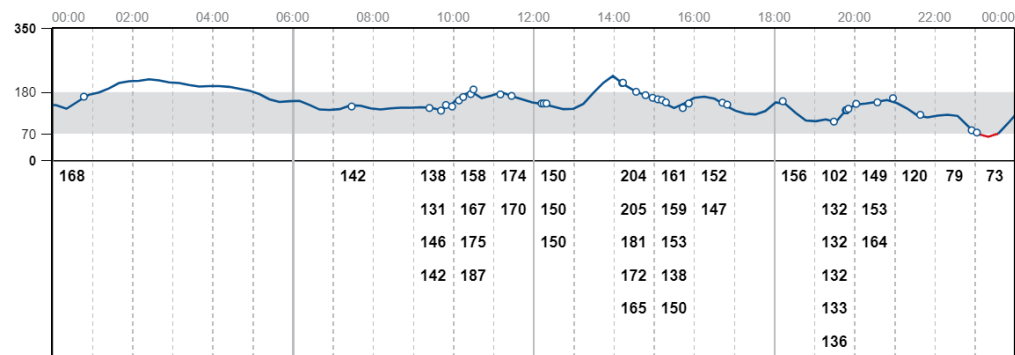
 Glicose mg/dL



Monitorização *Flash* da glicose

DOM 17 Out

Glicose mg/dL



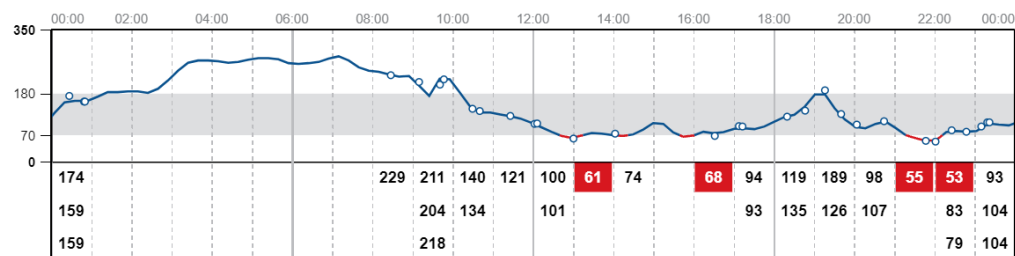
Domingo

Domingo	
PA (9h45)	200ml leite MG + 30 g cereais arroz tufado + 20 g cereais kellogs
MM (10h15)	130 g banana descascada + 35 g flocos de aveia
A (12h25)	Big Mac + batatas médias + 400ml limonada
L (18h00)	52 g pão trigo + 1 pacote leite achocolatado
J (19h45)	2 conchas de sopa + 273 g alheira + 25g pão integral + 90 tangerina

Monitorização *Flash* da glicose

SEG 18 Out

Glicose mg/dL



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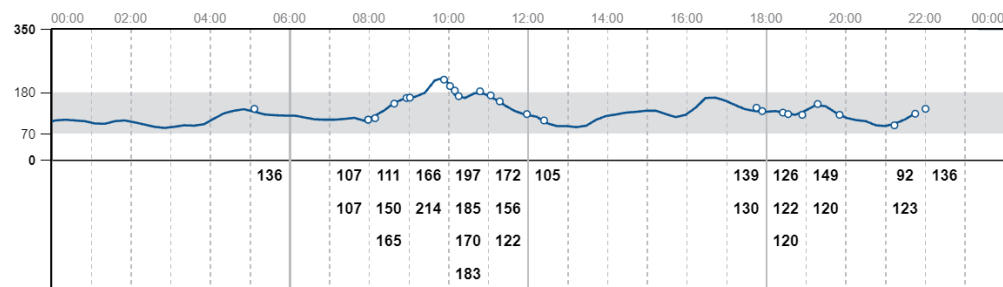
Segunda-feira

PA (9h30)	200ml leite MG + 47 g pão trigo
MM (10h)	1 iogurte straciatella + 1 barrita cereais e mel kellogs
A (12h)	2 conchas de sopa + 3ovos mexidos + 75 g esparguete
L (17h50)	2 barritas cereais e mel kellogs + 200 ml compal pessego
J (20h)	2 conchas de sopa + 180 g alheira + 112 g pera

Monitorização *Flash* da glicose

TER 19 Out

Glicose mg/dL



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Terça-feira

PA (10h)	90 g banana descascada + 35 g flocos de aveia
A (12h)	2 conchas de sopa + 200 g bacalhau à gomes de sá + 150 g melão c/ casca + 1 biscoito de aveia (9g)
L (16h30)	1 croissant chocolate + 1 pacote leite achocolatado
J (20h)	2 conchas de sopa + 100 g bacalhau à gomes de sá + 160 g maçã

Contagem de Hidratos de Carbono

Qual a quantidade ideal de hidratos de carbono?

Contagem por equivalentes/ Porções ou Gramas de Hidratos de Carbono, qual o melhor método?

Contagem de Hidratos de Carbono



A guide to the distribution of macronutrients

Carbohydrate 45% to 55% energy
Moderate sucrose intake (up to 10% total energy)
Fat 30% to 35% energy
<10% saturated fat + trans fatty acids
Protein 15% to 20% energy

ISPAD Clinical Practice Consensus Guidelines 2018

Recomendações nutricionais:

- ✓ semelhantes à população em geral
- ✓ Qualidade vs Quantidade

Restrição HC/ Dietas *pobres* HC:

- ✓ Carências nutricionais
- ✓ Atrasos crescimento e desenvolvimento

Contagem de Hidratos de Carbono

- **Equivalentes/ Porções**

Quantidade de alimento que contém 10, 12 ou 15 g de HC

- **Gramas de Hidratos de Carbono**

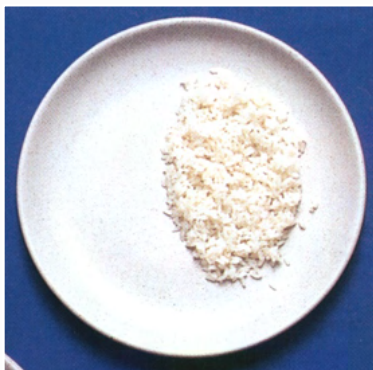
Gramas de HC/ 100g alimento

Contagem HC - GRAMAS VS EQUIVALENTES

- **Equivalentes (1 equivalente = 15 g HC)**

- ❖ Medidas caseiras (colheres)
- ❖ Quantidade de HC estimada
- ❖ Menor precisão

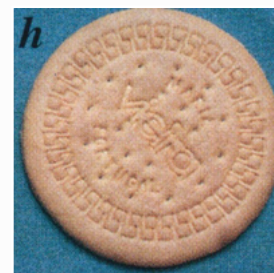
Exemplos: 1 equivalente



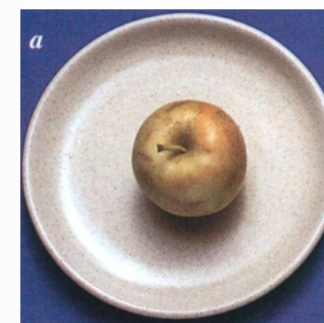
2 colheres de sopa



Meio pão



3 bolachas Maria



Maçã média

Contagem HC - GRAMAS VS EQUIVALENTES

• Gramas de Hidratos de Carbono

- ❖ Pesagem (balança)
- ❖ Quantidade de HC exata
- ❖ Maior precisão

✓ Melhor controlo glicémico
✓ Melhor HbA1c

	Hidratos de carbono por 100g/ml alimento
PÃO, CEREAIS E PRODUTOS AFINS	
Açorda com ovo	14
Broa de milho	37
Broa doce	50
Croutons	74
Farinha de trigo	74
Farinha láctea <i>Cerelac</i>	68
Fermento em pó	34
Flocos de arroz	83
Flocos de aveia	62
Flocos de milho <i>Corn Flakes</i>	81
Flocos de trigo	69
Flocos de trigo com mel <i>Nestum</i>	85
Gressinhos	67
Nachos	63
Pão trigo, mistura, centeio	57
Pão de forma branco	55
Pão de hambúrguer/cachorro	49
Pão de leite	51
Pão de milho	37
Pão de queijo	48

Valor nutricional médio	por 100 ml	por 200 ml	% DDR ⁽²⁾
Valor energético (kcal/kJ)	63/265	125/530	
Proteínas (g)	3,2	6,4	
Hidratos de carbono (g) dos quais:	10,0	20,0	
Açúcares (g)	10,0	20,0	
Lípidos (g) dos quais:	1,1	2,2	
Saturados (g)	0,8	1,6	
Fibras alimentares (g)	0	0	
Sódio (g)	0,04	0,1	
Cálcio (mg)	117	234	29
Fósforo (mg)	90	180	23
Vitamina B12 (µg)	0,2	0,4	40
Vitamina Riboflavina (mg)	0,15	0,3	19

(2) DDR - Dose Diária Recomendada

Contagem HC - GRAMAS VS EQUIVALENTES

Segunda-feira	
PA (9h30)	200ml leite MG + 47 g pão trigo

47 gramas

~ 2 equivalentes (= 30 g HC)

26,8g = **27 g HC**

- ✓ Menos “arredondamentos”
- ✓ Maior precisão na contagem HC e cálculo dose insulina

Contagem HC - Apps



x

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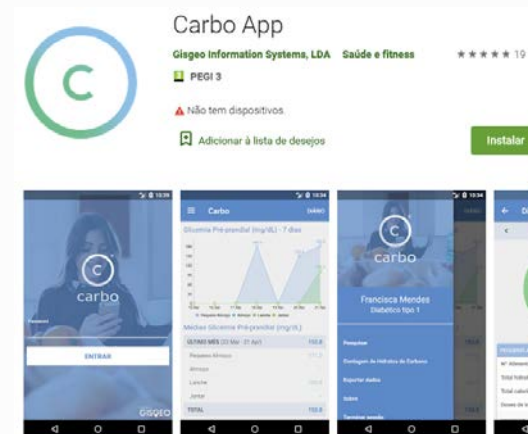
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7, AGOSTO, 2012

Carbs & Cals no smartphone contabiliza hidratos de carbono e calorias



Pergunta 1.

No caso de ingerir 200 ml, a quantas gramas de HC corresponde?

- 1. 8,5
- 2. 17 (verdadeira)
- 3. 18
- 4. 9
- 5. 8

<i>Informação nutricional</i>	100ml
Energia (kcal)	34
Hidratos de Carbono	8,5 g
Açúcares	8,5 g
Proteínas	0 g
Gorduras	0 g

Índice glicémico e Carga glicémica

O Índice glicémico (IG) deve ser utilizado na terapêutica nutricional da Diabetes?

O IG pode ser utilizado como ferramenta única no controlo glicémico?

Índice glicémico e Carga glicémica

- **Índice Glicémico (IG)**

Permite diferenciar os alimentos fornecedores de HC de acordo com o seu efeito na glicemia pós-prandial.

A resposta glicémica à ingestão de uma porção de alimento que forneça 50 g HC disponíveis, é comparada com a mesma dose (50 g HC) do alimento-padrão (pão branco ou glicose).

Os alimentos são classificados numa escala de 0 a 100 por comparação com um alimento padrão.

- **Carga Glicémica (CG)**

Combina a informação sobre o índice glicémico com a quantidade ingerida.

Dá a informação sobre como a ingestão de uma determinada quantidade de um alimento influencia a glicemia, em comparação com a proporção de outros alimentos.

É um indicador da **qualidade** e **quantidade** dos hidratos de carbono a partir de uma determinada porção consumida.

Índice glicémico e Carga glicémica

FRUIT AND FRUIT PRODUCTS	
Apple, raw†	36 ± 2
Orange, raw†	43 ± 3
Banana, raw†	51 ± 3
Pineapple, raw	59 ± 8
Mango, raw†	51 ± 5
Watermelon, raw	76 ± 4
Dates, raw	42 ± 4
Peaches, canned†	43 ± 5
Strawberry jam/jelly	49 ± 3
Apple juice	41 ± 2
Orange juice	50 ± 2

Exemplo:

1 Banana média (120g) contém:
24g de hidratos de carbono
IG de 51 (médio)
CG 12 (média)

1 porção de Melancia (152g) contém:
10g de hidratos de carbono
IG 76 (alto)
CG 7,2 (baixa)

✓ **Melancia** X **Banana**

Uma porção de melancia apresenta uma quantidade HC inferior do que uma porção de banana

Índice glicémico e a sua aplicação

- Alimentos com IG alto (>70) têm um impacto na glicémia pós-prandial.
- Substituir alimentos de IG alto por alimentos de IG baixo (< 55) melhora o controlo metabólico.

- Alimentos processados:
 - ✓ Diferenças significativas no valor de IG do mesmo produto
 - ✓ Falta de informação sobre IG de muitos alimentos
- O IG é uma ótima ferramenta mas não pode ser utilizado isoladamente:
 - ✓ Ingestão de um só alimento vs refeições compostas (vários alimentos).
 - ✓ Teor fibra e gordura (saturada) da refeição.

Pergunta 2.

Na definição de IG:
(Assinale a afirmação verdadeira)

1. Alimentos com IG baixo têm um maior impacto na glicémia pós-prandial
2. Apenas é necessário contabilizar a quantidade de proteína do alimento
3. Alimentos ricos em açúcares não são classificados
4. Alimentos com IG alto têm um maior impacto na glicémia pós- prandial (verdadeira)
5. Todas as alíneas anteriores são falsas

Contagem de proteínas e gorduras

- Apesar dos HC serem o macronutriente determinante da glicemia pós-prandial estudos têm demonstrado que as gorduras e proteínas também têm impacto significativo no controlo da Glicemia pós-prandial (GPP) e por isso, ajustar a dose de insulina prandial de acordo com estes macronutrientes pode ser benéfico.
- Alguns avanços tecnológicos (monitorização contínua da glicose) permitiram entender o perfil glicémico e analisar a relação entre gordura/ proteína ingerida e dose de insulina prandial.
- Autores concluíram que é necessário uma dose de insulina “extra” para refeições ricas em gordura e proteína.

Contagem de proteínas e gorduras

- Qual a quantidade mínima proteína/ gordura a contabilizar?
- Que tipo de bólus aplicar?
- Administrar bólus durante quanto tempo?

Contagem de proteínas e gorduras

FII (food insulin index)

- Algoritmo para calcular as necessidades individuais de insulina e baseia-se nas necessidades fisiológicas de insulina em indivíduos saudáveis.
- É a resposta de insulina relativa aos alimentos, e é baseada em testes de porções isoenergéticas de alimentos individuais (250kcal).
- Como o valor energético é uma constante, com este método a dose de insulina é calculada para alimentos que habitualmente não é administrado insulina, como ovos e carne.
- Melhor controlo glicémico pós-prandial após 2-3 horas.
- Limitações: Monitorização de um período pós-prandial curto (3 horas), e que por isso não deteta o verdadeiro impacto glicémico das gorduras e proteínas.

Brand-Miller et al

Impact of Fat, Protein, and Glycemic Index on Postprandial Glucose Control in Type 1 Diabetes: Implications for Intensive Diabetes Management in the Continuous Glucose Monitoring Era

Contagem de proteínas e gorduras

*FPU*s (fat-protein units)

- Uma unidade gordura-proteína é definida por 100kcal de gordura e/ ou proteína.
- Por cada *FPU*s calcula-se uma dose extra de insulina, que é administrado através de bólus prolongado/ quadrado durante horas de acordo com a quantidade consumida na refeição:
 - ❖ 1 *FPU* - 3 h
 - ❖ 2 *FPU* - 4 h
 - ❖ 3 *FPU* - 5 h
 - ❖ > 3 *FPU* - 8 h

Pańkowska et al

Contagem de proteínas e gorduras

*FPU*s (fat-protein units)

Table 1. The Warsaw School Procedure for calculating mealtime insulin dose

Meal	Ingredients	Nutrition data	Carb unit (CU) and fat-protein unit (FPU)	Insulin-to-carbohydrate ratio (U/L) CU OR FPU	Dose of insulin	
					Normal bolus	Square wave bolus/period of time
Hot-dog	Bread 50 g; sausage 100 g; mustard 10 g	Total kcal 484; carbohydrate 29.5 g; protein 15.7 g; fat 28.2 g	3 CU; 3 FPU	1.0	$3 \times 1.0 = 3 \text{ U}$	$3 \times 1.0 = 3 \text{ U/5 h}$

- Limitação: Neste estudo, apesar de resultar num melhor controlo glicémico o risco de hipoglicemia pós-prandial aumento 3 vezes mais, comparando com o cálculo apenas da dose para os HC.

Pańkowska et al

Contagem de proteínas e gorduras

Aumento 40% b́olus - refeição rica em gordura e proteína

- Refeição composta por: 30g HC, 40 g gordura e 50 g proteína
- Administrar B́olus duplo/ multionda - proporção 60:40
- Duração do b́olus: 3 horas
- Aumento de 40% da dose de insulina
- Sem risco de hipoglicemia
- **Recomendação**: Começar por aumento de 10-20% da dose insulina, se hiperglicemia persistir, aumentar mais 10% a dose (até ao máximo 40%).

In children and young people with type 1 diabetes using Pump therapy, an additional 40% of the insulin dose for a high-fat, highprotein breakfast improves postprandial glycaemic excursions: A cross-over trial



The graph shows a function on a coordinate plane. The function starts at the origin (0,0), increases linearly to a peak, and then decreases linearly to a constant value. The peak is at (2, 4), and the function remains constant at y=4 for x ≥ 2.

3,9 U (40%)

HC - 83 g
Prot - 31 g
Líp - 41 g



3 horas

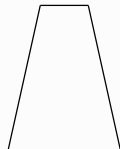
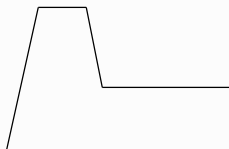
Pergunta 3.

Quais os fatores que interferem com a glicemia pós-prandial?
(Assinale a afirmação falsa)

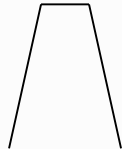
1. Apenas a quantidade de hidratos de carbono total da refeição (falsa)
2. A glicemia pré-prandial
3. A quantidade de hidratos de carbono, proteína e gordura
4. O índice glicêmico
5. O fator de sensibilidade

Aplicação de diferentes tipos de bólus

- Perfusão subcutânea de insulina -

Tipo de Bólus	
Normal Padrão	
Quadrado Prolongado	
Duplo Multionda	

Aplicação de diferentes tipos de bólus

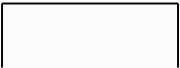
Tipo de Bólus	Objectivos
Normal Padrão 	Refeição composta por alimentos ricos em hidratos de carbono. Correção da hiperglicemia.

Quadrado/Prolongado

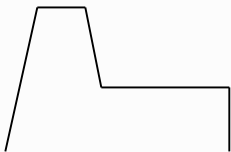
Duplo/Multionda

- Mínimo 30 minutos e máximo 8 horas, tendo em conta a composição e duração da refeição.
- Podem ser interrompidos durante a administração do bólus.
- Evitam hipoglicémias que ocorrem imediatamente após a refeição.
- Aplicação em situações em que há aumento da glicémia pós-prandial (3 – 5h).

Aplicação de diferentes tipos de bólus

Tipo de Bólus	Objetivos
Quadrado Prolongado 	Refeições pobres ou com poucos HC ricas em gordura e proteínas. Quando demoramos mais tempo a comer (ex: no cinema a comer pipocas, crianças mais pequenas que demoram muito tempo a comer).

Aplicação de diferentes tipos de bólus

Tipo de Bólus	Objetivos
Duplo Multionda 	Refeições ricas em HC, ricas em gordura e proteínas. Quando os alimentos da refeição são de digestão lenta/demorada (ex: pizza, massas com molho, comida chinesa,...).

Prato: 180 g alheira grelhada	33 g HC
	32 g Gordura (10 g saturada) + 24 g Proteína

Glicemia – 150 mg/ dl

FSI= 50

$$(150 - 100) / 50 = 1 \text{ UI}$$

↑ 20%

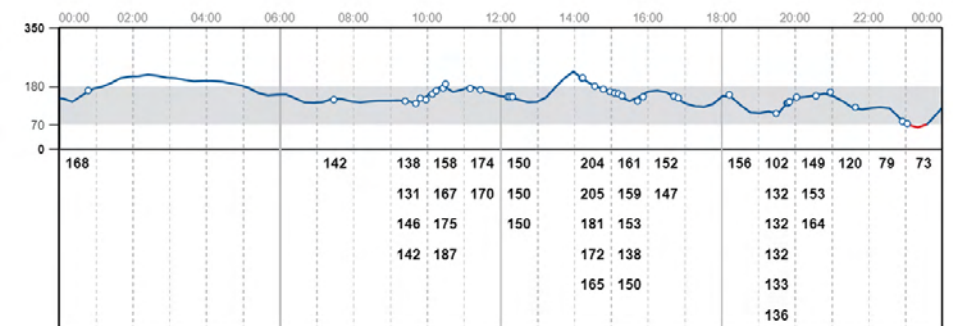
3,4 UI

Quadrado / Prolongado

Duração 2:00 – 3:00



Glucose mg/dL



De acordo com a tolerância, sensibilidade individual....

Bólus Duplo/ Multionda



Calorias (Kcal)	Proteínas (g)	Gorduras (g)	Gorduras Saturadas (g)	Hidratos de Carbono (g)	Açúcares Simples (g)	Sal (g)
862,7	37,9	41,2	20,6	95,0	9,6	5,1

Glicemia – 140 mg/ dl

Cálculos insulina:

19H – 22H: 1U ----- 18 gr HC

UI = 95gr HC/ 18 = 5,3 UI

Cálculos correção:

FSI= 50

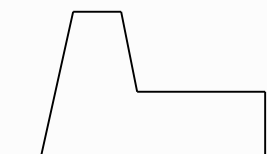
$(140 - 100) / 50 = 0,8 \text{ UI}$

↑20%

Bólus: 6,1 UI

Bólus total:

7,3 UI



**Bólus duplo/
multionda**

70 %	5,1 U
30 %	2,2 U

**Duração
2:00-3:00**

OU

60 %
40 %

OU

50 %
50 %

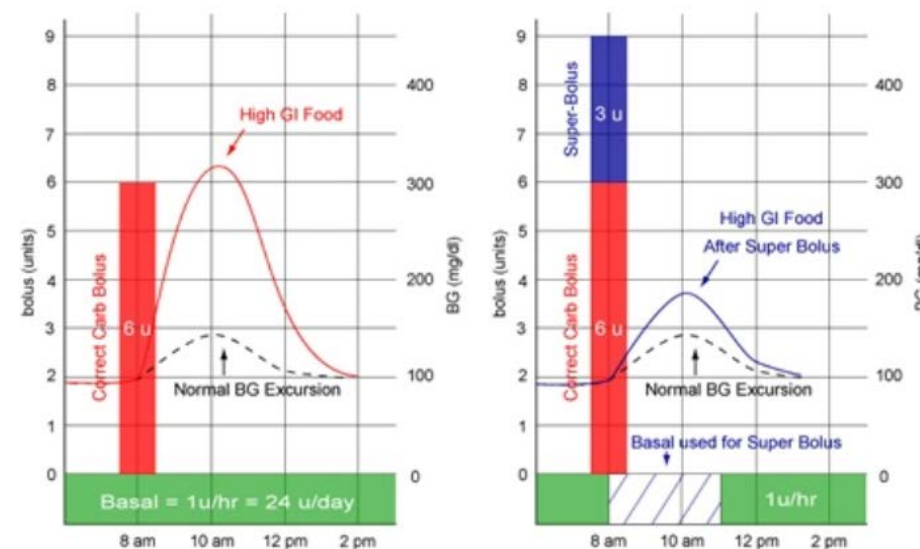
De acordo com a tolerância, sensibilidade individual....

Super bólus vs Bólus padrão

- Quando e como aplicar?

- Em refeições com alimentos com IG alto (cereais de PA)
- Quando a glicemia aumenta rapidamente logo após a ingestão e desce sem ser necessário correção.
- Basal: basal temporária 0% (2-3h)
- Administração Bólus padrão:

Super bólus = Insulina p/ HC + insulina correspondente à basal



Graphic 2

Effects of Super-Bolus on Postprandial Glycemia After High Glycemic Index Meal in Children With Type 1 Diabetes Mellitus- Randomized Study. January, 2020.

Pergunta 4.

O bólus duplo/ multionda deve ser aplicado em que situações?
(Assinale a afirmação verdadeira)

1. Em refeições pobres em hidratos de carbono
2. Quando se ingerem alimentos ricos hidratos de carbono de absorção rápida
3. Em refeições pobres em gorduras
4. Quando se verifica aumento da glicémia 3-4 horas após a refeição (verdadeira)
5. Antes do exercício físico

O que já sabemos....

- A importância de administração do bólus antes de iniciar a refeição (15 min antes em refeições ricas Gord/Prot)
- Contabilização rigorosa da quantidade de HC (pesagem)
- A quantidade de gordura e proteína da refeição tem impacto na GPP
- Ingestão de alimentos com IG baixo, melhoram o controlo glicémico

Refletir, questionar e continuar a estudar....

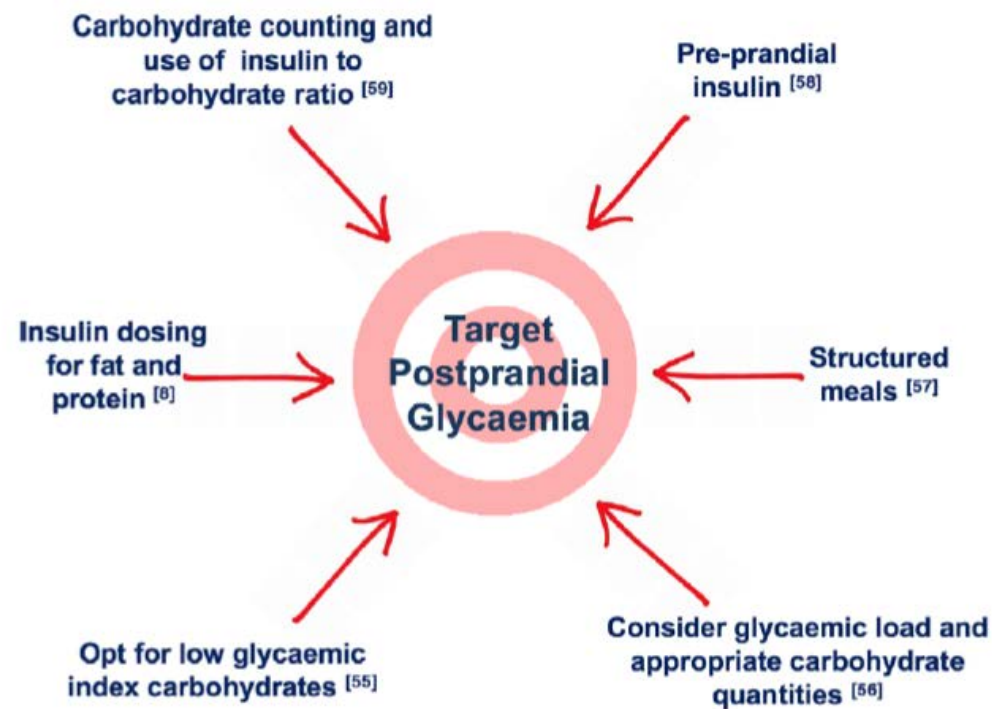


FIGURE 1 Strategies to minimize postprandial glycaemic excursions [8,55–59].



×

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Obrigada pela atenção.

Nanci Baptista



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CURSO TEÓRICO-PRÁTICO
DIABETES - TEMPO NO INTERVALO-ALVO

**ESTRATÉGIAS FARMACOLÓGICAS ÚTEIS PARA AUMENTAR O TEMPO
NO INTERVALO-ALVO**

CASO CLÍNICO 3

Painel de discussão: Prof. Dra. Helena Cardoso e Dra. Joana Campos

• Dra. Teresa Azevedo





×

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**Estratégias Farmacológicas úteis para
aumentar o Tempo no Intervalo Alvo**

Teresa Azevedo

Desafios no tratamento DM1

APESAR DE:

- Novas insulinas
- Novos dispositivos de administração de insulina (canetas, bombas infusoras)
- Monitorização contínua da glicose



Apenas 20% das pessoas com DM1 têm um controlo adequado!!

Caso Clínico 3

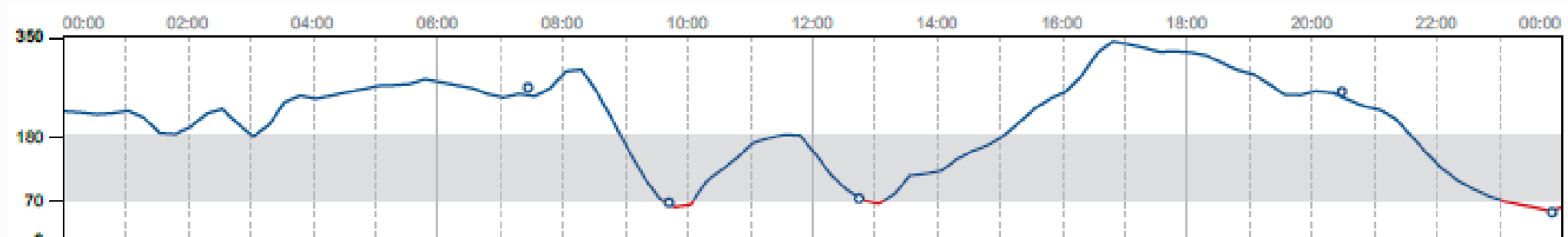
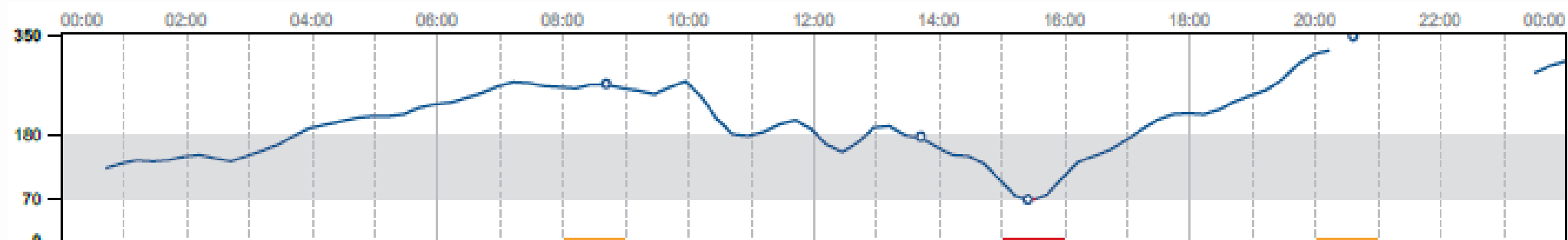
- Sexo feminino, 17 anos
- Frequenta o 11º ano; pratica voleibol 4x/sem
- DM1 desde os 12 anos
- Sem complicações agudas ou crónicas da diabetes
- Múltiplas administrações de insulina por dia com caneta (recusa CSII)
 - Glargina U100 24 unid. de manhã
 - Glulisina (I/HC 8 PA, 10 MM, 12 A, 12 L, 10 J; obj. 90-130 mg/dL, FSI 45).
- Sob monitorização da glicose intersticial e glicemia capilar
- Outros AP: irrelevantes
- Dados antropométricos: Peso 82 kg; Estatura 1,73 m; IMC 27,4 kg/m²
- Análises: HbA1c 7,9%, col tot. 222 mg/dL, HDL 56 mg/dL, LDL 132 mg/dL, trig. 168 mg/dL
- CGM...



Relatório CGM

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Pergunta 1

O que poderia melhorar?

- A. Controlo glicémico - A1c?
- B. Controlo glicémico - Tempo no Alvo?
- C. Reduzir o peso?
- D. Melhorar o perfil lipídico?
- E. Todas as anteriores

Pergunta 2

Nesta fase, qual seria a proposta terapêutica mais adequada?

- A. Aumentar a quantidade de insulina lenta
- B. Fazer duas administrações diárias de insulina Glargina U100
- C. Substituir a insulina Glargina U100 por Glargina U300 e titular a dose
- D. Alterar o objetivo glicêmico para 80-120 mg/dL (em vez de 90-130 mg/dL)
- E. Alterar o esquema de insulina Glulisina para unidades fixas às refeições em vez de contagem HC

Evolução das insulinas

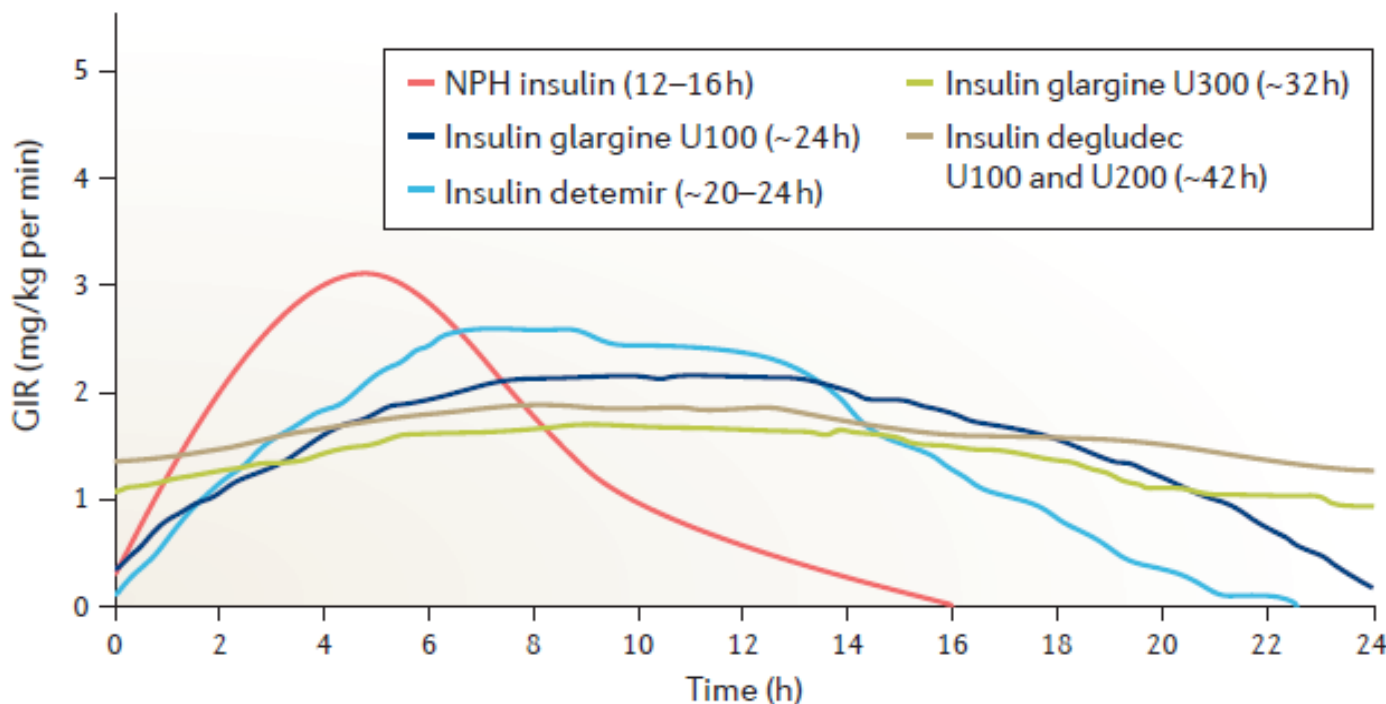
- **Insulinas de origem animal** purificadas
- **Insulinas humana**
 - de ação curta: insulina humana regular
 - de ação lenta: adição de protamina e zinco à insulina regular (NPH)
- **Análogos de insulina de 1ª geração**
 - Ação Curta: Aspart (NovoRapid®), Lispro (Humalog®), Glulisina (Apidra®)
 - Ação lenta: Glargina U100 (Lantus®, Abasaglar®, Semglee®), Detemir (Levemir®)
- **Análogos de insulina de 2ª geração**
 - Ação Curta: Aspart ultra-rápida (Fiasp®), Lispro Ultra-rápida (Lyumjev®)
 - Ação lenta: Glargina U300 (Toujeo®), Degludec (Tresiba®)

Perfis farmacocinéticos das insulinas de ação lenta

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✓ Menor risco de hipoglicemias noturnas

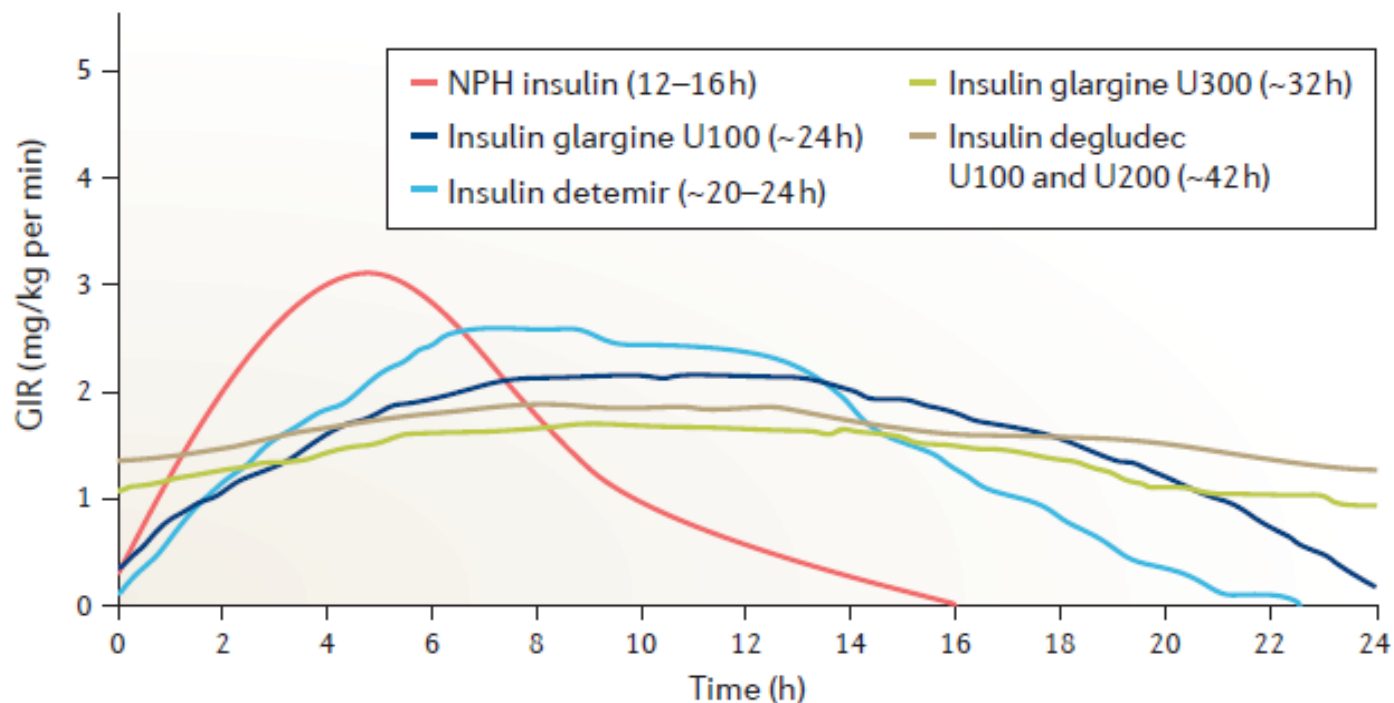
↓ 30% em DM1 com uso de análogos 1ª geração vs NPH

↓ 30% em DM1 com uso de análogos 2ª geração vs 1ª geração

- Em comparação com os análogos de ação lenta de 1ª geração, as **insulinas ultra-lentas Glargina U300** e a insulina **Degludec**:
 - Ainda maior estabilidade
 - Ainda menor risco de hipoglicemia noturna
 - Maior flexibilidade na hora administração

Nat Rev Endocrinol 13(7):385–399.

Insulina Glargina U300



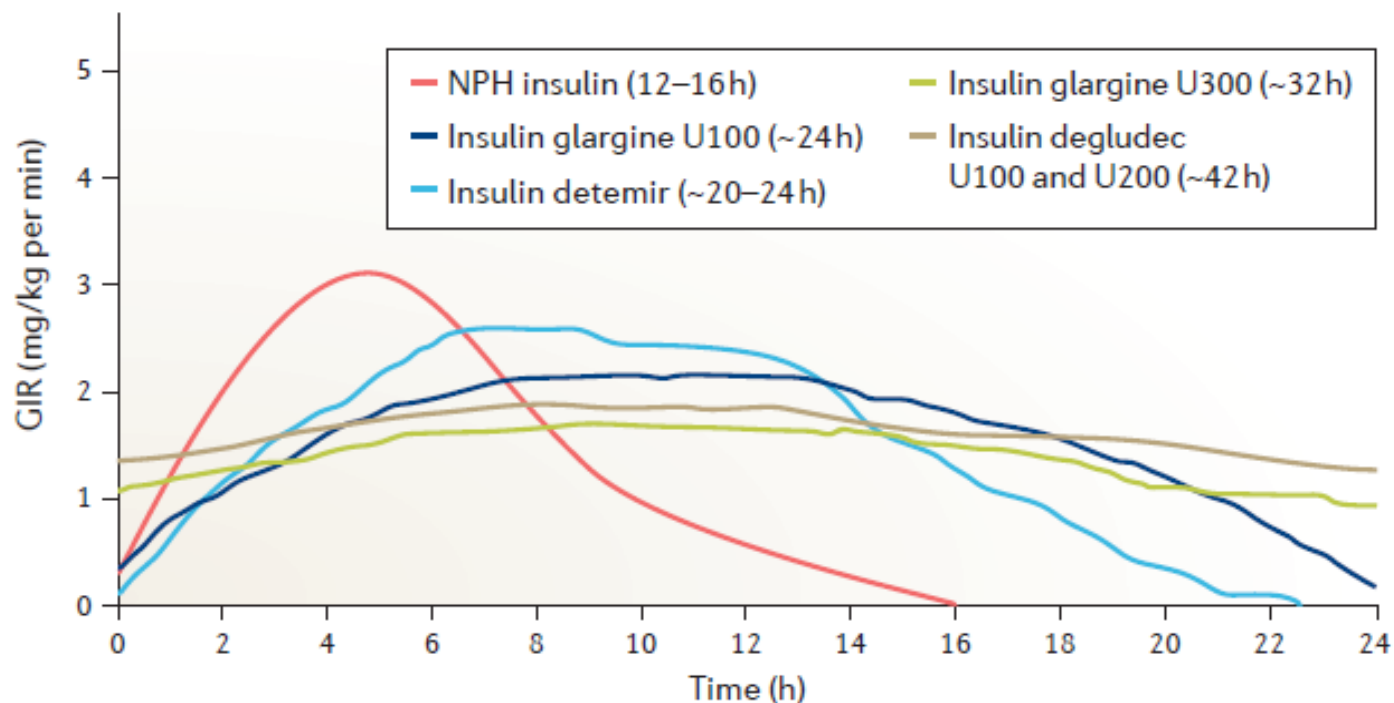
- **Maior duração de ação** (Glargina U300 ~32h vs Glargina U100 ~24h)
- Curva mais plana e menos variabilidade
- Menor risco de hipoglicemia
- **Menor biopotência** Glargina U300 vs U100 (necessidade de aumento de dose)

- Não aprovada na gravidez
- Sem informação de segurança abaixo dos 6 anos de idade

CONTUDO

Um vez que a molécula é a mesma que Glargina U100 não são expectáveis novas questões relacionadas com a segurança

Insulina Degludec



- **Maior duração de ação (~42h);** não há risco de acumulação de insulina ativa
- Após a 1ª administração, são necessários **3 dias para alcançar o plateau**; depois existe um perfil de ação muito estável
- Menor risco de hipoglicemia
- Comercializada em duas formulações (**U100** e U200), que não diferem em termos farmacocinéticos e farmacodinâmicos

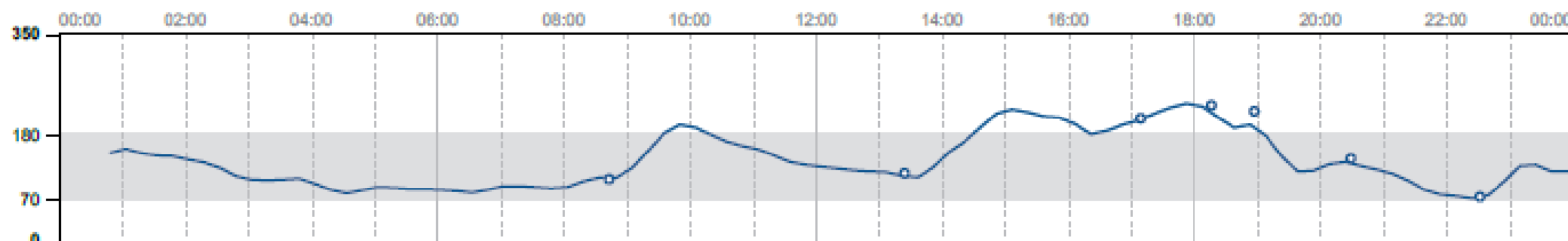
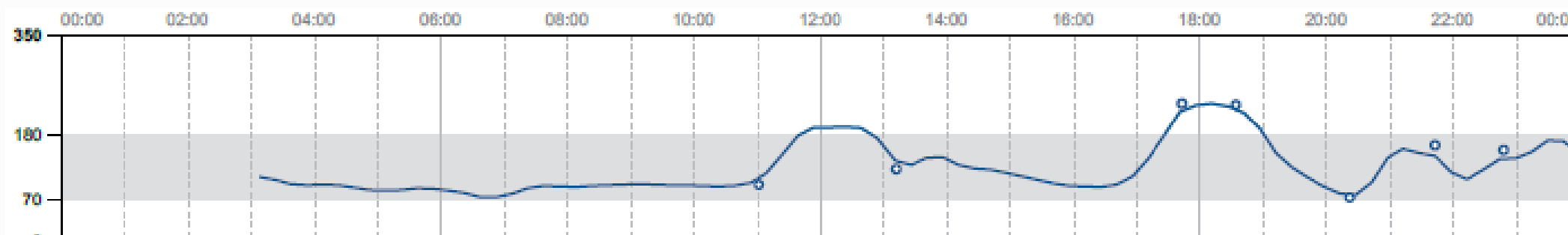
- **Aprovada em crianças a partir 1 ano de idade**
(estudos demonstram benefícios nas crianças semelhantes aos adultos)
- Não aprovada na gravidez

Relatório CGM

Após introdução de Glargina U300

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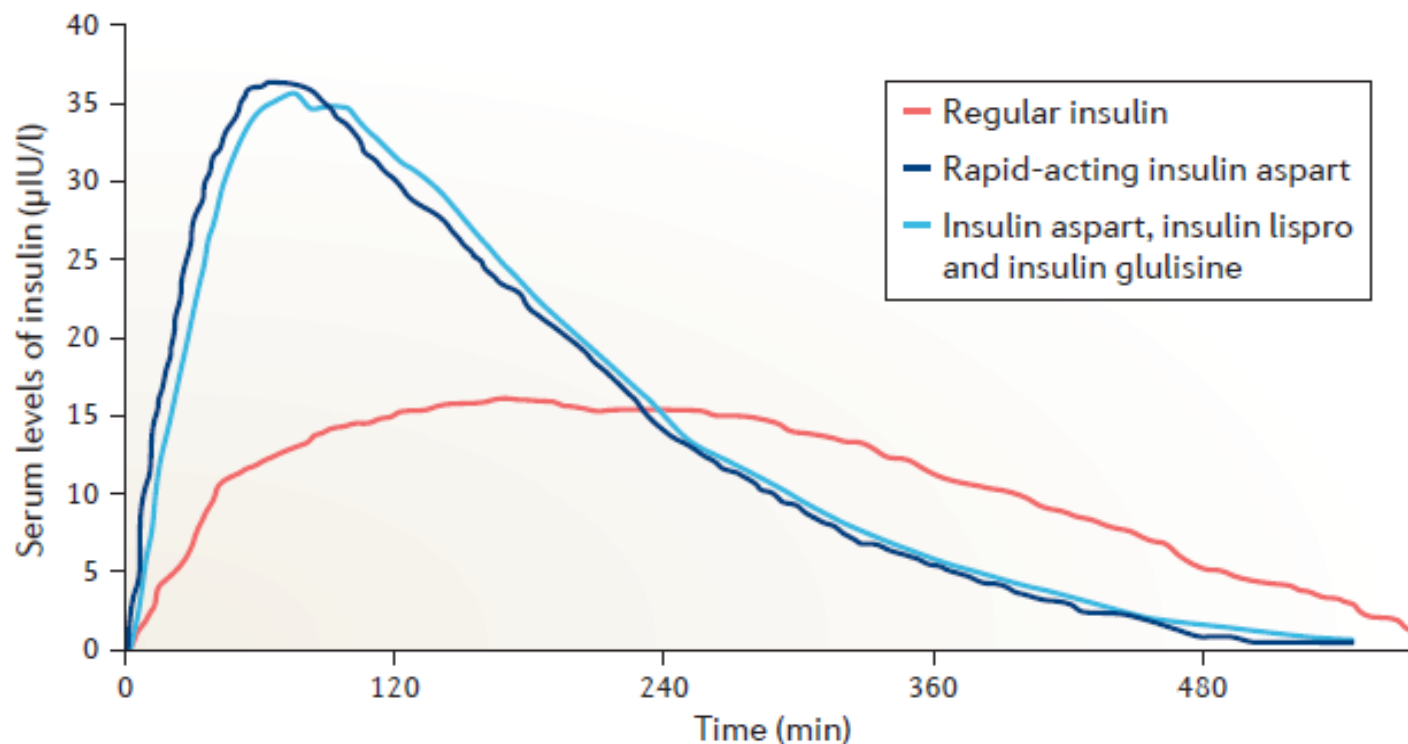


Pergunta 3

E agora? Qual a proposta terapêutica?

- A. Aumentar a quantidade de insulina lenta
- B. Alterar a insulina Glargina U300 para insulina Degludec
- C. Alterar a insulina Glulisina para insulina Aspart
- D. Alterar a insulina Glulisina para Insulina Aspart ultra-rápida
- E. Introduzir liraglutide

Perfis farmacocinéticos das insulinas de ação rápida



- ✓ Permitir maior flexibilidade
- ✓ Diminuir Hipoglicemias

- Em comparação com insulina humana regular, **os análogos de insulina (aspártica, lispro e glulisina):**
 - Início de ação mais rápido
 - Maior pico
 - Menor duração de ação
- Maior custo

Análogos de Insulina de ação rápida

2ª geração – Insulinas ultra-rápidas

- **Insulina Aspártica Ultra-rápida – Fiasp®**
- **Insulina Lispro Ultra-rápida - Lyumjev®**
- Em comparação com os análogos de 1ª geração, os análogos de 2ª geração:
 - Início de ação ainda mais rápido
 - Ainda menor duração de ação

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Ultra-rapid acting analog (faster aspart) ^{a,c}	0.1-0.2	1-3	3-5
Rapid-acting analogs (aspart, glulisine, and lispro)	0.15-0.35	1-3	3-5
Regular/soluble (short acting)	0.5-1	2-4	5-8



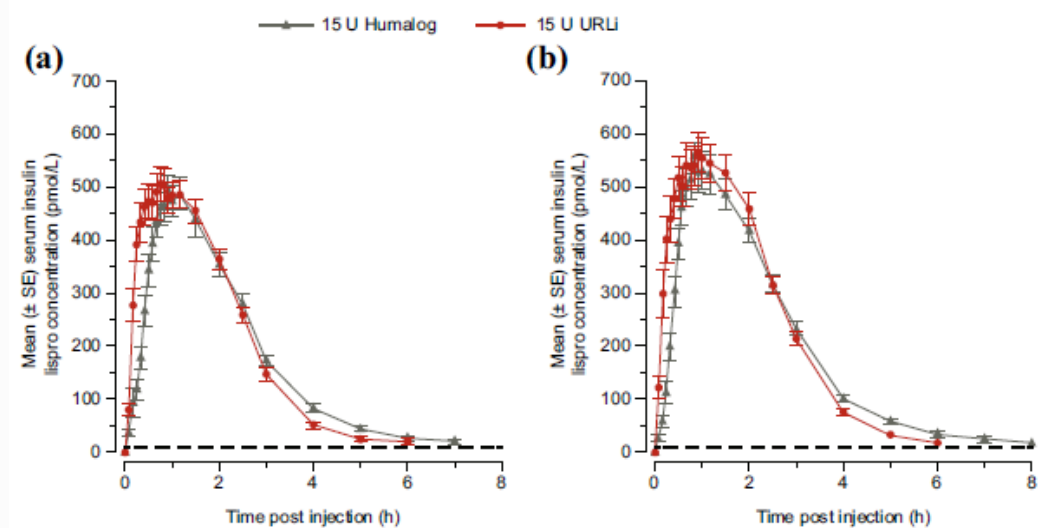
Pharmacokinetics and Glucodynamics of Ultra Rapid Lispro (URLi) versus Humalog® (Lispro) in Younger Adults and Elderly Patients with Type 1 Diabetes Mellitus: A Randomised Controlled Trial

Helle Linnebjerg¹ · Qianyi Zhang¹ · Elizabeth LaBell¹ · Mary Anne Dellva¹ · David E. Coutant¹ · Ulrike Hövelmann² · Leona Plum-Mörschel³ · Theresa Herbrand² · Jennifer Leohr¹

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- **Insulina Lispro Ultra-rápida** – nova formulação de insulina Lispro que contém dois excipientes que aceleram a sua absorção: treprostínil (induz vasodilatação local) e citrato (aumenta a permeabilidade vascular)
- **Insulina Lispro Ultra-rápida vs Insulina Lispro:**
 - **Início de ação mais rápido** (~ 11-12 minutos)
Aparece no sangue ~1 min após administração
 - **Menor duração de ação** (~ 34-44 minutos)
- ✓ Bem tolerada
- ✓ Resultados sobreponíveis em jovens e em idosos





Fast-Acting Insulin Aspart: A Review of its Pharmacokinetic and Pharmacodynamic Properties and the Clinical Consequences

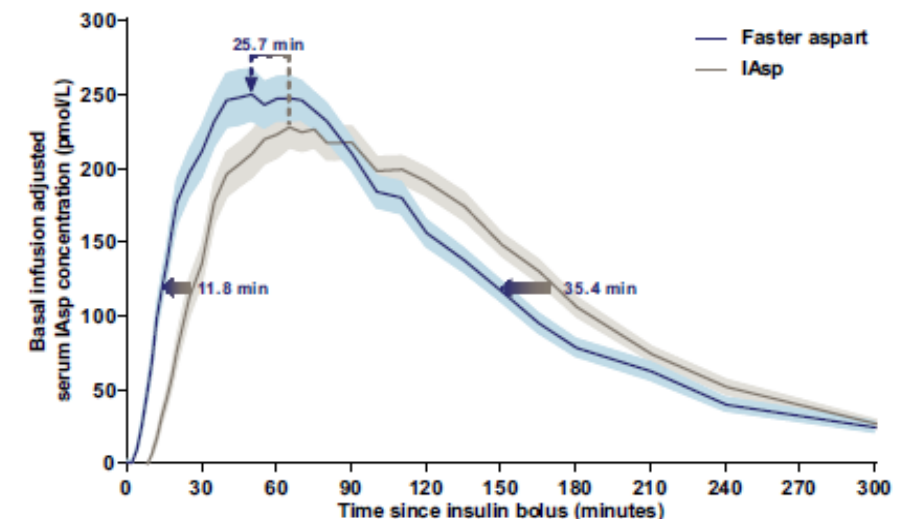
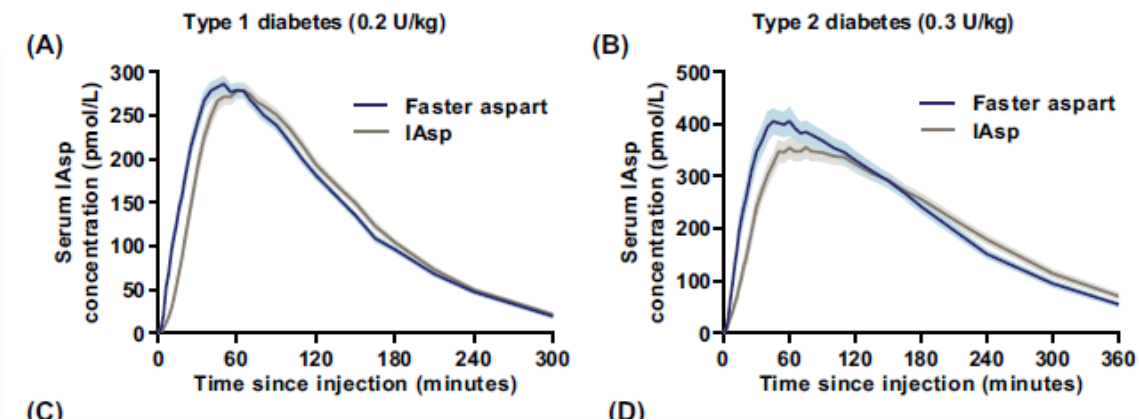
Hanne Haahr¹ · Tim Heise²

- **Insulina Aspártica Ultra-rápida** – adição à Insulina Aspart: niacinamida – vit. B3 (aumenta a absorção) e L-arginina (assegura a estabilidade da formulação)

- **Insulina Aspártica Ultra-rápida vs Insulina Aspártica**

- **Início de ação mais rápido**
- **Menor duração de ação**

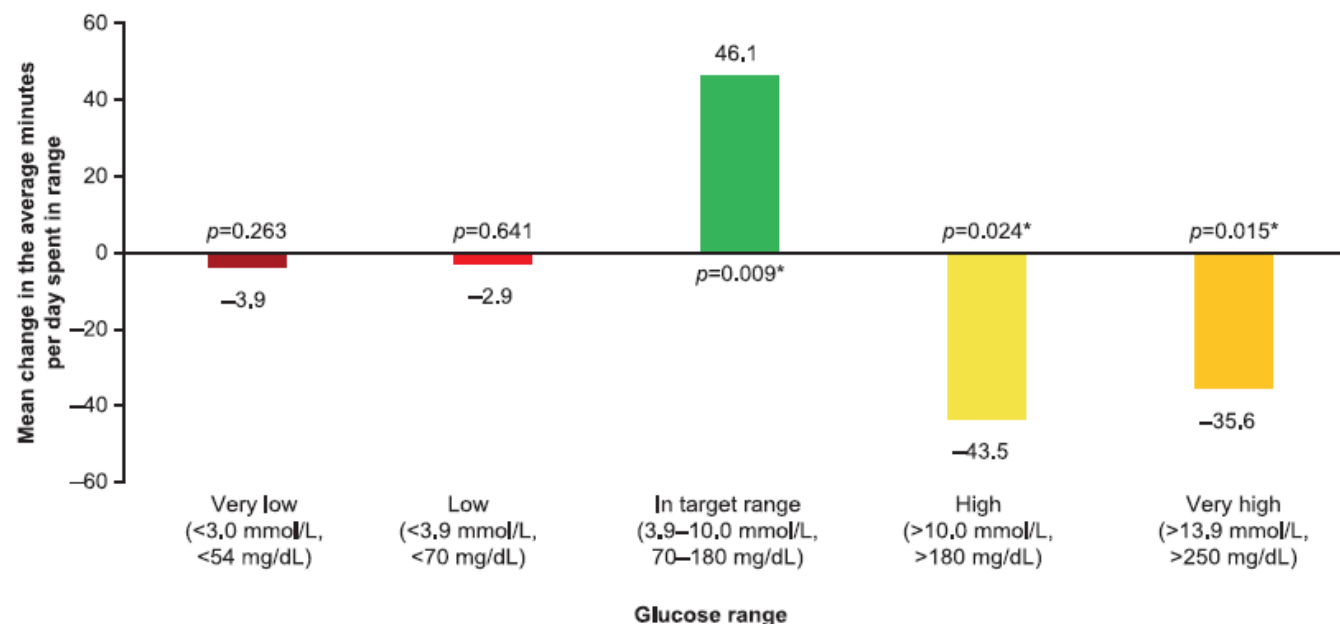
- ✓ Crianças (aprovada a partir 1 ano de idade) e idosos
- ✓ CSII



ORIGINAL ARTICLE

Impact of Fast-Acting Insulin Aspart on Glycemic Control in Patients with Type 1 Diabetes Using Intermittent-Scanning Continuous Glucose Monitoring Within a Real-World Setting: The GoBolus Study

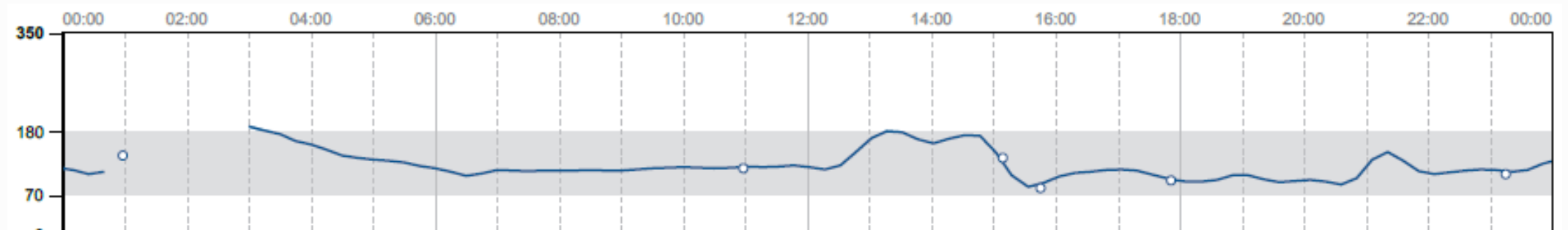
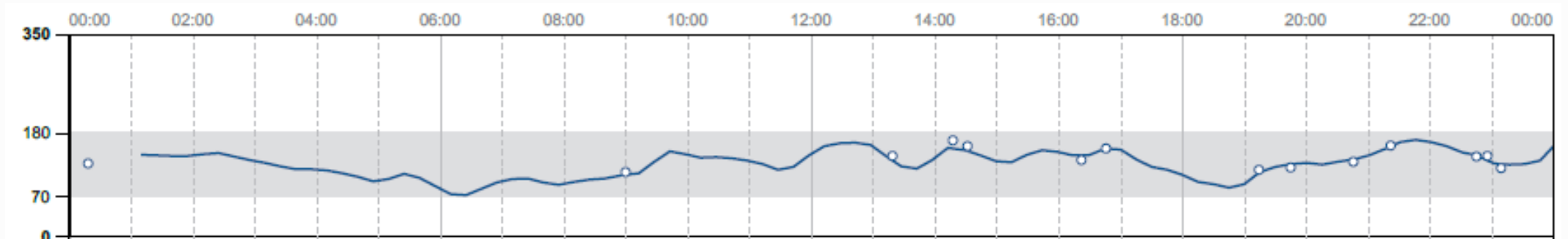
Thomas Danne, MD,¹ Matthias Axel Schweitzer, MD,² Winfried Keuthage, MD,³ Stefan Kipper, MS,² Yasmin Kretzschmar, MD,² Jörg Simon, MD,⁴ Tanja Wiedenmann, PhD,² and Ralph Ziegler, MD⁵



- Multicêntrico
- 243 adultos com DM1
- Mudança para Insulina Aspart ultra-rápida
- 24 semanas
- **Melhoria A1c (-0,19%), aumento TIR, sem afetar hipoglicemia**

Relatório CGM - Após introdução de Insulina Aspart Ultra-rápida

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Educação e motivação

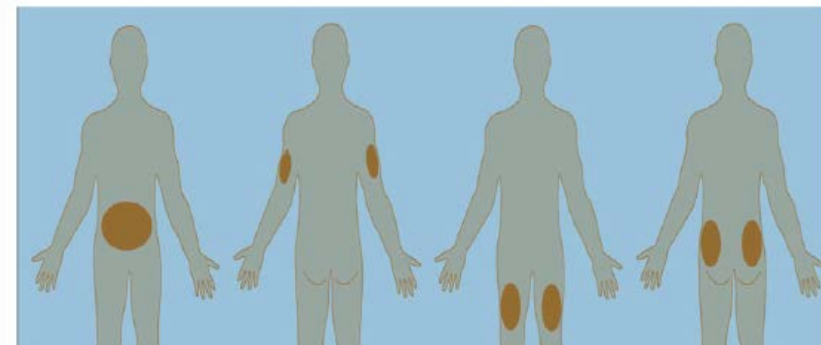
- Educação intensiva **para ajustar a dose de insulina prandial** em função de:
 - Nível de glicose
 - Composição da refeição
 - Exercício físico antes e/ou após a refeição
- Educação de **aspetos teóricos**, importantes no dia-a-dia:
 - Duração de ação das diferentes insulinas utilizadas
 - Tempo de administração da insulina em relação à refeição
- Educação de **aspetos práticos**:
 - Mudança frequente de agulha
 - Técnica e local de administração de insulina
 - Correta conservação da insulina



Fatores que influenciam a absorção de insulina

- Idade (crianças mais pequenas → menos tecido adiposo subcutâneo → maior rapidez de absorção)
- % Massa gorda (+ tecido adiposo subcutâneo, lipohipertrofias, mesmo com análogos → menor rapidez de absorção)
- Dose administrada (maior dose → menor rapidez de absorção)
- Local da injeção s.c (nas insulinas de ação rápida, absorção no abdômen mais rápida que na coxa)
- Tipo de injeção s.c vs i.m (injeção i.m. → maior rapidez de absorção)
- Exercício (Injeção na coxa + exercício pernas → maior rapidez de absorção)
- Temperatura ambiente e do corpo (maior temperatura -> maior rapidez de absorção)

➤ Os análogos são menos influenciados por estes fatores



Terapêuticas adjuvantes na DM1^x

- Objetivos:
 - Não é substituir a insulina
 - Melhorar o controlo glicémico (reduzir A1c).
 - Criar curvas glicémicas mais estáveis (aumentar Time In Range)
 - Reduzir o aumento de peso
 - Diminuir o risco de hipoglicemias

✓ **Metformina**

✓ **Inibidores SGLT2**

✓ **Análogos recetor GLP1**

Pergunta 4

Nesta jovem, poderemos pensar em utilizar terapêuticas adjuvantes como...

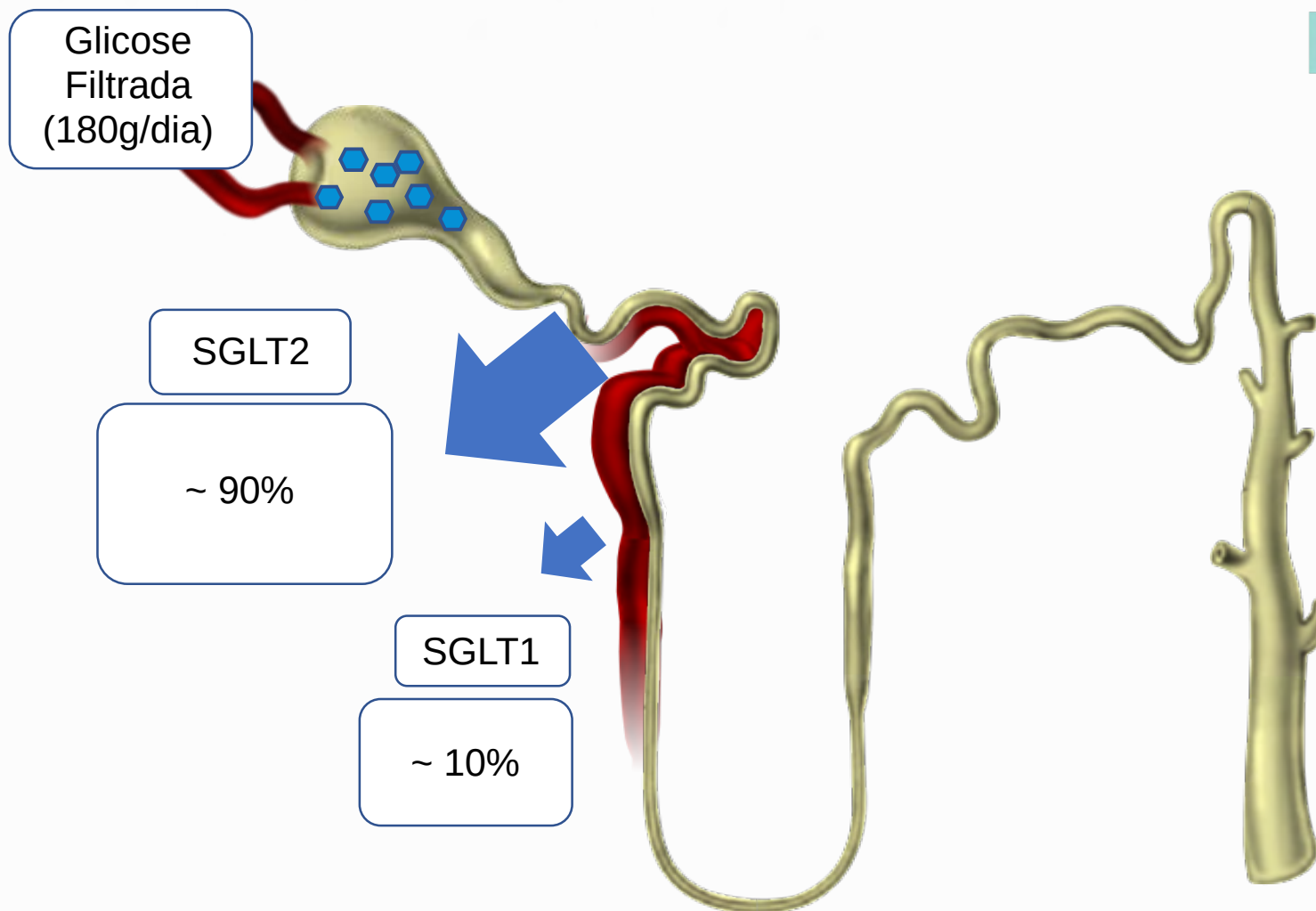
- A. Metformina, uma vez que existe excesso de peso e, nestes casos, está aprovado o seu uso na DM1
- B. Metformina, mesmo que o seu uso seja *off-label*, sabemos que reduz a insulinoresistência com redução da DDT de insulina e pode promover perda ponderal
- C. Dapagliflozina 10 mg, uma vez que existe excesso de peso
- D. Dapagliflozina 5 mg, quando a jovem completar 18 anos de idade
- E. B e D

O papel da Metformina na DM1^x

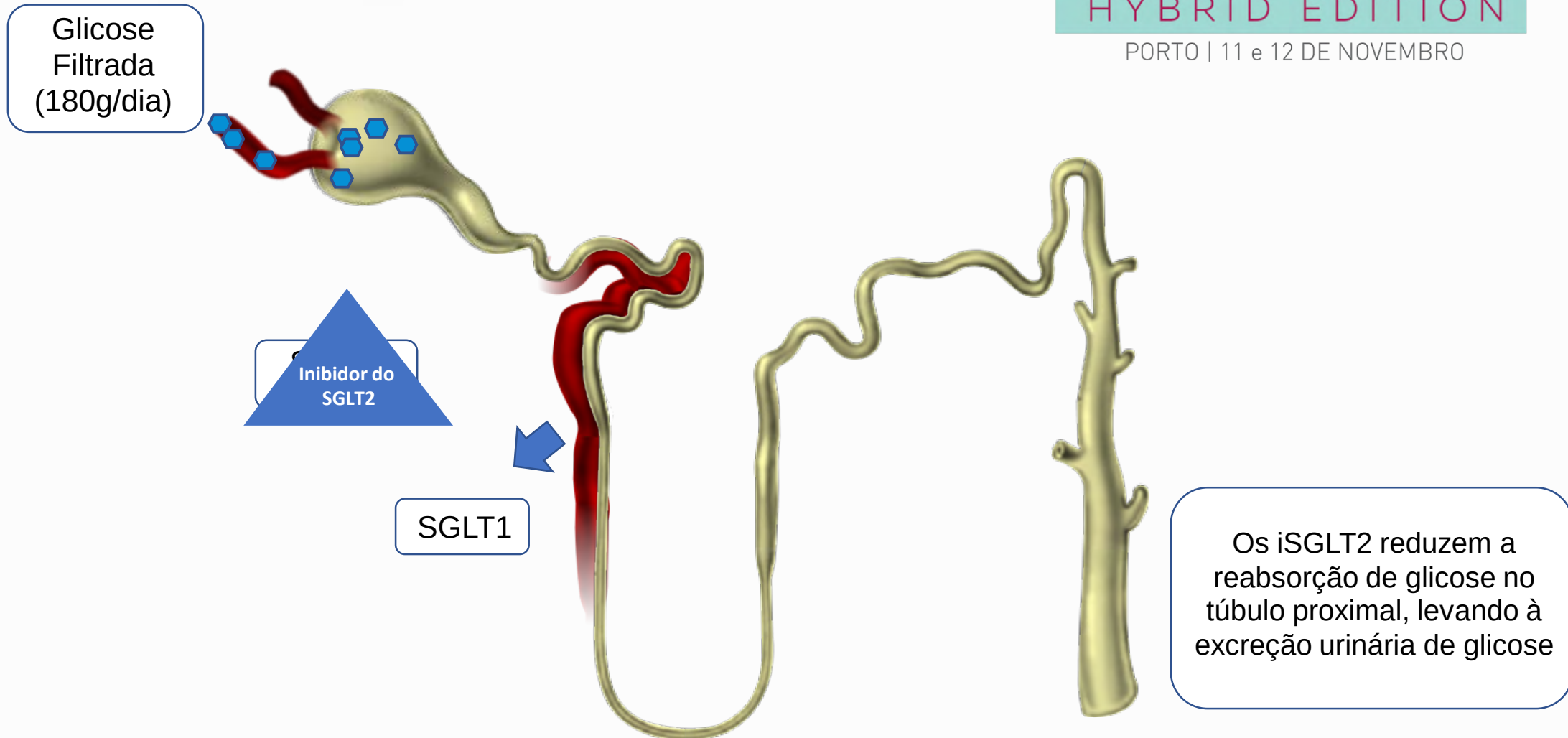
- A obesidade está a aumentar nas pessoas com DM1 → maior insulinoresistência (IR) e maior risco CV
 - Estudo de 2019 ***“Metformin Improves Peripheral Insulin Sensitivity in Youth With Type 1 Diabetes”***
 - jovens com DM1 12-20 anos de idade, sob metformina dose titulada até 1000 mg 2id
 - demonstrou redução IR a nível muscular, hepático e adipócitos em jovens DM1 com excesso peso/obesidade
 - Outros estudos em idade pediátrica demonstraram redução da IR → ↓ DDT insulina e ↓ IMC
- Apesar de ser utilizada off-label, em especial quando há excesso de peso ou obesidade, o papel da metformina na DM1 continua por definir.

NÃO HÁ EVIDÊNCIA QUE MELHORE O CONTROLO GLICÉMICO NA DM1

Reabsorção renal de glicose



Mecanismo de ação dos iSGLT2*



O papel dos Inibidores SGLT2 na DM1

- Na DM2, os iSGLT2 melhoram não apenas o controlo glicémico mas também têm benefícios demonstrados na proteção cardiovascular e renal
 - ✓ Demonstraram reduções na A1c e aumento do TIR
 - ✓ Redução no peso e na tensão arterial
 - ✓ Sem aumento das hipoglicemias
- **Maior risco de cetoacidose diabética? → Impediram o seu uso generalizado na população com DM1**
 - Efeito poupador de insulina → pode originar doses de insulina baixas (podem haver aumento da lipólise, gluconeogénese e formação de corpos cetónicos)
- **Seleção de doentes; vigilância de corpos cetónicos; programas de educação**
 - ✓ **EMA aprovou dapagliflozina em baixa dose (5 mg) em pessoas com DM1 e IMC ≥ 27 kg/m²**

Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and -2 trials in individuals with type 1 diabetes and body mass index ≥ 27 kg/m²

Chantal Mathieu MD¹  | Paresh Dandona MD² | Andreas L Birkenfeld MD^{3,4,5} |
Troels Krarup Hansen MD⁶ | Nayyar Iqbal MD⁷ | John Xu PhD⁷ |
Enrico Repetto MD⁸ | Markus Florian Scheerer PhD⁹ | Fredrik Thoren PhD¹⁰ |
Moshe Phillip PhD^{11,12}

×

- ✓ **Objetivo:** avaliar a eficácia e segurança da dapagliflozina em indivíduos com DM1
- ✓ **Resultados:** Às 52 semanas,
 - redução da A1c -0,5% no grupo dapagliflozina vs +0,05% grupo placebo
 - redução de peso -2,74 kg com dapagliflozina vs +0,81 kg grupo placebo
 - redução da DDT insulina -10,5% grupo dapagliflozina vs -1,4% grupo placebo
 - aumento de TIR em 2,2 h/dia no grupo dapagliflozina
 - Cetoacidose diabética em 1,7% grupo dapagliflozina vs 1,0% grupo placebo
- ✓ **Conclusões:** o risco benefício da utilização de dapagliflozina como terapêutica adjuvante na DM1 foi mais favorável nos indivíduos com IMC ≥ 27 kg/m² pelo menor risco de cetoacidose diabética nesta população.

Pergunta 5

Na utilização de dapagliflozina na DM1

- A. Selecionar os doentes – escolher os doentes com baixas doses de insulina e dietas pobres em HC
- B. Selecionar os doentes – escolher os doentes com A1c >10%
- C. Manter a dapagliflozina nos casos de cirurgias
- D. Instruir os doentes a dosear os corpos cetónicos 3x por dia
- E. Instruir os doentes a vigiar os corpos cetónicos se náuseas, vómitos ou dor abdominal

Programas de educação para utilização de iSGLT2 na DM1

- **Pesquisa de corpos cetônicos no sangue se:**
 - o Sintomas como mal-estar, náuseas, vômitos ou dor abdominal
 - o Alterações na dieta, padrão de atividade física ou ↓ dose de insulina
 - o Situação de stress, como infecção, desidratação ou cirurgia
- **Se corpos cetônicos > 0,6 mmol/L**
 - o Utilizar o Protocolo STICH
 - o Avaliar corpos cetônicos no sangue a cada 3-4 horas até resolução
 - o Avaliar glicemia capilar frequentemente
- **Parar iSGLT2 se:**
 - o Náuseas, vômitos ou dor abdominal
 - o Internamento, infecção, doença aguda, exames que exijam jejum
 - o 3 dias antes de uma cirurgia
 - o Diminuição significativa da ingestão alimentar
 - o Consumo excessivo de álcool

Protocolo STICH

S

T

STop SGLT inhibitor

I

inject bolus **Insulin**

C

consume 30 g **Carbohydrates**

H

Hydrate (drink water)

O papel dos arGLP1 na DM1

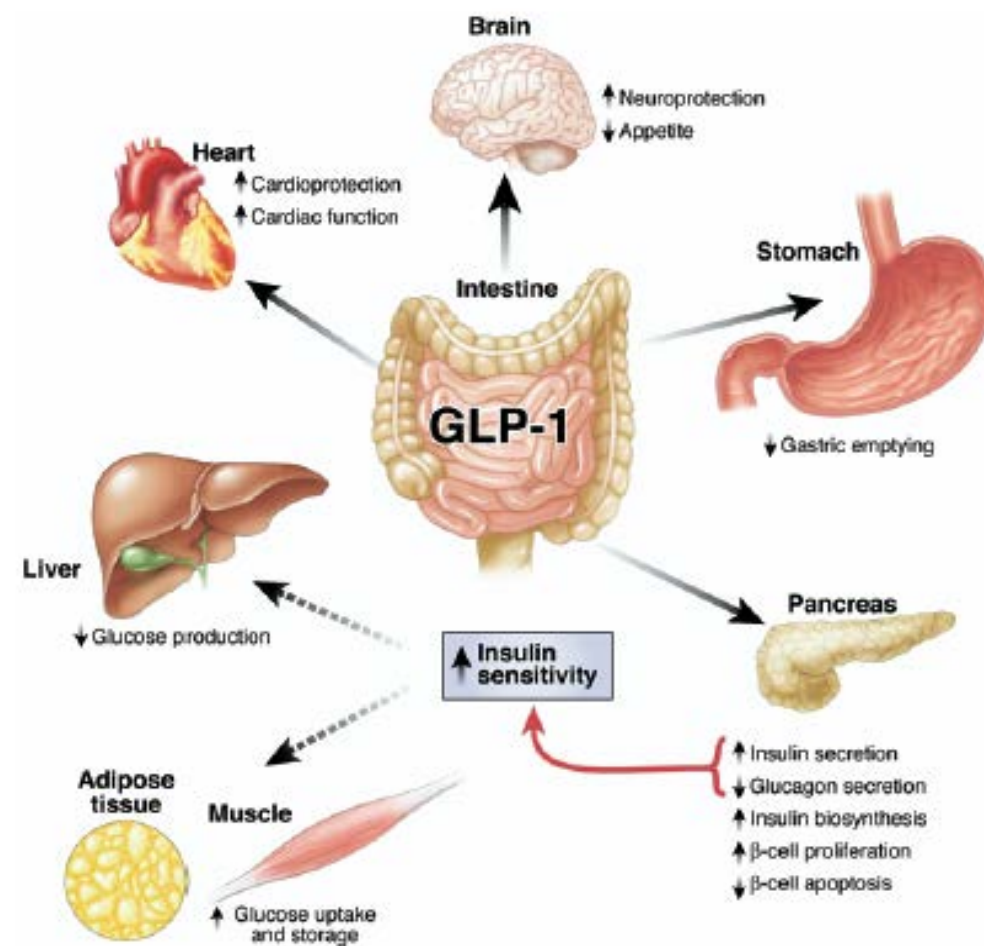
➤ Não estão aprovados na DM1

- Induzem libertação de insulina, por mecanismo dependente da glicose (efeito incretina)
- Podem ser úteis nos doentes com obesidade

Estudos **ADJUNCT ONE** e **ADJUNCT TWO** (liraglutide vs placebo)

- Redução A1c
- Perda ponderal
- Redução da DDT insulina (+ nos doentes com pep .C +)
- Efeitos GI: náusea (titular dose; transitória)
- Aumento da cetose sob liraglutide 1,8 mg (náusea? ↓ DDT insulina?)

Proteção CV e renal ?



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CURSO TEÓRICO-PRÁTICO
DIABETES - TEMPO NO INTERVALO-ALVO

**ESTRATÉGIAS TECNOLÓGICAS ÚTEIS PARA AUMENTAR O TEMPO
NO INTERVALO-ALVO**

CASO CLÍNICO 4

Painel de discussão: Prof. Dra. Cíntia Castro-Correia e Prof. Dr. Miguel Melo

• Dr. Luis Ribeiro





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PORTO | 11 e 12 DE NOVEMBRO

Estratégias Tecnológicas Úteis Para Aumentar O Tempo No Intervalo-alvo

Luís Ribeiro, Centro Materno Infantil do Norte, CHUP

Caso 1

- Menino de 6 anos
- Antecedentes familiares
 - Mãe 46 anos, saudável, Engenheira
 - Pai 46 anos, litíase renal, Empresário
 - Irmãs de 4 e 9 anos, saudáveis
 - Tio paterno com diabetes tipo 1 diagnosticada aos 18 anos
- Antecedentes pessoais
 - Asma controlada com fluticasona pMDI
- Transferida da UPIP por Diabetes mellitus inaugural sem cetoacidose

Caso 1

Internamento no Serviço de Pediatria para educação terapêutica

- Múltiplas administrações diárias de insulina
 - DDT 12U/Kg/dia (0,5U/Kg/dia)
 - Insulina de acção lenta: 6 U à noite
 - Insulina de acção rápida de acordo com glicemia e contagem de hidratos de carbono

Partes do dia		Limite inferior	Limite superior	Razão de insulina Hidratos de carbono		Sensibilidade à insulina Insulina	
Iniciar	Fim	mg/dL	mg/dL	Unidades de insulina	Quantidade HC (g)	Unidades de insulina	mg/dL
00:00	06:59	100	140	1.0	40.0	1.0	150
07:00	10:59	80	120	1.0	40.0	1.0	150
11:00	14:29	80	120	1.0	40.0	1.0	150
14:30	17:59	80	120	1.0	40.0	1.0	150
18:00	21:29	80	120	1.0	40.0	1.0	150
21:30	23:59	100	140	1.0	40.0	1.0	150



Caso 1

Qual a melhor estratégia?

1. Bomba de insulina
2. Bomba de insulina + Monitorização intermitente da glicose
3. Manter MADi + Monitorização intermitente da glicose
4. Manter MADi sem monitorização intermitente da glicose
5. Ouvir a opinião dos pais e da criança

Caso 1

Opinião dos pais:

“... Estamos muito preocupados com o número de “picadas” para a administração de insulina ... Ele chora sempre que temos de administrar insulina... e notamos que não quer comer para não ter de administrar insulina... queremos encontrar uma solução para reduzir o número de “picadas”. ”

Caso 1

iPort Advance®



- Dispositivo para administração direta de fármacos (incluindo insulina)
- Locais administração: mesmos da insulina
- Mudança a cada 3 dias
- Agulhas 5 e 8mm
- Intervalo 60' entre basal e bólus
- Pode ser utilizado no banho e actividades aquáticas

ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes

Thomas Danne¹  | Moshe Phillip² | Bruce A. Buckingham³ | Przemyslaw Jarosz-Chobot⁴ |
Banshi Saboo⁵ | Tatsuhiko Urakami⁶  | Tadej Battelino⁷  | Ragnar Hanas⁸ |
Ethel Codner⁹ 

Caso 1

E a bomba de insulina não poderia ser uma solução?

- ✓ Permite um esquema personalizado - programação débito basal h/h; débito basal temporário; bólus mais precisos; vários tipos de bólus
- ✓ Utiliza análogo de insulina de acção rápida: início + rápido, < duração acção, menor variabilidade absorção >> efeito mais previsível
- ✓ Diminui risco de hipoglicemia
- ✓ Facilidade de administração de doses (extra) de insulina
- ✓ **Redução do número de "picadas" por dia**
- ✓ **Melhoria da qualidade de vida**

Caso 1

Opinião dos pais:

“... Neste momento não queremos considerar essa opção... percebemos as vantagens mas faz-nos muita confusão a bomba... principalmente o facto de ter “um fio” a ligar o cateter à bomba.”

Caso 1

Evaluation of Pump Discontinuation and Associated Factors in the T1D Exchange Clinic Registry

Journal of Diabetes Science and Technology
2017, Vol. 11(2) 224–232
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DOI: 10.1177/1932296816663963
journals.sagepub.com/home/dst
SAGE

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Lucy D. Mastrandrea, MD, PhD⁴, Kimber-Lee Abel, RN, BSN, CPN, CDE⁵,
Eda Cengiz, MD, MHS⁶, Pinar A. Cemeroglu, MD⁷, Grazia Aleppo, MD⁸,
Joseph F. Largay, PA-C, CDE⁹, Nicole C. Foster, MS², Roy W. Beck, MD, PhD²,
and Saleh Adi, MD¹ for the T1D Exchange Clinic Network

Abstract

Background: The objectives of this study were to examine factors associated with insulin pump discontinuation among children and adults followed longitudinally for 1 year in the multicenter T1D Exchange clinic registry, and to provide participant-reported reasons for stopping pump therapy.

Methods: We longitudinally followed 8935 participants of all ages using an insulin pump at the time of registry enrollment. Logistic regressions were used to identify demographic and clinical factors associated with pump discontinuation. Pump discontinuation was self-reported by participants on a first annual follow-up survey.

Results: The overall frequency of pump discontinuation was 3%. Discontinuation was higher in adolescents (4%) and young adults (4%) than in younger children (3%) or older adults (1%). In multivariate analysis of children between 6 and <13 and 13 and <18 years, participants who discontinued pump use were more likely to have higher HbA1c levels at baseline (adjusted $P < .001$ for both). The top participant-reported reasons for discontinuing the pump included problems with wearability (57%), disliking the pump or feeling anxious (44%), and problems with glycemic control (30%).

Conclusions: In T1D Exchange registry participants, insulin pump discontinuation is uncommon, but more prevalent among adolescents and young adults, and youth with poor glycemic control. Given the known benefits of pump therapy, these populations should be targeted for support and education on troubleshooting pump use. Common reasons for discontinuation should also be considered in future device design and technological improvement.

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PORTO | 11 e 12 DE NOVEMBRO

Caso 1

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The majority of the participants who discontinued pump use in this study reported issues with wearability, including problems with insertion, pump discomfort, skin reactions, adhesive problems, and interference with sports and activities. These reasons are similar to those given in previous studies, in which the pump interfered with physical activity or sports, or felt too much like a foreign body.²³ Other common reasons for pump discontinuation included disliking the pump or feeling anxious, discontinuation recommended by health care practitioner, problems with glycemic control and the pump working properly, and not finding the pump helpful. These results are similar to previous studies, which confirmed diabetes burnout, concern with body image and weight gain, clinical and technical difficulties with the device as common reasons for pump discontinuation based on questionnaires similar to those completed in this study.^{16,22} One study of German adolescents and young adults found that although technical and clinical reasons for pump discontinuation were common, social and psychological factors seemed to be more prevalent, as many found the pump bothersome and a constant reminder of diabetes.²³ However, when asked what would prompt resuming pump therapy, numerous participants described technical solutions, including improvement of catheters, reduced size of the device, water resistance, reduction in noise level, and integration of blood glucose measurement with the pump.

Caso 1

E a monitorização do controlo glicémico?

- ✓ Glicemia capilar – ocasional será suficiente?
- ✓ Monitorização intermitente/”flash” da glicose intersticial
- ✓ Monitorização contínua da glicose intersticial



Caso 1

E a monitorização do controlo glicémico?

- ✓ Glicemia capilar – ocasional será suficiente?
- ✓ Monitorização intermitente/"flash" da glicose intersticial
- ✓ Monitorização contínua da glicose intersticial

Real-time continuous
glucose monitoring (CGM)

Wearable technology that provides real-time continuous glucose measurements with the options of alerts for hyperglycemia, hypoglycemia, or projected glucose out of target ranges

Flash glucose monitoring (FGM)

Glucose monitoring system in which data are stored in a wearable sensor and obtained by scanning the sensor with dedicated receiver or smartphone

Caso 1

FreeStyle Libre®

- ✓ **Sistema de monitorização intermitente**, utilizado para medir os níveis de glicose no líquido intersticial de pessoas com Diabetes Mellitus a partir dos 4 anos de idade
- ✓ Sensor (colocado no tecido celular subcutâneo na parte posterior do braço) + Leitor
- ✓ Sensor dura 14 dias (no máximo)
- ✓ Pequeno (35 X 5 mm)
- ✓ Resistente à água
- ✓ Transmissão de dados NFC
- ✓ A leitura pode ser efetuada por cima da roupa



Caso 1

FreeStyle Libre®

- ✓ Glicose intersticial
- ✓ ~4 min diferença entre glicemia capilar e intersticial (desfasamento temporal)
- ✓ Não necessita de calibração manual com recurso à glicemia capilar
- ✓ Leitura instantânea glicose, o histórico da variação nas 8h prévias e tendência (direção e intensidade da variação prevista da glicose)
- ✓ Sem alarmes
- ✓ Deve ser **usado em complementaridade** com a glicemia capilar



Caso 1

2016

MARD 11.7%

ALGO GEN1



Indicado na medição da glicose no líquido intersticial ≥ 4 anos

Punção capilar necessária:

- Rápida alteração da glicose
- Situação de hipoglicemia ou hipoglicemia iminente
- Ou se os sintomas não corresponderem aos valores da leitura

2019

MARD 9.5%

ALGO GEN2



Adicionado ao labeling e indicação:

Indicado para substituição do teste de glicemia no doseamento de inulina

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Monitorização contínua/intermitente:

- ✓ Melhoria do controlo metabólico
- ✓ Redução de nº hipoglicemias
- ✓ Redução da variabilidade glicémica

Caso 2

Média de HbA1C de acordo com a tecnologia utilizada

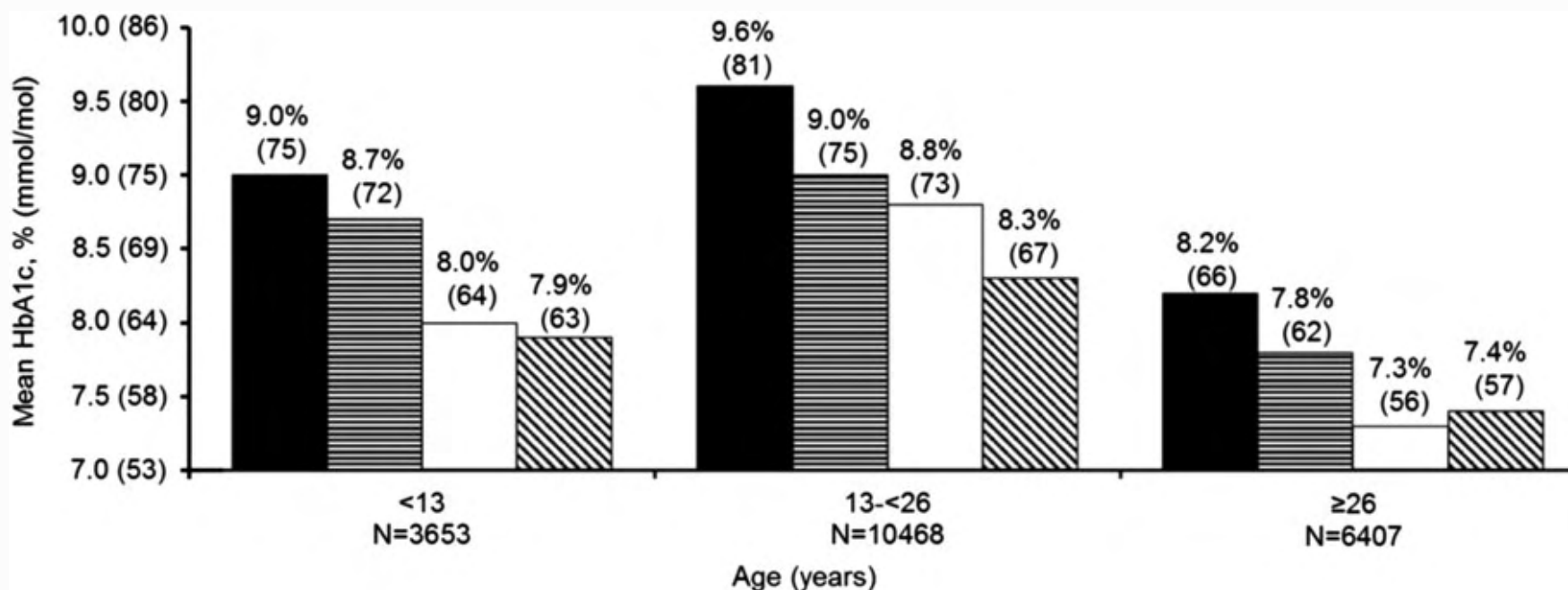


FIG. 3. Mean HbA1c by technology use in 2016–2018. Solid black represents injection only. Horizontal stripes represent pump only. Solid white represents injection+CGM. Diagonal stripes represent pump+CGM.

Caso 1

Opinião dos pais:

“... Parece-nos uma boa ferramenta do ponto de vista da monitorização... podemos reduzir o nº de vezes que medimos a glicemia capilar .”

Caso 1

Qual a melhor estratégia?

1. Bomba de insulina
2. Bomba de insulina + Monitorização intermitente da glicose
3. Manter MADl + Monitorização intermitente da glicose
4. Manter MADl sem monitorização intermitente da glicose
5. Ouvir a opinião dos pais e da criança

Manter MADl
Utilizar iPort Advance®
Freestyle Libre®

Caso 1

Na consulta seguinte... Opinião dos pais:

“... Não conseguimos dormir... estivemos a ver em grupos do Facebook® que existem muitos meninos com um dispositivo em cima do sensor que passa os dados para o telemóvel e permite colocar alarmes.”

Caso 1



	Dexcom G6	MedtronicGuardian Sensor 3	GlucoMenDay®	Abbott FreeStyle Libre®
Tipo de sensor	SMCG	SMCG	SMCG	Sistema Flash de Monitorização de Glicose - sistema de monitorização contínua intermitente
Localização	Inserido no tecido subcutâneo	Inserido no tecido subcutâneo	Inserido no tecido subcutâneo	Inserido no tecido subcutâneo
Tempo de utilização	10 dias	7 dias	14 dias	14 dias
Calibração	Na fábrica	Com teste de glicémia capilar, 2x/dia	Com teste de glicémia capilar, 1x/dia	Na fábrica
Alarmes e Alertas	✓	✓	✓	Na primeira versão não. Está presente no Abbott FreeStyle Libre® 2

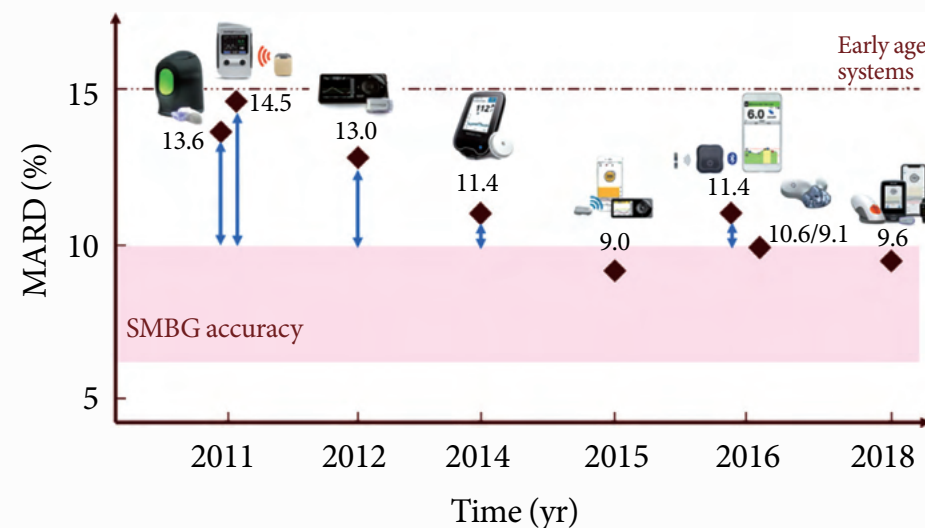
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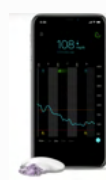
PORTO | 11 e 12 DE NOVEMBRO

Monitorização contínua/intermitente

- ✓ Custo – comparticipação
- ✓ Alarmes e alertas
- ✓ Fiabilidade – MARD



Caso 1



	Dexcom G6	MedtronicGuardian Sensor 3	GlucoMenDay®	Abbott FreeStyle Libre®
Tipo de sensor	SMCG	SMCG	SMCG	Sistema Flash de Monitorização de Glicose - sistema de monitorização contínua intermitente
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Alarmes e Alertas	✓	✓	✓	Na primeira versão não. Está presente no Abbott FreeStyle Libre® 2

Monitorização contínua/intermitente

Particularidades:

- ✓ Paracetamol – Guardian Sensor 3
- ✓ Ressonância Magnética – Todos

Caso 1



DIY CGM

- Aparelho colocado sobre o sensor do isCGM. Usa NFC para ler os dados do sensor isCGM para transmitir por Bluetooth para uma App do telemóvel.
- Estas Apps processam os dados e podem transmitir à distância para outros telemóveis ou um smartwatch
- Permite alarmes e calibrações

Caso 1



DIY CGM

- Mais económico para as famílias dos que os actuais CGM
- Não regulado (sem aprovação)
- Ausência de estudos de segurança e eficácia
- Protecção de dados?
- Sugestão proactiva *versus* apoio na sua correcta utilização

Caso 1

Opinião dos pais:

“... Conseguimos finalmente dormir a noite toda... temos acesso em tempo real aos dados de glicose intersticial quando ele esta na escola... ele vê os dados no *smartwatch* e já consegue antecipar alguns cenários.”

Caso 1

Passado 6 meses... Opinião dos pais:

“... Estivemos a pensar e achamos que queremos experimentar uma bomba de insulina, mas não queremos nenhuma das que são comercializadas em Portugal porque têm todas “fio”... encontramos uma forma de comprar uma *patch pump*...”

Caso 1

Table 2. Advantages (a) and Limitations (b) of Patch Pumps: Some of the Advantages/Disadvantages Are Present in Patch Pumps, but the Respective Design Defines What Is Actually Applicable.

a.

- Tubeless, eg, reduction of problems with the insulin infusion set (IIS) (catheter/needle/tube), needle is not visible
- IIS is inside the pump or within the base part of the patch pump
- Reduced risk of clogging of the insulin in the IIS, insulin remains at similar temperature level inside the patch pump
- Full freedom of movement
- Water resistant; some patch pumps can also be used under the shower, for swimming and sport
- Ease of use, simpler handling, design features that are appreciated by patients
- Simplified training, fewer steps to initiate CSII
- Many parts of the body can be used to attach patch pumps, ie, they provide more discretion
- Patch pumps are smaller and lighter than conventional insulin pumps
- Their application is almost pain-free; many patch pumps provide an automatic insertion of the needle
- Many patch pumps enable control of insulin infusion rate by a remote control (like a number of conventional pumps as well)
- At least in some patch pumps bolus calculators are integrated in the remote control

b.

- Waste of insulin when patch pumps are replaced but the remaining insulin was not used
- Waste of plastic material, batteries
- Infusion site is not visible, ie, an infection could not be seen
- Accuracy with which the insulin is infused varies between patch pumps, also the time required to infuse a given bolus varies depending on the pumping technology used
- Need for an additional device to control insulin infusion (not via smartphone), ie, the patch pumps themselves are smaller, etc; however, need to have another charger for the remote control, etc
- Patch pumps look quite similar, but their properties differ massively; need for adequate training; not easy to switch
- Costs should be lower compared with conventional pumps

Caso 1

SPEDP 2021 REUNIÃO ANUAL HYBRID EDITION

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Name	Accu-Chek Solo micropump system	Cellnovo	JewelPump	OmniPod	OneTouch Via (formerly Calibra Finesse)	PAQ	V-Go
Manufacturer Intended for	Roche The micropump system is intended to be used by insulin-dependent persons with diabetes mellitus	Cellnovo Insulin Dependent	Debiotec Types 1 + 2	Insulet Corp Types 1 + 2	LifeScan —	CeQur Type 2	Valeritas Type 2
Approval	FDA (predecessor from Medingo; CE mark is expected end of 2018)	(Pending) + CE		FDA + CE	FDA, not yet released	CE, not yet released	FDA, CE, available in US
Components	Cradle with inserter, detachable 2 part minipump (reservoir + pump base), remote controller	Disposable insulin cartridge + reusable electronics + handset	Disposable reservoir/ pumping mechanism/ battery + reusable electronics + remote controller (touch)	Pod + PDM	Disposable pump	Disposable insulin reservoir + reusable electronic messenger	100% disposable
Principle	Piston driven by step motor	Paraffin wax micro-actuator; intelligent delivery system	Micro electro mechanical system, volumetric membrane pump	Microprocessor control, shape memory allow wire assembly	Manual piston, volume displacement by pressing button, non-electrically powered	Elastomer bladder drives basal flow, capillary flow restrictors control basal rate	Nonelectronic spring-force drive with flow restrictor
Insertion	Soft cannula 6 or 9 mm, reusable insertion device	Soft/steel cannula + minitubing (priming required)	Auto-inserted infusion cannula (can be changed every 3 days, reattached to patch)	Integrated soft cannula, inserted automatically	Inserter, flexible cannula	Inserter, flexible cannula	"Floating" steel needle, push needle button
Functions	5 basal rate profiles with up to 24 segments, temporary basal (0-250%), different bolus types	20 basal rate profiles with hourly segments, temporary basal, different bolus types	5 editable basal profiles, temporary basal, different bolus types	7 basal rate programs with 24 segments, temporary basal, different bolus types	Only 2 U boluses, no basal	7 preset basal rates (16, 20, 24, 32, 40, 50, 60 U/d), 2 U manual bolus on demand	Preset basal rates (20, 30, 40 U/d), 2 U manual bolus on demand
Size	68 × 40 × 15 mm, 32 g	54 × 35 × 14 mm, 32 g	70 × 40 × 12 mm, 25 g	1.6 × 2.4 × 0.7 inches, 34 g	51 × 25 × 6.4mm	50 × 70 × 17 mm, 32 g	61 × 33 × 13 mm, 20-50 g
Insulin reservoir	80-200 U	150 U	500 U	200 U	200 U	330 U	20 option, 30 option, 40 option, +36 U for meals
Wearing time	Reservoir up to 4 days and cannula 2-3 days, pump base 90 120 days	3 days	7 days	3 days	3 days	3 days	24 hours
Further	Integrated BGM, bolus advice, flight mode, bolusing remotely and directly on pump	Cloud-based, integrated BGM, activity monitor	Integrated BGM, additional bolus buttons on pump	Integrated BGM	Dose count card	Message card	—
References	25-26	8, 25-27	Homepage, 11, 25, 26	23-27	25-26	25, 26, 28	Manual, 25, 26, 29

PDM



Pod



Omnipod Eros

PDM

Pod

The pumps are sorted in alphabetical order and not into "simple" or mechanical-driven devices and electrically driven pumps. The latter have the full features of traditional pumps (high upfront costs and training time) and those that are simpler to use, but with less basal and bolus dosing options. Not all information for all pumps was available.

Caso 1

Resultados... Opinião dos pais:

“... adora... pode brincar livremente... O que fica no corpo é tão pequeno e sente-se tão confortável que até se esquece que tem o dispositivo...”



Caso 1

SPEDP 2021 REUNIÃO ANUAL

HYBRID EDITION

PORTO | 11 e 12 DE NOVEMBRO

Accu-Check Solo®

- ✓ Microbomba
- ✓ Portugal (fase lançamento)

Name	Accu-Check Solo micropump system	Cellnovo	JewelPump	OmniPod	OneTouch Via (formerly Calibra Finesse)	PAQ	V-Go
Manufacturer	Roche	Cellnovo	Debiotec	Insulet Corp	LifeScan	CeQur	Valeritas
Intended for	The micropump system is intended to be used by insulin-dependent persons with diabetes mellitus	Insulin Dependent	Types 1 + 2	Types 1 + 2	—	Type 2	Type 2
Approval	FDA (predecessor from Medingo; CE mark is expected end of 2018)	(Pending) + CE		FDA + CE	FDA, not yet released	CE, not yet released	FDA, CE, available in US
Components	Cradle with inserter, detachable 2 part minipump (reservoir + pump base), remote controller	Disposable insulin cartridge + reusable electronics + handset	Disposable reservoir/ pumping mechanism/ battery + reusable electronics + remote controller (touch)	Pod + PDM	Disposable pump	Disposable insulin reservoir + reusable electronic messenger	100% disposable
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References	25-26	8, 25-27	Homepage, 11, 25, 26	23-27	25-26	25, 26, 28	Manual, 25, 26, 29

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Caso 1

Telemedicina

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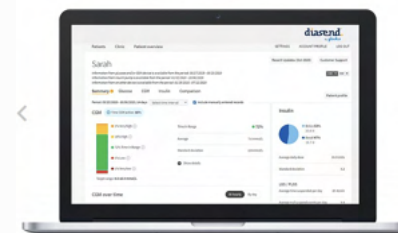
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Omnipod Eros



TIDEPOOL



diasend[®]
by glooko



O LibreView

Caso 1

Relatório AGP

Relatório do AGP

1 Outubro 2021 - 14 Outubro 2021 (14 Dias)

ALVOS E ESTATÍSTICAS DE GLICOSE

1 Outubro 2021 - 14 Outubro 2021

14 Dias ✓

0 % que o sensor de tempo está ativo

100% ✓

Intervalos e alvos para	Diabetes tipo 1 ou tipo 2
Intervalos de glicose	Alvos % de leituras (hora/dia)
Intervalo-alvo 70-180 mg/dL	Maior que 70% (16h 48min)
Abaixo de 70 mg/dL	Menor que 4% (58min)
Abaixo de 54 mg/dL	Menor que 1% (14min)
Acima de 180 mg/dL	Menor que 25% (6h)
Acima de 250 mg/dL	Menor que 5% (1h 12min)
Cada aumento de 5% no tempo no intervalo (70-180 mg/dL) é clinicamente benéfico.	

Glicose média

171 mg/dL

Indicador de gestão da glicose (GMI)

7,4% ou 57 mmol/mol

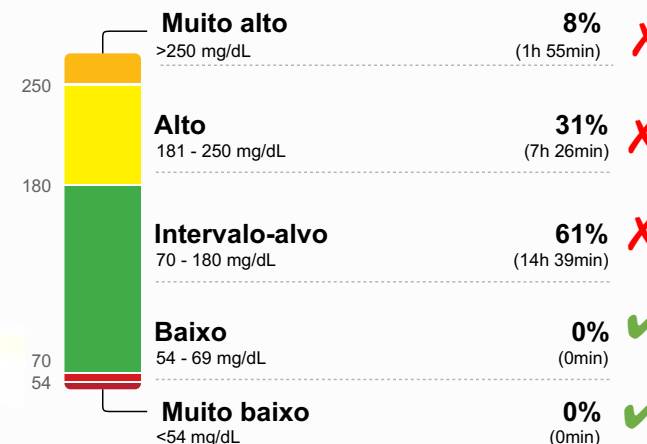
Variabilidade da glicose

28,4% ✓

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

LibreView

PERÍODO NOS INTERVALOS



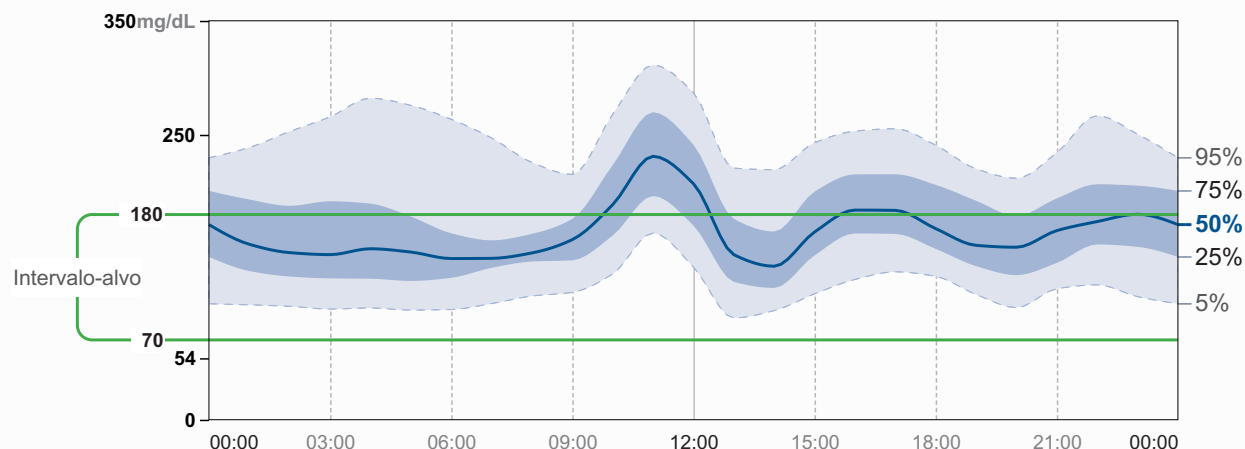
Caso 1

Como ajustar?

1. Reduzir rel I/HC PA
2. Reduzir rel I/HC LAN
3. Reduzir rel I/HC JAN
4. Aumentar basal (0-10h; 13-24h)
5. Todas são correctas

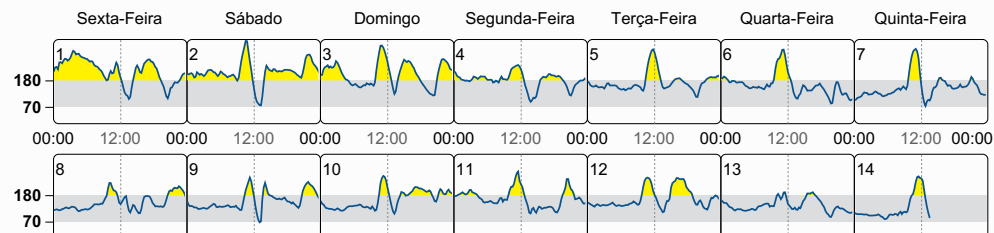
PERFIL DE GLICOSE EM AMBULATÓRIO (AGP)

O AGP é um resumo dos valores de glicose do período de relatório, com a mediana (50%) e outros percentis apresentados como se ocorressem num único dia.



PERFIS DE GLICOSE DIÁRIOS

Cada perfil diário representa um período da meia-noite de um dia até à meia-noite do dia seguinte, com a data apresentada no canto superior esquerdo.



Caso 2

- Adolescente de 15 anos, natural da Guiné. Adotado aos 10 meses.
- Antecedentes familiares
 - Mãe faleceu por complicações relacionadas com o parto. Sem dados da família biológica.
 - Mãe adotiva 43 anos, saudável, não fumadora, Gestora de Empresas.
 - Pai adotivo 50 anos, saudável, Gerente Comercial.
- Antecedentes pessoais
 - Diabetes mellitus tipo 1 diagnosticada aos 4 anos.
 - Sob esquema de MADI.
 - Monitorização do controlo glicémico: Glicómetro com aconselhamento de bólus e sistema de monitorização intermitente da glicose
- Transferido para colocação de Bomba Perfusora de insulina

Caso 2

Bomba perfusora de insulina + monitorização intermitente da glicose



Glicómetro
Contour® Next Link

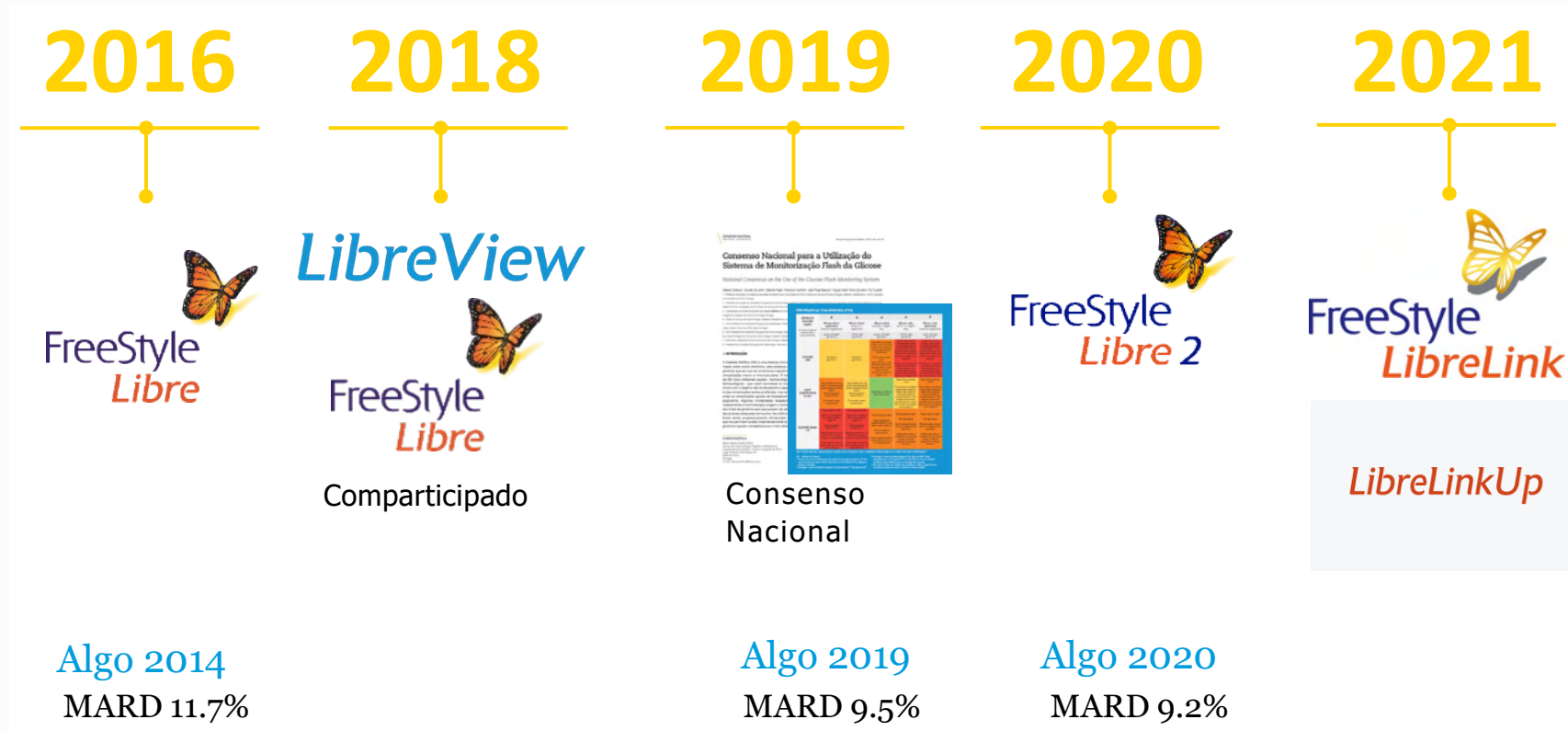
Bomba insulina
Minimed Paradigm Veo®



**Monitorização
intermitente da glicose**
FreeStyle Libre 2®

Caso 2

FreeStyle Libre 1 *versus* 2



Caso 2

FreeStyle Libre 1 *versus* 2



Caso 2

ALVOS E ESTATÍSTICAS DE GLICOSE

4 Junho 2021 - 17 Junho 2021

14 Dias

O % que o sensor de tempo está ativo

87%

Intervalos e alvos para

Diabetes tipo 1 ou tipo 2

Intervalos de glicose	Alvos % de leituras (hora/dia)
Intervalo-alvo 70-180 mg/dL	Maior que 70% (16h 48min)
Abaixo de 70 mg/dL	Menor que 4% (58min)
Abaixo de 54 mg/dL	Menor que 1% (14min)
Acima de 180 mg/dL	Menor que 25% (6h)
Acima de 250 mg/dL	Menor que 5% (1h 12min)

Cada aumento de 5% no tempo no intervalo (70-180 mg/dL) é clinicamente benéfico.

Glicose média

205 mg/dL

Indicador de gestão da glicose (GMI)

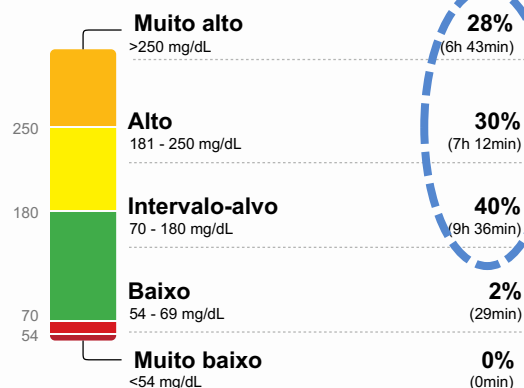
8,2% ou 66 mmol/mol

Variabilidade da glicose

40,8%

Definido como percentagem do coeficiente de variação (%CV); alvo ≤36%

PERÍODO NOS INTERVALOS



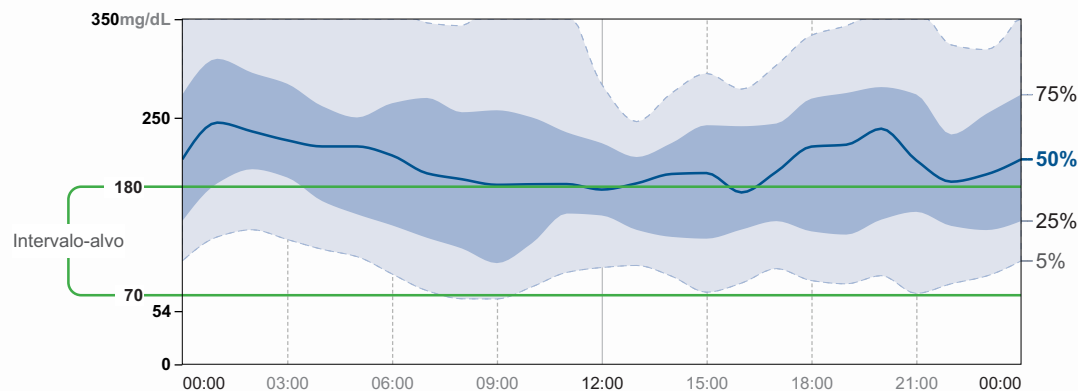
Grande variabilidade glicémica

GMI e glicose média ↑

Sem hipoglicemias

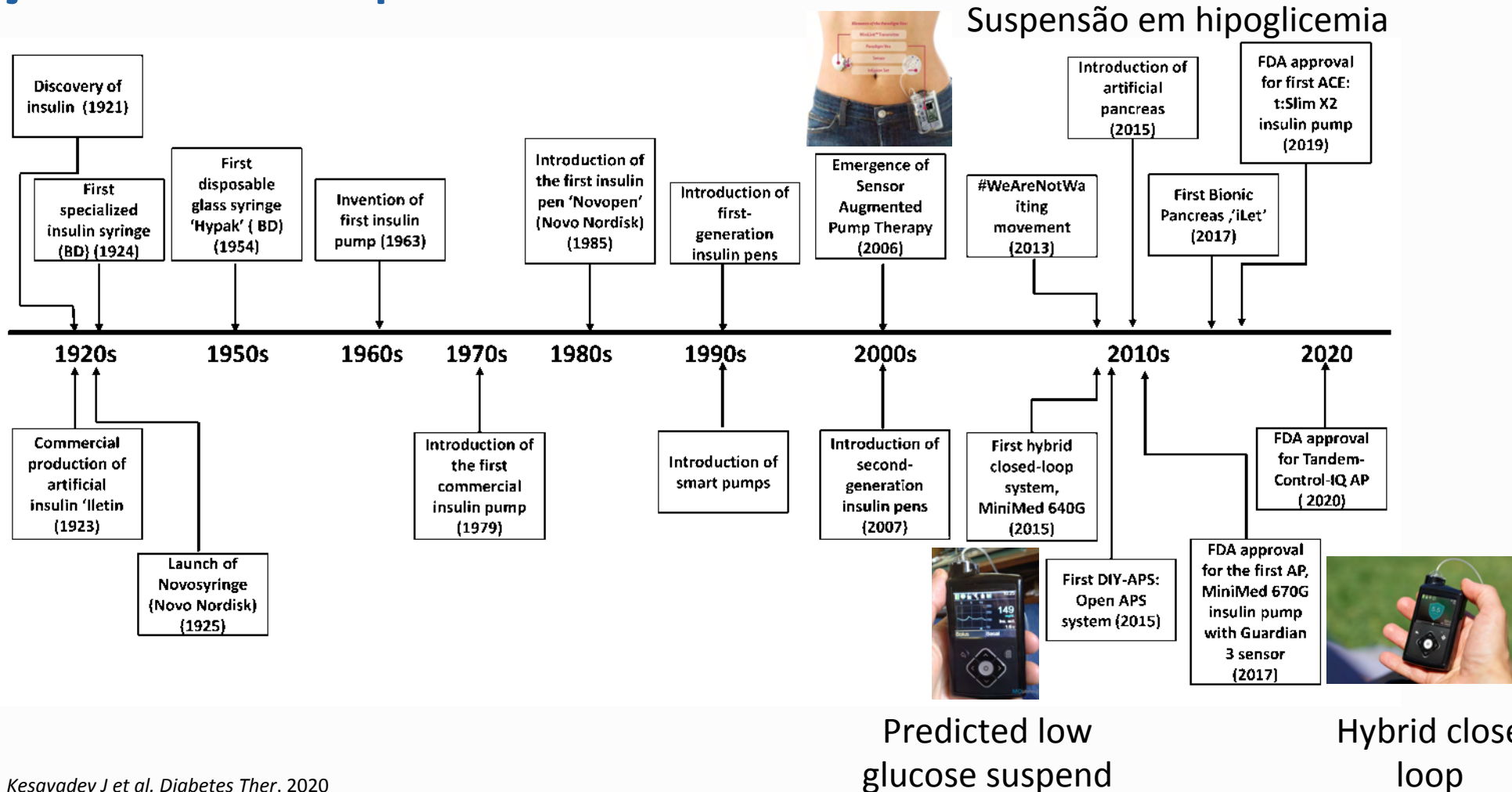
PERFIL DE GLICOSE EM AMBULATÓRIO (AGP)

O AGP é um resumo dos valores de glicose do período de relatório, com a mediana (50%) e outros percentis apresentados como se ocorressem num único dia.



Caso 2

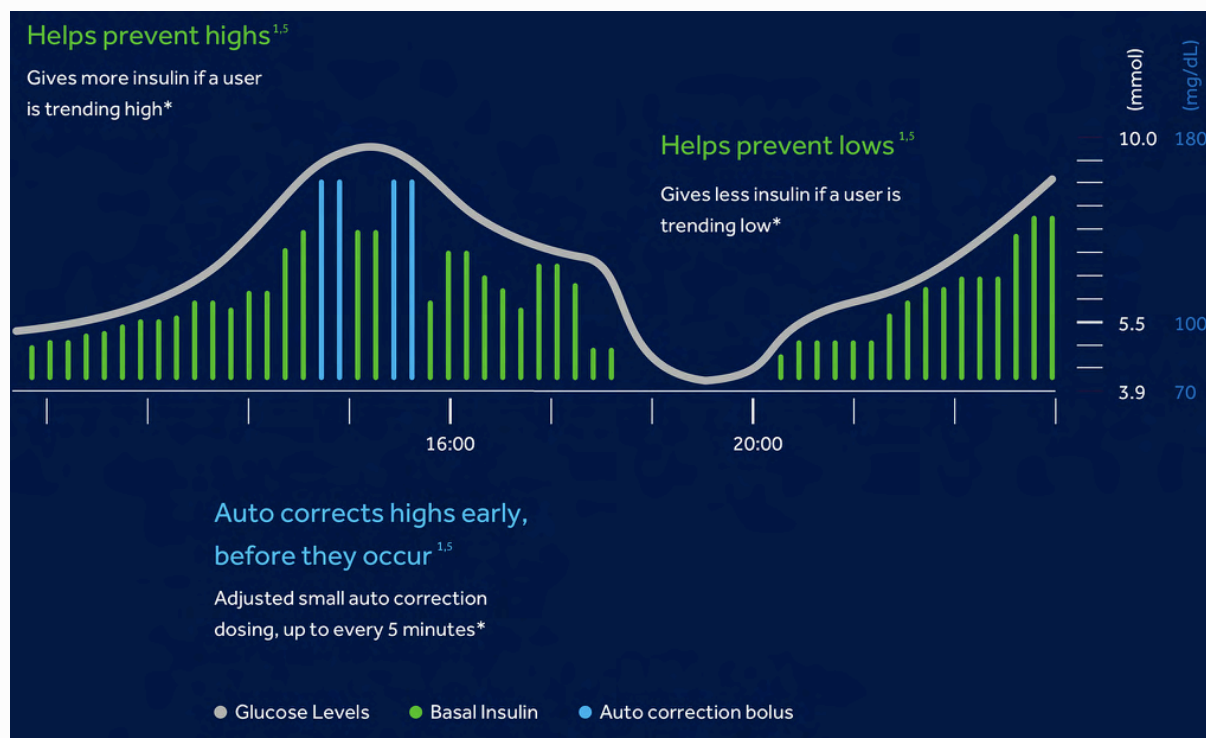
Evolução das bombas perfusoras de insulina



Caso 2

Hybrid close loop

Sistema de perfusão automática de insulina (acoplado a monitorização contínua da glicose intersticial) mas que necessita da introdução da quantidade de hidratos de carbono ingeridos pelo utilizador



Insulin pump

Based on up-to-date information received from CGM at five-minute intervals, the waterproof pump * makes automatic adjustments and corrections to the insulin delivery you need. If the trend is upward, the pump delivers more insulin. If the tendency is to decrease, it delivers less insulin.



Continuous Blood Glucose Monitoring (CGM) System

Guardian™ Sensor 3 measures blood glucose values 288 times per day every 5 minutes and automatically sends this information to the pump so that you can see your blood glucose values and associated trends.



Blood Glucose meter

Test results from the Accu-Chek® Guide Link blood glucose meter are sent wirelessly to the pump for quick sensor calibrations.

Caso 2

Hybrid close loop

> [Diabetes Technol Ther.](#) 2021 Sep 15. doi: 10.1089/dia.2021.0203. Online ahead of print.

Real-world Performance of the MiniMed™ 780G System: First Report of Outcomes from 4'120 Users

Julien Da Silva ¹, Giuseppe Lepore ^{2 3}, Tadej Battelino ^{4 5}, Arcelia Arrieta ⁶,
Javier Castañeda ⁷, Benyamin Grosman ⁸, John Shin ⁹, Ohad Cohen ¹⁰

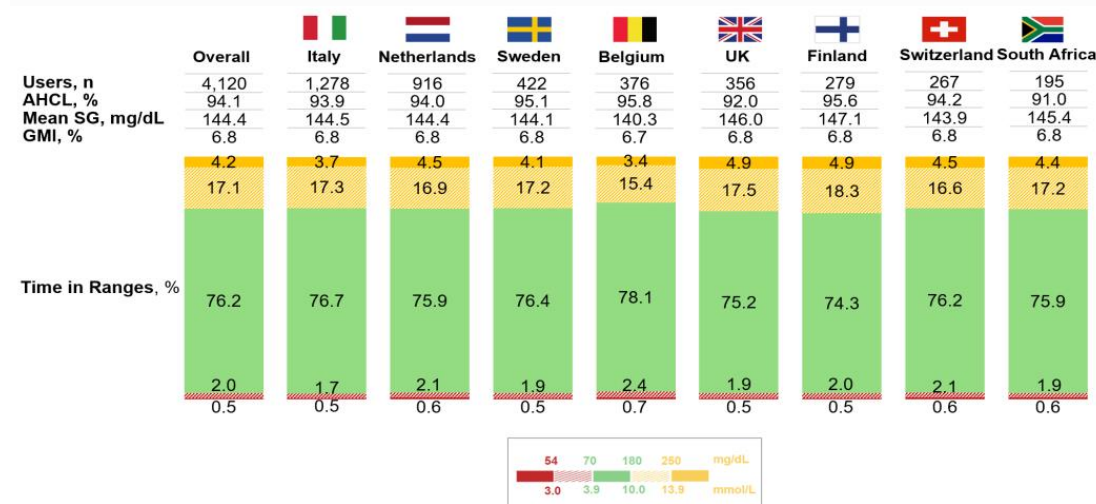
Affiliations + expand

PMID: 34524003 DOI: [10.1089/dia.2021.0203](#)

Abstract

Background: The MiniMed™ 780G system includes an Advanced Hybrid Closed Loop (AHCL) algorithm which provides for both automated basal and correction bolus insulin delivery. The preliminary performance of the system in real-world settings was evaluated.

Methods: Data uploaded from August 2020 to March 2021 by individuals living in Belgium, Finland, Italy, the Netherlands, Qatar, South Africa, Sweden, Switzerland and the United Kingdom were aggregated and retrospectively analyzed to determine the mean Glucose Management Indicator (GMI), percentage of time spent within (TIR), below (TBR) and above (TAR) glycemic ranges, system use and insulin consumption in users having ≥10 days of sensor glucose (SG) data after initiating AHCL. The impact of initiating AHCL was evaluated in a sub-group of users also having ≥10 days of SG data, before AHCL initiation.



Número participantes: **4120**

Países: Itália, Holanda, Qatar, África do Sul, Suécia, Suíça e UK

Média utilização: 54 +/- 32 dias

% tempo AHCL: 94 +/- 11,4%

GMI médio: 6,8 +/- 0,3%

Time In Range: 76,2 +/- 9,1%

Time Above Range > 180: 21,3 +/- 9,4%

Time Below Range < 70: 2,5 +/- 2,1%

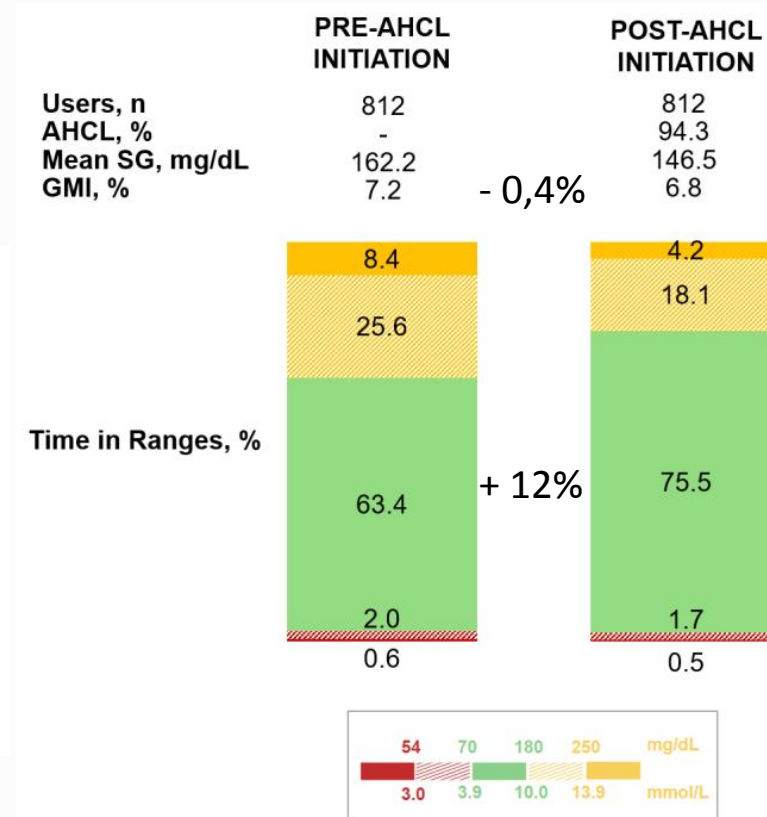
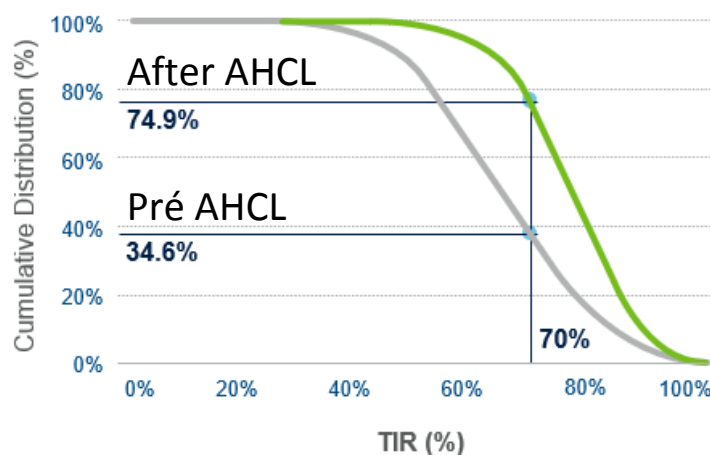
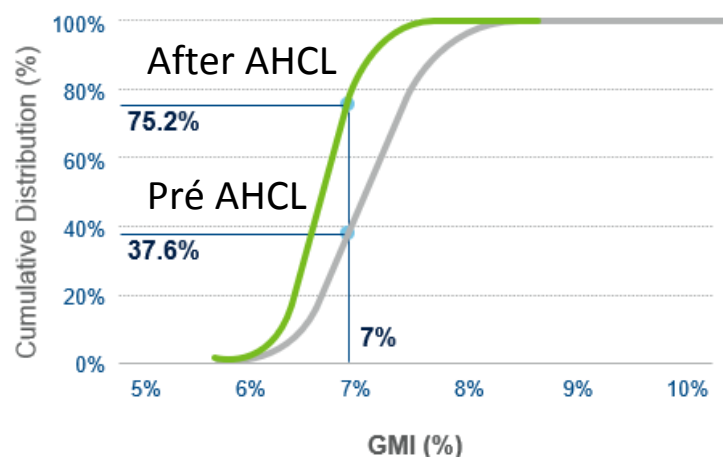
Caso 2

Hybrid close loop

> Diabetes Technol Ther. 2021 Sep 15. doi: 10.1089/dia.2021.0203. Online ahead of print.

Real-world Performance of the MiniMed™ 780G System: First Report of Outcomes from 4'120 Users

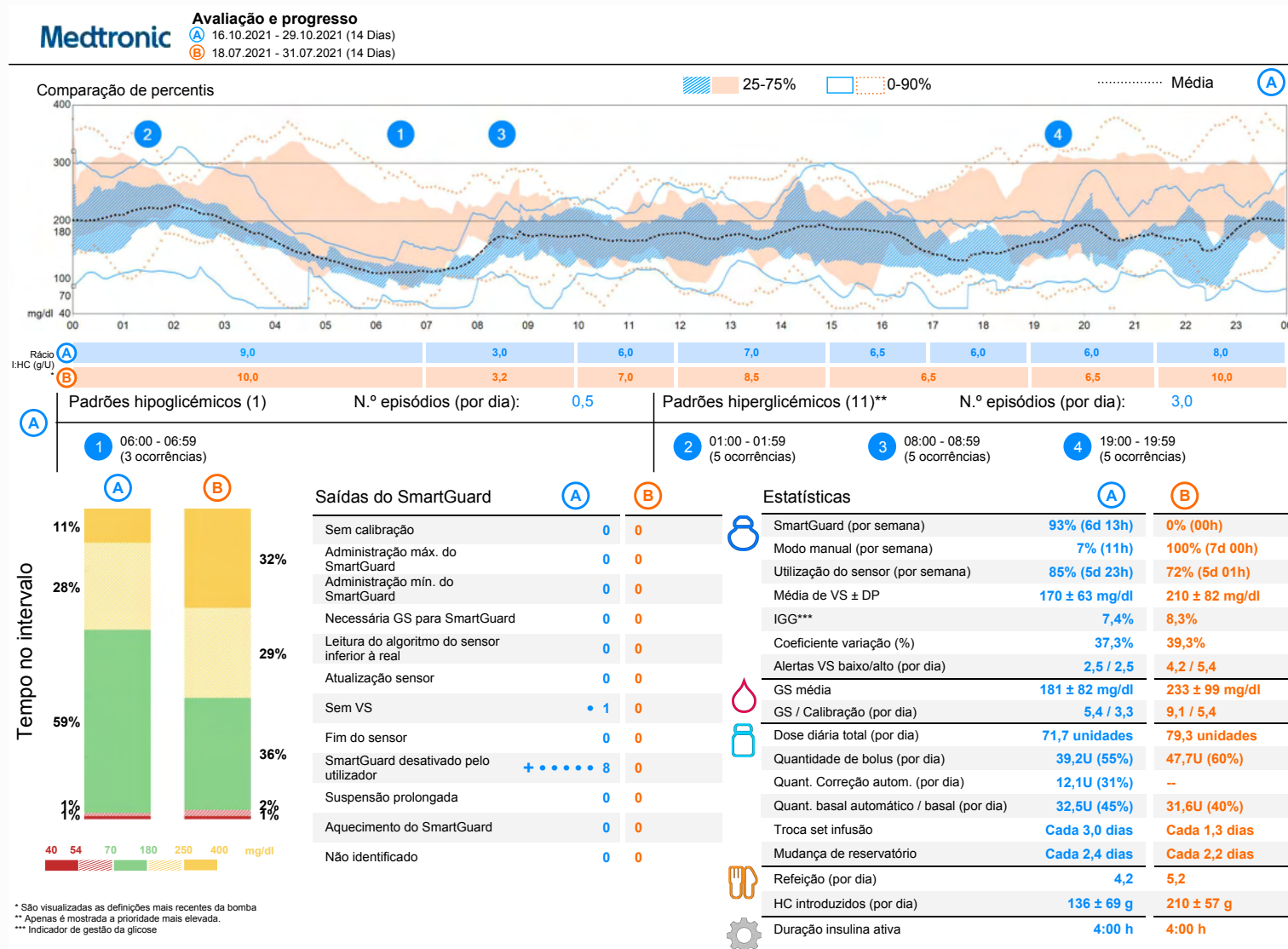
Julien Da Silva ¹, Giuseppe Lepore ^{2 3}, Tadej Battelino ^{4 5}, Arcelia Arrieta ⁶,
Javier Castañeda ⁷, Benyamin Grosman ⁸, John Shin ⁹, Ohad Cohen ¹⁰



Caso 2

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↓ Variabilidade glicémica

↓ GMI

↓ Glicose média

↑ Tempo no alvo

Sem ↑ hipoglicemias

Caso 2

Que parâmetros podemos programar no modo automático?

1. Factor de sensibilidade
2. Ritmo de administração basal de insulina
3. Relação insulina / hidratos de carbono das refeições
4. % de redução de basal e bólus no exercício
5. % de aumento da insulina basal nos dias de doença

Caso 2

Programação

- ✓ Alvo glicémico (100, 110 ou 120mg/dL)
- ✓ Duração da insulina activa
- ✓ Relação Insulina / hidratos de carbono das refeições
- ✓ Alarmes

SPEDP 2021 REUNIÃO ANUAL

HYBRID EDITION

PORTO | 11 e 12 DE NOVEMBRO

SmartGuard	
SmartGuard	On
Alvo	110 mg/dl
Correção autom.	On

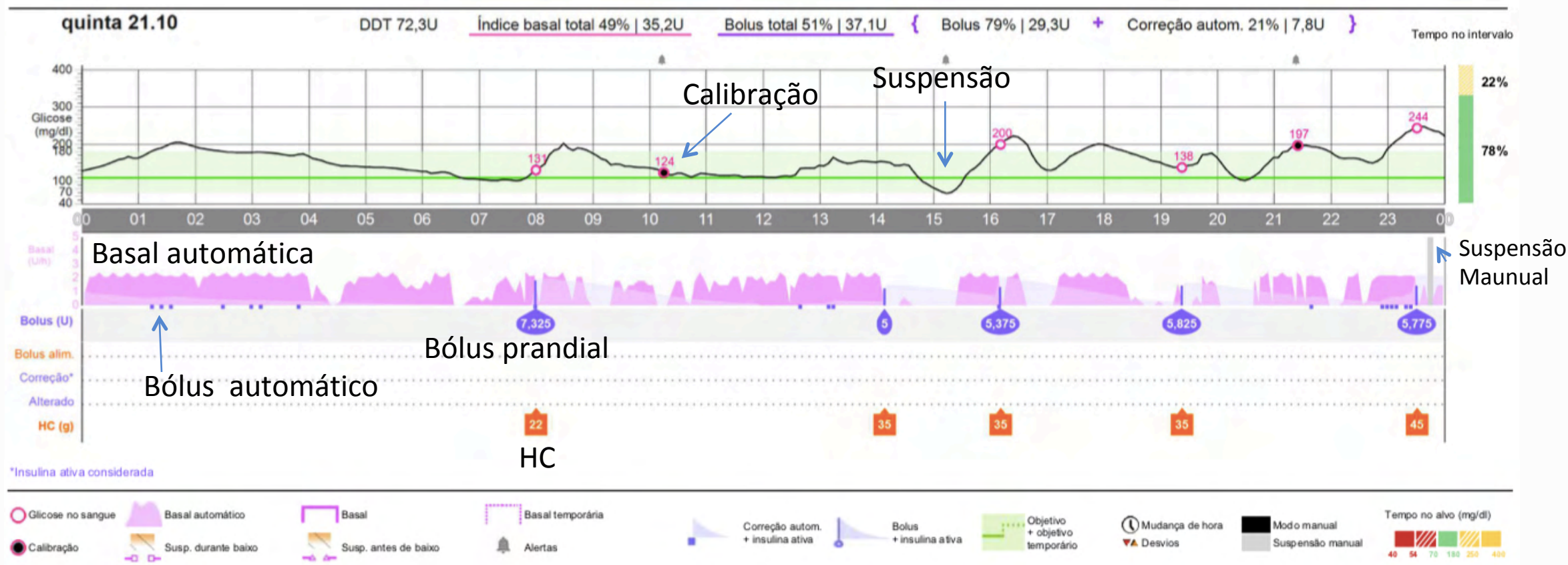
Bolus		Rácio de hidratos de carbono (g/U)	
Bolus Wizard	On	Hora	Rácio
Unid.	g, mg/dl	0:00	9,0
Dur. ins. ativa (h:mm)	4:00	7:00	3,0
Bolus máximo	25,0 U	10:00	6,0
		12:00	7,0
		15:00	6,5
		17:00	6,0
		19:00	6,0
		21:30	8,0

Alertas glicose alta		On (Intervalo 2:00)		
Início	Alta (mg/dl)	Alerta durante alto	Alerta antes de alto	Limite alerta subida (mg/dl)
0:00	250	x		

Alertas de glicose baixa			On (Intervalo 0:20)		
Início	Baixa (mg/dl)	Suspender	Alerta durante baixo	Alerta antes baixo	Alerta retomar basal
0:00	70	Ant. baixo	x		

Caso 2

Exemplo de dia



Caso 3

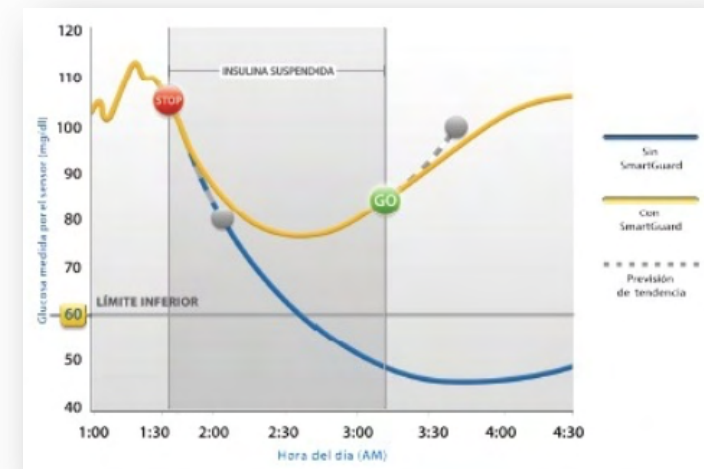
- Criança de 9 anos
- Diabetes tipo 1 desde os 5 anos
 - Bomba perfusora de insulina com suspensão predictiva antes do baixo com monitorização contínua da glicose.

Glicómetro
Contour® Next Link



Bomba insulina
Minimed® 640G

Sensor
Guardian® 3



Caso 3

Medtronic Avaliação e progresso
 (A) 29.07.2021 - 11.08.2021 (14 Dias)
 (B) 29.06.2021 - 12.07.2021 (14 Dias)

Comparação de percentis

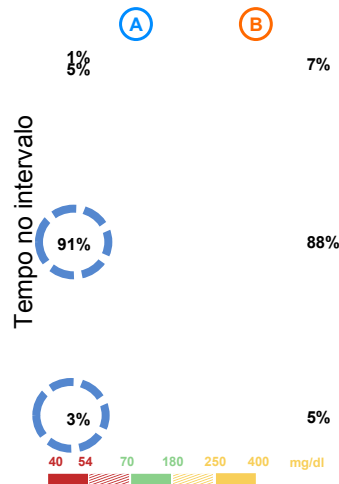
25-75% 0-90%

Média

(A)

Rácio I:HC (g/U)	(A) 60,0	9,5	65,0	20,0	20,0	40,0	50,0
	(B) 60,0	9,5	65,0	25,0	20,0	40,0	50,0

A	Padrões hipoglicêmicos (2)		N.º episódios (por dia): 0,8	Padrões hiperglicêmicos (3)		N.º episódios (por dia): 1,0
	1 10:00 - 10:59 (3 ocorrências)	2 16:00 - 16:59 (2 ocorrências)		3 11:00 - 11:59 (3 ocorrências)	4 21:00 - 21:59 (3 ocorrências)	5 12:00 - 12:59 (2 ocorrências)



Estatísticas

Utilização do sensor (por semana)	(A) 98% (6d 21h)	(B) 98% (6d 21h)
Média de VS ± DP	120 ± 35 mg/dl	117 ± 38 mg/dl
IGG***	6,2%	6,1%
Coefficiente variação (%)	29,4%	32,6%
Alertas VS baixo/alto (por dia)	9,9 / 4,2	12,6 / 4,2
GS média	125 ± 43 mg/dl	125 ± 49 mg/dl
GS / Calibração (por dia)	4,1 / 3,5	5,2 / 4,5
Dose diária total (por dia)	23,8 unidades	21,0 unidades
Quantidade de bolus (por dia)	14,6U (61%)	13,0U (62%)
Quantidade de basal (por dia)	9,2U (39%)	8,0U (38%)
Troca set infusão	Cada 3,3 dias	Cada 3,3 dias
Mudança de reservatório	Cada 2,5 dias	Cada 3,3 dias
Refeição (por dia)	7,0	5,7
HC introduzidos (por dia)	223 ± 30 g	194 ± 20 g
Duração insulina ativa	3:00 h	3:00 h

* São visualizadas as definições mais recentes da bomba
 *** Indicador de gestão da glicose

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Sensor: 98% (14 dias)

Glicose média: 120mg/dL

GMI: 6,2%

Tempo no alvo: 91%

Tempo 54-70: 3%

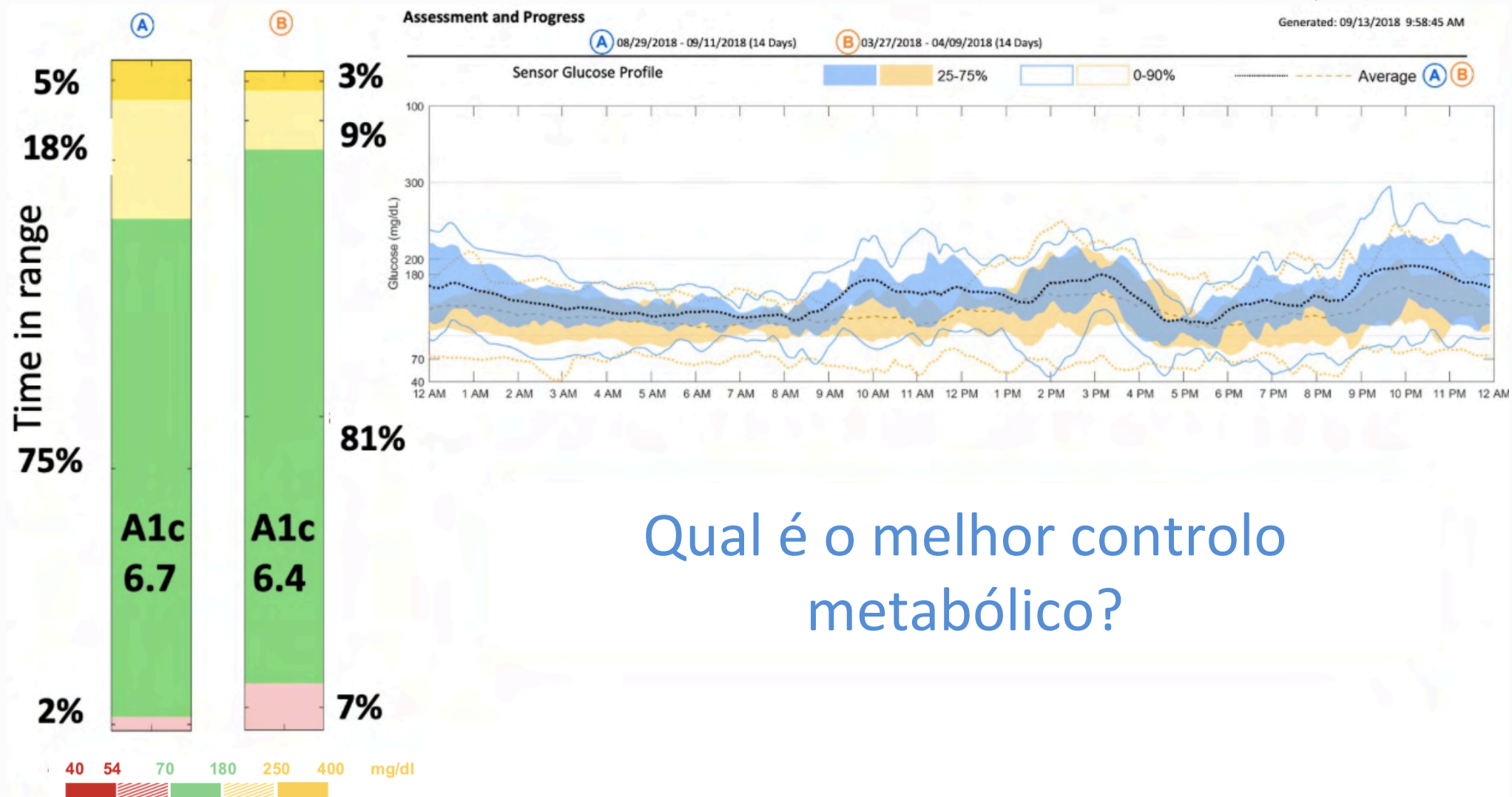
Tempo < 54: 0%

Caso 3

Escolha a afirmação correcta?

1. O tempo no alvo não está no objectivo pretendido
2. O tempo de utilização do sensor não é adequado
3. O GMI é muito baixo
4. O GMI, o tempo no alvo e abaixo do alvo são adequados
5. Um sistema tipo *Hybrid Close Loop* tinha muitas vantagens metabólicas

Considerações finais

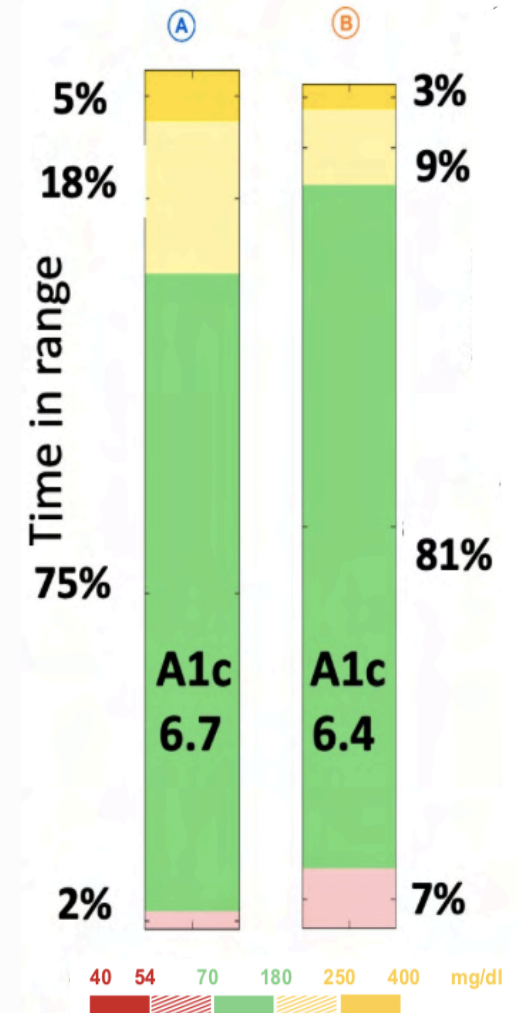


Qual é o melhor controle metabólico?

Considerações finais

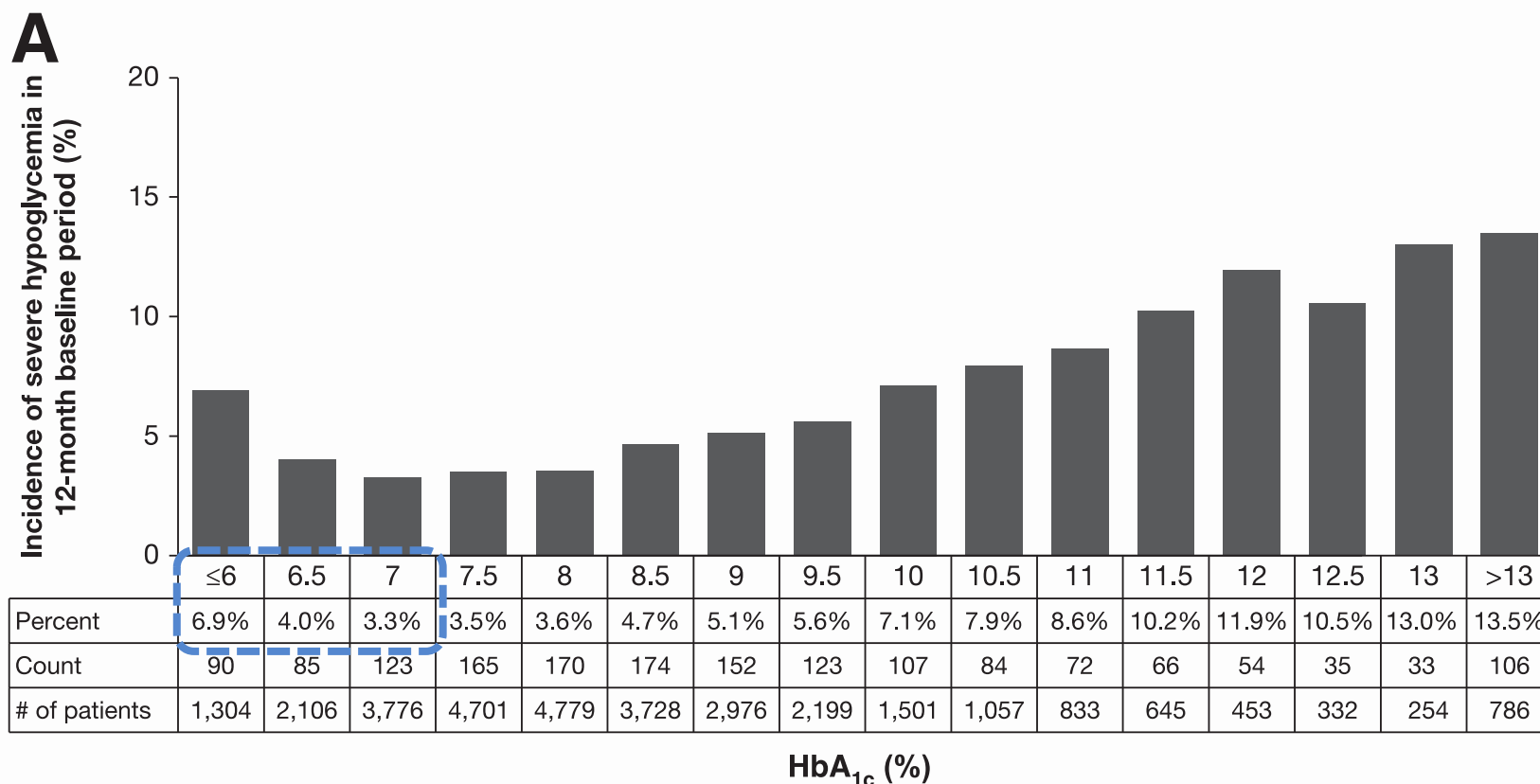
Qual é o melhor controlo metabólico?

1. A
2. B, porque tem maior tempo no alvo
3. B, porque tem menor tempo acima do alvo > 180 mg/dL
4. B, porque tem menor tempo acima do alvo > 250mgdL
5. B, porque tem menor HbA1C



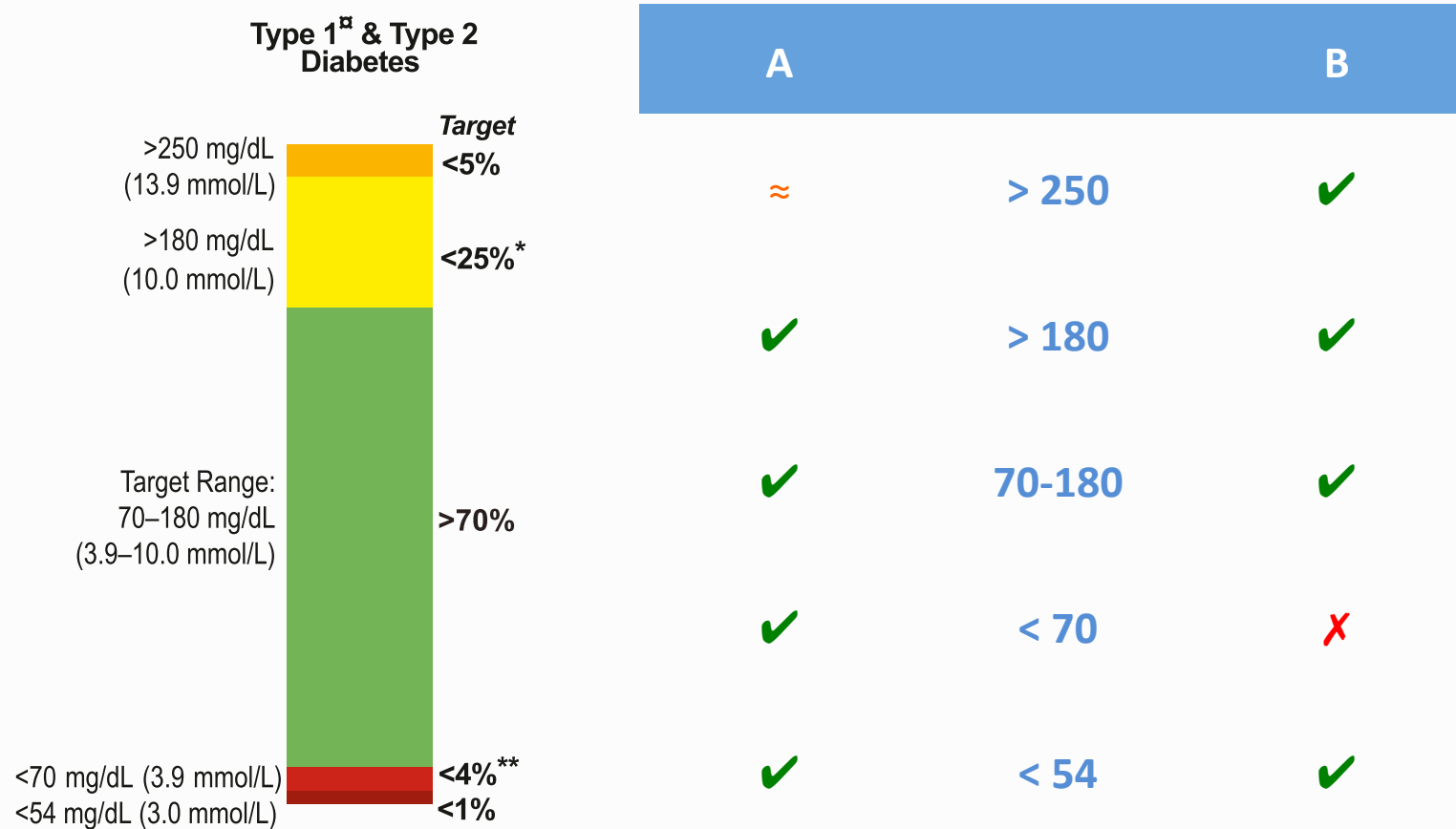
Considerações finais

Risco de hipoglicemia grave de acordo com HbA1C

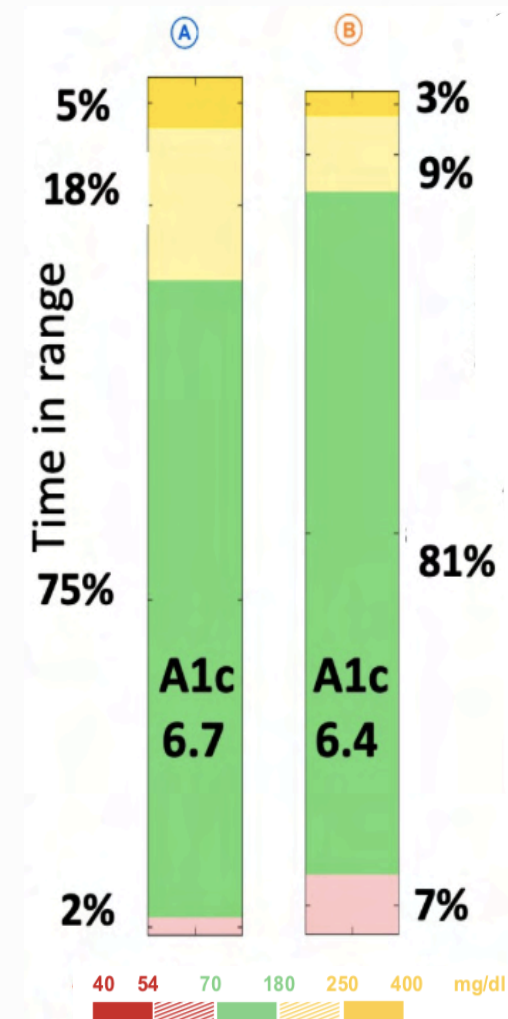


Considerações finais

Alvos glicêmicos baseados no CGM



Battelino J et al. Diabetes Care. 2019



Considerações finais

7. Diabetes Technology: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2021;44(Suppl. 1):S85–S99 | <https://doi.org/10.2337/dc21-S007>

The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc21-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc21-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

x

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Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to help manage their condition, from lifestyle to blood glucose levels. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump, and blood glucose monitoring as assessed by meter or continuous glucose monitor. More recently, diabetes technology has expanded to include hybrid devices that both monitor glucose and deliver insulin, some automatically, as well as software that serves as a medical device, providing diabetes self-management support. Diabetes technology, when coupled with education and follow-up, can improve the lives and health of people with diabetes; however, the complexity and rapid change of the diabetes technology landscape can also be a barrier to patient and provider implementation.

Recommendation

7.1 Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices. **E**

Technology is rapidly changing, but there is no “one-size-fits-all” approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, patient interest in devices and willingness to change can vary, and providers may have trouble keeping up with newly released technology. Not-for-profit websites can help providers and patients make decisions as to the initial choice of devices. Other sources, including health care providers and device manufacturers, can help people troubleshoot when difficulties arise.

Bibliografia aconselhada

SPEDP 2021
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HYBRID EDITION
PORTO | 11 e 12 DE NOVEMBRO

DOI: 10.1111/pedi.12731



ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies

Jennifer L. Sherr¹ | Martin Tauschmann^{2,3} | Tadej Battelino^{4,5} | Martin de Bock⁶ | Gregory Forlenza⁷ | Rossana Roman⁸ | Korey K. Hood⁹ | David M. Maahs¹⁰

Diabetes Care Volume 44, Supplement 1, January 2021

7. Diabetes Technology: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S85–S99 | <https://doi.org/10.2337/dc21-S007>

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

Diabetes Care 2019;42:1593–1603 | <https://doi.org/10.2337/dci19-0028>

Tadej Battelino,¹ Thomas Danne,² Richard M. Bergenstal,³ Stephanie A. Amiel,⁴ Roy Beck,⁵ Torben Biester,² Emanuele Bosi,⁶ Bruce A. Buckingham,⁷ William T. Cefalu,⁸ Kelly L. Close,⁹ Claudio Cobelli,¹⁰ Eyal Dassau,¹¹ J. Hans DeVries,^{12,13} Kim C. Donaghue,¹⁴ Klemen Dovc,¹ Francis J. Doyle III,¹¹ Satish Garg,¹⁵ George Grunberger,¹⁶ Simon Heller,¹⁷ Lutz Heinemann,¹⁸ Irl B. Hirsch,¹⁹

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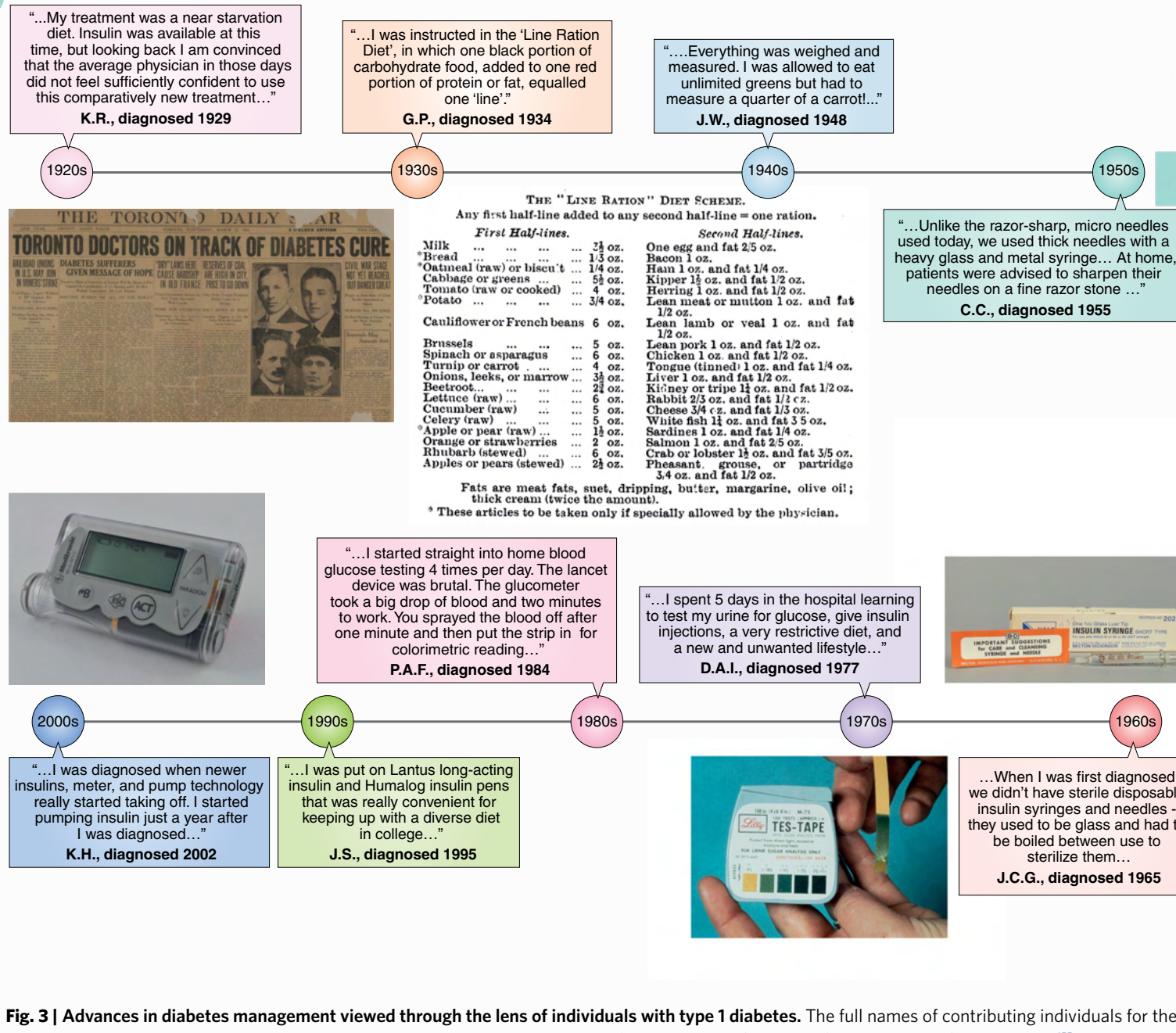
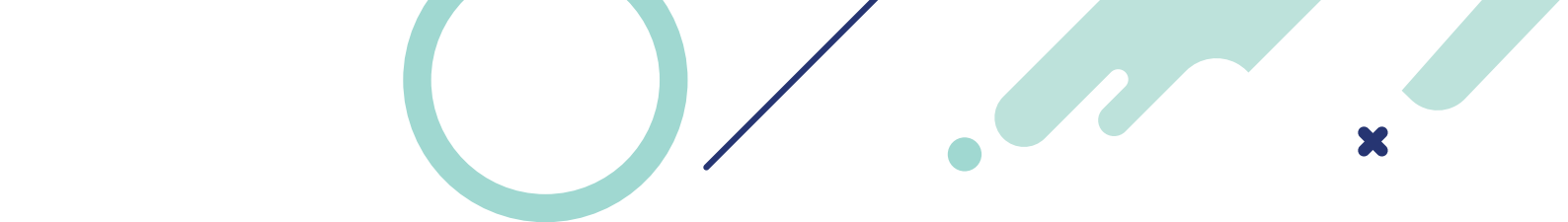


Fig. 3 | Advances in diabetes management viewed through the lens of individuals with type 1 diabetes. The full names of contributing individuals for the years 1965–2006 are included in the Acknowledgements. The quotes from K.R. (diagnosed 1929) and G.P. (diagnosed 1934) are from ref.¹⁵⁵. The quote from J.W. (diagnosed 1948) is from ref.¹⁵⁶. The quote from C.C. (diagnosed 1955) is from ref.¹⁵⁷.

Thank You!!



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HYBRID EDITION

CURSO TEÓRICO-PRÁTICO
DIABETES - TEMPO NO INTERVALO-ALVO

ESTUDOS DE APOIO



Time in range centered diabetes care

Klemen Dovc^{1, 2} and Tadej Battelino^{1, 2}

¹University Children's Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia

²Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Abstract. Optimal glycemic control remains challenging and elusive for many people with diabetes. With the comprehensive clinical evidence on safety and efficiency in large populations, and with broader reimbursement, the adoption of continuous glucose monitoring (CGM) is rapidly increasing. Standardized visual reporting and interpretation of CGM data and clear and understandable clinical targets will help professionals and individuals with diabetes use diabetes technology more efficiently, and finally improve long-term outcomes with less everyday disease burden. For the majority of people with type 1 or type 2 diabetes, time in range (between 70 and 180 mg/dL, or 3.9 and 10 mmol/L) target of more than 70% is recommended, with each incremental increase of 5% towards this target being clinically meaningful. At the same time, the goal is to minimize glycemic excursions: a recommended target for a time below range (< 70 mg/dL or < 3.9 mmol/L) is less than 4%, and time above range (> 180 mg/dL or 10 mmol/L) less than 25%, with less stringent goals for older individuals or those at increased risk. These targets should be individualized: the personal use of CGM with the standardized data presentation provides all necessary means to accurately tailor diabetes management to the needs of each individual with diabetes.

Key words: time in range, glucose variability, continuous glucose monitoring, diabetes technology, closed-loop, self-monitoring of blood glucose, diabetes mellitus

Introduction

Diabetes has an increasing worldwide prevalence over the past decades from 151 million in 2000 to estimated 463 million (9.3% of all adults aged 20–79 yr) in 2020, and an additional 1.1 million children and adolescents with type 1 diabetes (1). Living with diabetes is challenging for individuals with this chronic condition as well as for those taking care of them. The lifelong goal of diabetes care is maintaining glucose levels as close to normal as possible and as early as possible in the course of the disease, thus delaying or possibly preventing devastating long-term diabetes complications (2–5).

Optimal diabetes management should be multidisciplinary and tailored for each person with diabetes (PWD), and is dependent on regular glucose monitoring, precise insulin dosing, and rational decision-making support. However, everyday diabetes care is complicated by the variability in insulin requirements for each PWD as insulin dose needed to maintain normoglycemia fluctuates from one day (or night) to another, and might be, especially in children and

adolescents, challenging to achieve with conventional treatment modalities (6, 7).

In the past decades, glucose management was primarily assessed with the glycated hemoglobin A1c (HbA1c), an evidence-based and broadly-accepted surrogate outcome measure for evaluating the efficacy of diabetes care in routine clinical practice and in numerous clinical trials (including Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the DCCT cohort), and was recognized as a reliable and indirect biomarker that reflects long-term average glucose control (2–5, 8). Current international guidelines recommend that HbA1c for the majority of children and nonpregnant adults should be below 53 mmol/mol (7%) or even below 47.5 mmol/mol (6.5%) if this can be achieved safely (9, 10).

While HbA1c realistically captures the average glycemic control in the retrospect, it is limited in assessing short-term outcomes and day-to-day glucose fluctuations (11, 12). There is substantial evidence that these glucose excursions »beyond HbA1c« are

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associated with the damage to susceptible organs or/and chromosomes, likely through oxidative stress (13–15), and were highlighted as significant risk factors for cognitive function and evolving brain structures early in the disease course, especially in young children with type 1 diabetes (16–18). Additionally, HbA1c lacks the information about acute complications, such as severe hypoglycemia or diabetic ketoacidosis that are, together with the fear of hypoglycemia, important barriers towards diabetes care optimization. Moreover, acute complications cause stress and anxiety, increase treatment costs, and decrease the quality of life (QoL) and psychological well-being of the youth with diabetes and their families (12, 19, 20).

Continuous glucose monitoring (CGM), either real-time (rtCGM) or intermittently scanned (isCGM), effectively addresses these barriers: data derived from CGM present a more comprehensive glucose control picture than HbA1c alone (21). CGM devices provide a broad spectrum of additional glucose management metrics, including proportions of time in range (TIR), time below range (TBR), time above range (TAR), and glucose variability (GV), that are at hand to PWDs and their health-care providers (HCPs) for individualizing the diabetes management and for making real-time treatment modifications.

From Intermittent to Continuous Glucose Monitoring

Regular glucose monitoring allows PWDs to guide their insulin therapy and assess whether their glucose targets are safely achieved. Frequent self-monitoring of blood glucose (SMBG) from capillary blood has considerably improved glycemic control by giving users the capacity to self-manage and individually tailor insulin dosing, and is considered a fundamental component of effective diabetes treatment and daily management of PWDs on insulin therapy (22).

SMBG has several limitations as blood is sampled intermittently, pinpointing only fragments of real glucose fluctuations, thus failing to reveal ongoing glucose excursions even if performed frequently. Episodes of asymptomatic hypoglycemia and also hyperglycemia could therefore be overlooked and not incorporated into decision-making. Additionally, a recent study demonstrated that many glucometers for personal use previously cleared by authorities in real life do not meet the level of accuracy currently required for regulatory clearance (23).

SMBG is throughout the world being replaced with CGM as the glucose monitoring of choice for insulin dosing; this replacement is based on a considerable body of evidence generated over the past 15 years. Contrary to SMBG, CGM provides an almost continuous string of glucose concentration measurements (every 1–5 min). CGM devices generally consist of a disposable on-body sensor that measures glucose concentration in the interstitial fluid, and a transmitter that broadcasts

the sensor values (usually in 5–15 min intervals) to a dedicated receiver and/or other portable devices (e.g. smartphone, smart-watch, tablet). Data can be seen in real-time (rtCGM), stored in the cloud and shared with other family members. The CGM sensor values usually closely correlate with blood glucose concentration when glucose is stable, with a mean time lag of 5 min or less; during episodes of rapid glucose changes like post-simple-carbohydrate meal or exercise, however, the time lag can exceed 10 minutes (24). isCGM is a variety of CGM that presents glucose concentration only on demand (25, 26) but with recently enabled alarms it is coming closer to rtCGMs.

The only currently approved implantable CGM system has a sensor that is fully implanted under the skin by a healthcare provider, and functions for 90–180 days with data visualization through an on-body device (27).

Following the first major randomized controlled trial (RCT) with CGM use funded by JDRF (28), numerous RCTs confirmed efficacy and safety of CGM devices in both people affected with type 1 and type 2 diabetes (29–35), including individuals with severe hypoglycemia and/or hypoglycemia unawareness (36–39), on multiple daily injections (MDI) therapy (40), and particularly during pregnancy complicated by type 1 diabetes (41). Importantly, these positive outcomes were associated with a projected yearly reduction in diabetes-related cost worth several million USD (42). Additionally, user satisfaction and consequently mean sensor usage was significantly higher, including significant improvement of QoL measures (43).

The use of CGMs has been endorsed by the American Diabetes Association (ADA) in its 2020 Standards of Medical Care in Diabetes (33) the American Association of Clinical Endocrinologists (AACE) (44, 45), the International Society for Pediatric and Adolescent Diabetes (ISPAD) (46), and the Endocrine Society (47). The use of CGM is globally increasing exponentially in all age groups. Recent data from the T1D Exchange Registry reported that about 30% of participants have been using CGM in the period from 2016 to 2018 compared to 7% in 2010 to 2012 (48). Similarly, the most recent DPV Registry reported extensive CGM use in the majority of children with type 1 diabetes aged below 10 yr and overall usage in 38% of individuals with type 1 diabetes (49). This significant increase is likely related to the approval of isCGM and rtCGM systems for non-adjunctive use, better accuracy and reliability of CGM devices, as well as broader reimbursement policy, some with demonstrated cost-effectiveness (50, 51).

Real-world efficacy data are in line with observations from RTCs: in a European registry, the CGM use was associated with better mean glucose and less hypoglycemia (52), in the T1D Exchange Registry, CGM usage was associated with lower HbA1c (48), and similarly in the DPV Registry CGM initiation lowered HbA1c and reduced risk for both SH and DKA (53). Recently, in the largest real-world data set including

more than 10,000 individuals with type 1 diabetes from the UK, isCGM use improved glycemic control, especially in those with a higher baseline HbA1c, improved hypoglycemic awareness, reduced diabetes-related distress, and reduced hospital admissions (54). A recent head-to-head comparison between rtCGM and isCGM demonstrated potential advantages of the former, which may influence further development of CGM devices (55).

Standardized Data Reporting Interpretation

CGM data can be accessed in real-time on personal devices and curated personal data can be viewed using software packages. The data analysis tools offer PWDs and HCPs a wide range of metrics of glucose control quality, including proportion of sensor use, mean glucose, glucose management indicator (GMI; previously “estimated HbA1c”), glycemic variability (coefficient of variation – CV) and time in ranges – TIR, TBR and TAR (21, 56). Some of these metrics are useful research tools and others have been welcomed by patient-groups for providing insights into the quality of glucose control. However, until recently, these metrics were reported in various ways and ranges were defined diversely, therefore, it was almost impossible to compare results from one report to another.

In 2017, an international consensus recommended standardized CGM reporting and defined outcomes definitions with a core set of ten CGM metrics for reports (21). Definitions of the minimum requirements for CGM performance, such as meeting ISO (International Organization for Standardization) standards, the relationship of dependence of CGM calibration with glucometers (non-adjunctive use), and an acceptable CGM accuracy, defined as an absolute relative difference (MARD), were agreed upon. For reliable data assessment, studies have demonstrated that 10–14 d of CGM data generally provide a good approximation of 3 months of glucose data (57).

It is imperative that all CGM users should be trained in how to access, interpret, and answer questions regarding their glycemic control with accessible devices and tools.

Decision Making and Time in Range Targets

To make CGM data clinically meaningful for routine day-to-day diabetes management, clear guidance on CGM-derived glycemic targets should be provided to both PWDs and HCPs.

Recently, several major international societies formally endorsed an international consensus report on clinical targets for CGM data (58); notably, the consensus participants included also individuals with diabetes outside the medical profession.

The consensus suggested easy to understand TIR targets, along with TBR and TAR targets for routine

management of type 1 and type 2 diabetes (Table 1). The reporting, presentation and visualization of CGM data should smoothen the communication between PWDs and HCPs, particularly when a standardized report (eg. Ambulatory Glucose Profile - AGP (59)) displays the key CGM metrics, including proportions of glucose values in different ranges over a specified time period, the recommended target for each CGM data range, and a visual demonstration of the CGM values distribution according to the time of day.

The principal goal for all children and adults with type 1 diabetes and type 2 diabetes is to maintain:

- At least 70% ((16 h and 48 min per d) of TIR (70–180 mg/dL / 3.9–10 mmol/L),
- while at the same time minimizing both TBR and TAR:
- less than 4% (1 h per d) of TBR (< 70 mg/dL / 3.9 mmol/L) and
- less than 25% (6 h per d) of TAR (> 180 mg/dL / 10 mmol/L).

Targets should be individualized and in line with personal needs and circumstances. Each incremental 5% improvement in TIR is associated with clinically significant benefit.

While for pregnancy complicated with diabetes recommended targets remain the same, TIR is defined tighter (63–140 mg/dL) as glucose levels are physiologically lower during pregnancy (60).

A relevant improvement in diabetes care with the use of the new metrics is only possible through its broad understanding and adoption by PWDs and HCPs. It is therefore important to demonstrate that TIR metrics relate to and predict clinical outcomes so that we can together finally improve long-term diabetes outcomes with less day-to-day disease burden.

Because TIR can be evaluated on a near-hourly basis, it provides an important advantage over HbA1c: interpreting glycemic control in terms of TIR offers a more nuanced, cause-and-effect related understanding of glucose fluctuations. One can recognize behaviours and decisions that drive glucose levels out-of-range and prospectively find where/when changes can be made. From PWDs perspective, TIR is more accessible and at the same time more intuitive. For example, in one survey of 3461 PWDs, TIR emerged as the top outcome measure considered to have a ‘big impact’ on daily life with diabetes that both reflects PWDs’ priorities and can be used to quantitatively evaluate treatment efficacy (12).

To show the correlation between HbA1c and TIR, Vigersky and McMahon analyzed data from 18 studies including 2577 PWD and found a strong relationship between TIR and HbA1c ($R = -0.84$; $R^2 = 0.71$) (60). Their results showed that for every 10% change in TIR, there was a 0.8% change in HbA1c.

Similar relationships were observed by Hirsch and colleagues who analyzed individual-level data from four randomized trials including 545 PWDs who had central laboratory measurements of HbA1c. TIR of 70% and 50% strongly corresponded with an HbA1c of approximately 7% (53 mmol/mol) and 8% (64 mmol/mol), respectively.

Table 1. Targets for glycemic control: Type 1 / Type 2 and older / high-risk individuals

		Type 1 / Type 2	Older/high-risk Type 1 / Type 2
Time above range (TAR)	Above target range	> 180 mg/dL > 10.0 mmol/L	
	% of time/d	< 25% < 6 h	
	Above target range	> 250 mg/dL > 13.9 mmol/L	> 250 mg/dL > 13.9 mmol/L
	% of time/d	< 5% < 1 h, 12 min	< 10% < 2 h, 24 min
Time in range (TIR)	Target range	70–180 mg/dL 3.9–10.0 mmol/L	70–180 mg/dL 3.9–10.0 mmol/L
	% of time/d	> 70% > 16 h, 48 min	> 50% > 12 h
Time below range (TBR)	Below target range	< 70 mg/dL < 3.9 mmol/L	< 70 mg/dL < 3.9 mmol/L
	% of time/d	< 4% < 1 h	< 1% < 5 min
	Below target range	< 54 mg/dL < 3.0 mmol/L	
	% of time/d	< 1% < 15 min	

Each incremental 5% increase towards time in range (TIR) targets is associated with clinically significant benefits for Type 1 / Type 2. Adapted from: Battelino T, *et al.* Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range (58).

An increase in TIR of 10% (2.4 h per day) decreased HbA1c for about 0.5% (5.0 mmol/mol) (61). Petersson and coworkers analyzed data from 133 children with type 1 diabetes from Sweden and demonstrated a significant non-linear relationship between time in tighter range 70–140 mg/dL and HbA1c ($R^2 = 0.69$) over 60 days in frequent CGM (at 80% of the time) users (62). Beck and coworkers (63) re-analyzed data from the DCCT study. They used 7-point blood glucose profiles to validate the use of TIR as an outcome measure for clinical trials and demonstrated that the hazard ratio for retinopathy progression increased by 64% for each 10% decrease in TIR. Similarly, the hazard ratio for microalbuminuria development increased by 40% for each 10% reduction in TIR. Lu and colleagues evaluated the association between the TIR, assessed by CGM, diabetic retinopathy as a marker of microvascular complications (64), and intima media thickness, as a marker of macrovascular complications (65), in individuals with type 2 diabetes. Individuals with more progressive retinopathy, regardless of stage, and with abnormal intima media thickness had significantly lower TIR, and a decreased risk for complications with improved TIR was demonstrated (64, 65). Recently, an association between higher TIR and reduction in the urinary creatinine-albumin ration was demonstrated from a prospective randomized controlled

trial (66). Several prospective clinical trials with TIR as the primary outcome are ongoing.

Finally, TIR can be used for evaluating the efficacy of different treatment modalities. Automated glucose-responsive insulin therapy (closed-loop) was revitalized (67) and a roadmap towards closing-the-loop in six steps was defined 15 yr ago (68, 69). Consequently, a broad spectrum of treatment modalities for closing the loop is currently available on the market (in details discussed elsewhere (70)), including low-glucose suspend (71, 72), predictive low-glucose suspend systems MiniMed 640G (*Medtronic Diabetes, USA*) and Tandem t:slim X2 Insulin Pump with Basal IQ® Technology (*Tandem Diabetes care, USA*) (73, 74) and automated insulin delivery systems Medtronic MiniMed 670G and 780G (*Medtronic Diabetes, USA*) (75), DBLG1 (*Diabeloop, France*) (76), Tandem Diabetes Care t:slim X2 with Control IQ (*Tandem Diabetes care, USA*) (77) and CamAPX FX (*CamDiab Ltd, UK*) (78).

The efficacy of newer technologies was evaluated in a recent network meta-analysis: closed-loop systems are demonstrated to have several advantages over other treatment modalities (79). **Figure 1** summarizes data regarding TIR from recent randomized controlled trials including individuals with type 1 diabetes using either closed-loop therapy, predictive low glucose suspend or

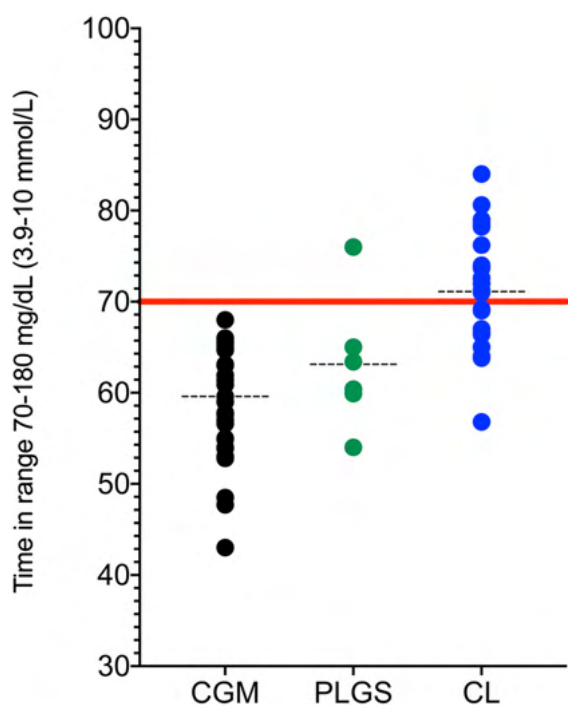


Fig. 1. Time in range for different treatment modalities from recent randomized controlled trials. CGM, Continuous Glucose Monitoring; PLGS, Predictive Low Glucose Suspend; CL, Closed-loop. Data from randomized controlled trials including children, adolescents and adults with type 1 diabetes for the last 5 years are included (34–36, 38, 39, 55, 73, 74, 77, 78, 80–116).

CGM alone.

Summary

In conclusion, with a proven benefit on glycemic

outcomes and QoL, CGM devices are being increasingly adopted worldwide. To unify and improve clinical outcomes and quality of life with our routine diabetes care, we need to constantly improve the presentation and usage of provided CGM data. Individual CGM daily glucose profiles within the AGP can be used as a standardized overview and can effectively guide shared decision-making between a user and her/his HCP to personalize diabetes care and enable real-time treatment adjustments. This communication can be facilitated with clear and understandable time in ranges targets. Based on existing data, current recommendations set time in range (70–180 mg/dL, or 3.9–10 mmol/L) of more than 70%, with time below range (< 70 mg/dL, or < 3.9 mmol/L) of less than 4% for the majority of people with type 1 or type 2 diabetes. Every 5% increment towards the time in range target is clinically meaningful. All treatment targets can be effective in practice only if personalized and agreed upon with each individual with diabetes.

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Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

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Improvements in sensor accuracy, greater convenience and ease of use, and expanding reimbursement have led to growing adoption of continuous glucose monitoring (CGM). However, successful utilization of CGM technology in routine clinical practice remains relatively low. This may be due in part to the lack of clear and agreed-upon glycemic targets that both diabetes teams and people with diabetes can work toward. Although unified recommendations for use of key CGM metrics have been established in three separate peer-reviewed articles, formal adoption by diabetes professional organizations and guidance in the practical application of these metrics in clinical practice have been lacking. In February 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel of physicians, researchers, and individuals with diabetes who are expert in CGM technologies to address this issue. This article summarizes the ATTD consensus recommendations for relevant aspects of CGM data utilization and reporting among the various diabetes populations.

Adoption of continuous glucose monitoring (CGM), which includes both real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), has grown rapidly over the past few years as a result of improvements in sensor accuracy, greater convenience and ease of use, and expanding reimbursement. Numerous studies have demonstrated significant clinical benefits of CGM use in people with diabetes regardless of insulin delivery method (1–15). In many countries, the benefits and utility of CGM are now recognized by national and international medical organizations for individuals with insulin-requiring diabetes and/or those at risk for hypoglycemia (16–21). However, despite increased CGM adoption (22,23), successful utilization of CGM data in routine clinical practice remains relatively low. This may be due in part to the lack of clear and agreed-upon glycemic targets toward which both diabetes teams and people with diabetes can work.

In 2012 the Helmsley Charitable Trust sponsored the first expert panel to recommend the standardization of CGM metrics and CGM report visualization (24). This was followed by a series of CGM consensus statements refining the core CGM metrics, but the conclusions were never in alignment. In 2017, several articles supported use of systematic approaches to CGM data evaluation (18–20). To date, the key CGM metrics remain as unified recommendations in three separate peer-reviewed articles, yet formal adoption by diabetes professional organizations and

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This international consensus report has been endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society.

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guidance in the practical application of these metrics in clinical practice have been lacking (19).

In February 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel of individuals with diabetes and clinicians and researchers with expertise in CGM. Our objective was to develop clinical CGM targets to supplement the currently agreed-upon metrics for CGM-derived times in glucose ranges (within target range, below target range, above target range) in order to provide guidance for clinicians, researchers, and individuals with diabetes in using, interpreting, and reporting CGM data in routine clinical care and research. Importantly, in order to make the recommendations generalizable and comprehensive, the consensus panel included individuals living with diabetes and had international representation from physicians and researchers from all geographic regions.

The panel was divided into subgroups to review literature and provide recommendations for relevant aspects of CGM data utilization and reporting among the various diabetes populations. Long-term trials demonstrating how CGM metrics relate to and/or predict clinical outcomes have not been conducted, and many of

the published reports assessed here are not at the highest evidence level (25). However, there is suggestive evidence from a number of recent studies, including a cross-sectional study correlating current retrospective 3-day time in target range with varying degrees of diabetes retinopathy (26) and an analysis of the 7-point self-monitored blood glucose (SMBG) data from the Diabetes Control and Complications Trial (DCCT) (27), showing correlations of time in target range (70–180 mg/dL [3.9–10.0 mmol/L]) with diabetes complications. Relationships between time in target range and A1C (26,27) and number of severe and non-severe hypoglycemic events (28–32) have also been observed. Recommendations from each subgroup were presented to the full panel and voted upon. This article summarizes the consensus recommendations and represents the panel members' evaluation of the issues.

NEED FOR METRICS BEYOND A1C

A1C is currently recognized as the key surrogate marker for the development of long-term diabetes complications in people with type 1 and type 2 diabetes and has been used as the primary end point for many CGM studies (1,3,4,6,33,34). While A1C reflects average glucose over the last 2–3 months, its limitation is the

lack of information about acute glycemic excursions and the acute complications of hypo- and hyperglycemia. A1C also fails to identify the magnitude and frequency of intra- and interday glucose variation (35,36). Moreover, certain conditions such as anemia (37), hemoglobinopathies (38), iron deficiency (39), and pregnancy (40) can confound A1C measurements. Importantly, as reported by Beck et al. (41), the A1C test can fail at times to accurately reflect mean glucose even when none of those conditions are present. Despite these limitations, A1C is the only prospectively evaluated tool for assessing the risk for diabetes complications, and its importance in clinical decision making should not be undervalued. Rather, the utility of A1C is further enhanced when used as a complement to glycemic data measured by CGM.

Unlike A1C measurement, use of CGM allows for the direct observation of glycemic excursions and daily profiles, which can inform on immediate therapy decisions and/or lifestyle modifications. CGM also provides the ability to assess glucose variability and identify patterns of hypo- and hyperglycemia. However, potential drawbacks of CGM use include the need to be actively used in order to be effective; that it may induce anxiety;

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Table 1—Standardized CGM metrics
2017 international consensus on CGM metrics (18)

1. Number of days CGM worn
2. Percentage of time CGM is active
3. Mean glucose
4. Estimated A1C
5. Glycemic variability (%CV or SD)
6. Time > 250 mg/dL (> 13.9 mmol/L)
7. Time > 180 mg/dL (> 10.0 mmol/L)
8. Time 70–180 mg/dL (3.9–10.0 mmol/L)
9. Time < 70 mg/dL (< 3.9 mmol/L)
10. Time < 54 mg/dL (< 3.0 mmol/L)
11. LBGI and HBGI (risk indices)
12. Episodes (hypoglycemia and hyperglycemia) 15 min
13. Area under the curve
14. Time blocks (24-h, day, night)
Use of Ambulatory Glucose Profile (AGP) for CGM report

CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index.

that it may have accuracy limitations, particularly with the delay in registering blood glucose changes in dynamic situations; and that it can provoke allergies. Another limitation of CGM is that this technology is not yet widely available in several regions of the world.

Effective use of CGM data to optimize clinical outcomes requires the user to interpret the collected data and act upon them appropriately. This requires 1) common metrics for assessment of CGM glycemic status, 2) graphical visualization of the glucose data and CGM daily profile, and 3) clear clinical targets.

STANDARDIZATION OF CGM METRICS

In February 2017, the ATTD Congress convened an international panel of expert clinicians and researchers to define core metrics for assessing CGM data (18) (Table 1).

The list of core CGM metrics has now been streamlined for use in clinical practice based on the expert opinion of this international consensus group (18). Of the 14 core metrics, the panel selected that 10 metrics that may be most useful in clinical practice (Table 2).

Fundamental to accurate and meaningful interpretation of CGM is ensuring that adequate glucose data are available for evaluation. As shown in studies, > 70%

use of CGM over the most recent 14 days correlates strongly with 3 months of mean glucose, time in ranges, and hyperglycemia metrics (42,43). In individuals with type 1 diabetes, correlations are weaker for hypoglycemia and glycemic variability; however, these correlations have not been shown to increase with longer sampling periods (43). Longer CGM data collection periods may be required for individuals with more variable glycemic control (e.g., 4 weeks of data to investigate hypoglycemia exposure).

TIME IN RANGES

The development of blood glucose testing provided individuals with diabetes the ability to obtain immediate information about their current glucose levels and adjust their therapy accordingly. Over the past decades, national and international medical organizations have been successful in developing, harmonizing, and disseminating standardized glycemic targets based on risk for acute and chronic complications. CGM technology greatly expands the ability to assess glycemic control throughout the day, presenting critical data to inform daily treatment decisions and quantifying time below, within, and above the established glycemic targets.

Although each of the core metrics established in the 2017 ATTD consensus conference (18) provides important information about various aspects of glycemic status, it is often impractical to assess and fully utilize many of these metrics in real-world clinical practices. To

streamline data interpretation, the consensus panel identified “time in ranges” as a metric of glycemic control that provides more actionable information than A1C alone. The panel agreed that establishing target percentages of time in the various glycemic ranges with the ability to adjust the percentage cut points to address the specific needs of special diabetes populations (e.g., pregnancy, high-risk) would facilitate safe and effective therapeutic decision making within the parameters of the established glycemic goals.

The metric includes three key CGM measurements: percentage of readings and time per day within target glucose range (TIR), time below target glucose range (TBR), and time above target glucose range (TAR) (Table 3). The primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR. The consensus group agreed that expressing time in the various ranges can be done as the percentage (%) of CGM readings, average hours and minutes spent in each range per day, or both, depending on the circumstances.

It was agreed that CGM-based glycemic targets must be personalized to meet the needs of each individual with diabetes. In addition, the group reached consensus on glycemic cutpoints (a target range of 70–180 mg/dL [3.9–10.0 mmol/L] for individuals with type 1 diabetes and type 2 diabetes and 63–140 mg/dL [3.5–7.8 mmol/L] during pregnancy, along with a set of targets for the time per day [% of CGM readings or minutes/

Table 2—Standardized CGM metrics for clinical care: 2019

1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
3. Mean glucose	
4. Glucose management indicator (GMI) (75)	
5. Glycemic variability (%CV) target #36% (90)*	
6. Time above range (TAR): % of readings and time > 250 mg/dL (> 13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time < 54 mg/dL (< 3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CV, coefficient of variation. *Some studies suggest that lower %CV targets (< 33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas (45,90,91).

Table 3—Guidance on targets for assessment of glycemic control for adults with type 1 or type 2 diabetes and older/high-risk individuals

Diabetes group	TIR		TBR		TAR	
	% of readings; time per day	Target range	% of readings; time per day	Below target level	% of readings; time per day	Above target level
Type 1*/type 2	. 70%; . 16 h, 48 min	70–180 mg/dL (3.9–10.0 mmol/L)	. 4%; . 1 h . 1%; . 15 min	. 70 mg/dL (. 3.9 mmol/L) . 54 mg/dL (. 3.0 mmol/L)	. 25%; . 6 h . 5%; . 1 h, 12 min	. 180 mg/dL (. 10.0 mmol/L) . 250 mg/dL (. 13.9 mmol/L)
Older/high-risk# type 1/type 2	. 50%; . 12 h	70–180 mg/dL (3.9–10 mmol/L)	. 1%; . 15 min	. 70 mg/dL (. 3.9 mmol/L)	. 10%; . 2 h, 24 min	. 250 mg/dL (. 13.9 mmol/L)

Each incremental 5% increase in TIR is associated with clinically significant benefits for individuals with type 1 or type 2 diabetes (26,27). *For age ≥ 25 years, if the A1C goal is 7.5%, set TIR target to approximately 60%. See the section CLINICAL APPLICATION OF TIME IN RANGES for additional information regarding target goal setting in pediatric management. #See the section OLDER AND/OR HIGH-RISK INDIVIDUALS WITH DIABETES for additional information regarding target goal setting.

hours)] individuals with type 1 diabetes and type 2 diabetes (Table 3) and women during pregnancy (Table 4) should strive to achieve. It should be noted that pre-meal and postprandial SMBG targets remain for diabetes in pregnancy (44), in addition to the new CGM TIR targets for overall glycemia.

Although the metric includes TIR, TBR, and TAR, achieving the goals for both TBR and TIR would result in reduced time spent above range and thereby improve glycemic control. However, some clinicians may choose to target the reduction of the high glucose values and minimize hypoglycemia, thereby arriving at more time in the target range. In both approaches, the first priority is to reduce TBR to target levels and then address TIR or TAR targets.

Note that for people with type 1 diabetes, the targets are informed by the ability to reach the targets with hybrid closed-loop therapy (11), the first example of which is now commercially available with several more systems in final stages of testing. Importantly, recent studies have shown the potential of

reaching these targets with CGM in individuals using multiple daily injections (6). In type 2 diabetes, there is generally less glycemic variability and hypoglycemia than in type 1 diabetes (45). Thus, people with type 2 diabetes can often achieve more time in the target range while minimizing hypoglycemia (4). As demonstrated by Beck et al. (4), individuals with type 2 diabetes increased their TIR by 10.3% (from 55.6% to 61.3%) after 24 weeks of CGM use with slight reductions in TBR. Most recently, the beneficial effects of new medications, such as sodium–glucose cotransporter 2 agents have helped individuals with type 1 diabetes increase TIR (46–48). Targets for type 1 diabetes and type 2 diabetes were close enough to combine into one set of targets, outside of pregnancy.

Another way to visualize the CGM-derived targets for the four categories of diabetes is shown in Fig. 1, which displays and compares the targets for TIR (green), TBR (two categories in light and dark red), and TAR (two categories in yellow and orange). It becomes clear at a glance

that there are different expectations for the various time in ranges relating to safety concerns and efficacy based on currently available therapies and medical practice.

CLINICAL VALIDITY OF MEASURES

To fundamentally change clinical care with use of the new metrics, it would be important to demonstrate that the metrics relate to and predict clinical outcomes. In this regard, longer-term studies relating to time spent within specific CGM glycemic ranges, diabetes complications, and other outcomes are required. However, there is evidence from a number of recent studies that have shown correlations of TIR (70–180 mg/dL [3.9–10.0 mmol/L]) with diabetes complications (49,50) as well as a relationship between TIR and A1C (26,27). Although evidence regarding TIR for older and/or high-risk individuals is lacking, numerous studies have shown the elevated risk for hypoglycemia in these populations (51–56). Therefore, we have lowered the TIR target from

Table 4—Guidance on targets for assessment of glycemic control during pregnancy

Diabetes group	TIR		TBR		TAR	
	% of readings; time per day	Target range	% of readings; time per day	Below target level	% of readings; time per day	Above target level
Pregnancy, type 1§	. 70%; . 16 h, 48 min	63–140 mg/dL† (3.5–7.8 mmol/L†)	. 4%; . 1 h . 1%; . 15 min	. 63 mg/dL† (. 3.5 mmol/L†) . 54 mg/dL (. 3.0 mmol/L)	. 25%; . 6 h	. 140 mg/dL (. 7.8 mmol/L)
Pregnancy, type 2/GDMS	See PREGNANCY section	63–140 mg/dL† (3.5–7.8 mmol/L†)	See PREGNANCY section	. 63 mg/dL† (. 3.5 mmol/L†) . 54 mg/dL (. 3.0 mmol/L)	See PREGNANCY section	. 140 mg/dL (. 7.8 mmol/L)

Each incremental 5% increase in TIR is associated with clinically significant benefits for pregnancy in women with type 1 diabetes (59,60). †Glucose levels are physiologically lower during pregnancy. §Percentages of TIR are based on limited evidence. More research is needed.

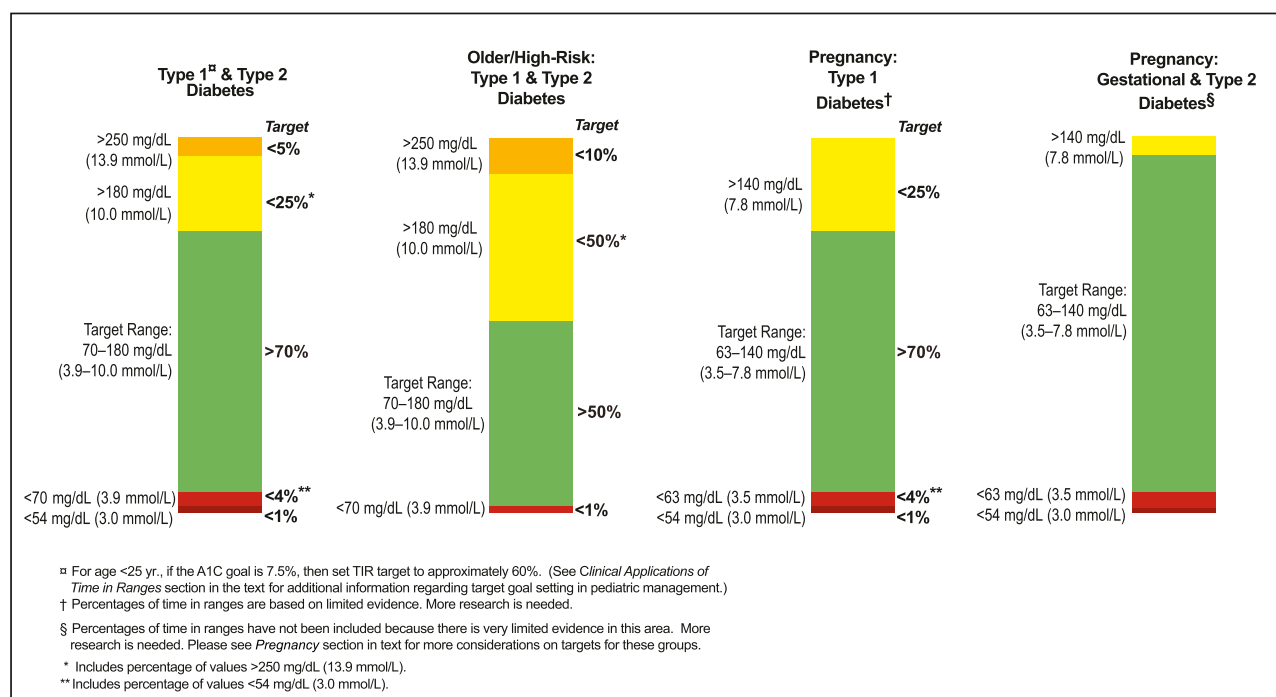


Figure 1—CGM-based targets for different diabetes populations.

.70% to .50% and reduced TBR to .1% at .70 mg/dL (.3.9 mmol/L) to place greater emphasis on reducing hypoglycemia with less emphasis on maintaining target glucose levels (Table 3).

Type 1 Diabetes and Type 2 Diabetes Association With Complications

Associations between TIR and progression of both diabetic retinopathy (DR) and development of microalbuminuria were reported by Beck et al. (50), using 7-point blood glucose profiles from the DCCT data set to validate the use of TIR as an outcome measure for clinical trials. Their analysis showed that the hazard rate for retinopathy progression increased by 64% for each 10% reduction in TIR. The hazard rate for microalbuminuria development increased by 40% for each 10% reduction in TIR. A post hoc analysis of the same DCCT data set showed a link between glucose of .70 mg/dL (.3.9 mmol/L) and .54 mg/dL (.3.0 mmol/L) and an increased risk for severe hypoglycemia (57).

Similar associations between DR and TIR were reported in a recent study by Lu et al. (49) in which 3,262 individuals with type 2 diabetes were evaluated for DR, which was graded as non-DR, mild non-proliferative DR (NPDR), moderate NPDR, or vision-threatening DR. Results showed

that individuals with more advanced DR spent significantly less time within target range (70–180 mg/dL [3.9–10.0 mmol/L]) and that prevalence of DR decreased with increasing TIR.

Relationship Between TIR and A1C

Analyses were conducted utilizing datasets from four randomized trials encompassing 545 adults with type 1 diabetes who had central laboratory measurements of A1C (26). TIR (70–180 mg/dL [3.9–10.0 mmol/L]) of 70% and 50% strongly corresponded with an A1C of approximately 7% (53 mmol/mol) and 8% (64 mmol/mol), respectively. An increase in TIR of 10% (2.4 h per day) corresponded to a decrease in A1C of approximately 0.5% (5.0 mmol/mol); similar associations were seen in an analysis of 18 randomized controlled trials (RCTs) by Vigersky and McMahon (27) that included over 2,500 individuals with type 1 diabetes and type 2 diabetes over a wide range of ages and A1C levels (Table 5).

Pregnancy

During pregnancy, the goal is to safely increase TIR as quickly as possible, while reducing TAR and glycemic variability. Data from the first study of longitudinal CGM use in pregnancy demonstrated a 13–percentage point increase in TIR (43% to 56% TIR 70–140 mg/dL [3.9–7.8 mmol/L])

(58). TBR .50 mg/dL was reduced from 6% to 4%, although the higher TBR .70 mg/dL was high (13–15%) using older-generation sensors. With improved sensor accuracy, recent type 1 diabetes pregnancy studies report a lower threshold of .63 mg/dL (.3.5 mmol/L) for TBR and \$63 mg/dL (\$3.5 mmol/L) for TIR (59,60). Data from Sweden, and the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) control group, report 50% TIR in the first trimester, improving to 60% TIR in the third trimester, reflecting contemporary antenatal care. Of note, these data confirm that the TBR .63 mg/dL (.3.5 mmol/L) recommendation of .4% is safely achievable, especially after the first trimester. Furthermore, 33% of women achieved the recommendation of 70% TIR 63–140 mg/dL (3.5–7.8 mmol/L) in the final (.34) weeks of pregnancy. Preliminary data suggest that closed-loop systems may allow pregnant women to safely achieve 70% TIR at an earlier (.24 weeks) stage of gestation (61,62). Law et al. (63) analyzed data from two early CGM trials (64,65) describing the associations between CGM measures and risk of large-for-gestational-age (LGA) infants. Taken together, the Swedish and CONCEPTT data confirm that a 5–7% higher

Table 5—Estimate of A1C for a given TIR level based on type 1 diabetes and type 2 diabetes studies

Beck et al. (26) (n = 545 participants with type 1 diabetes)			Vigersky and McMahon (27) (n = 1,137 participants with type 1 or type 2 diabetes)	
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)	95% CI for predicted A1C values, %	TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)
20%	9.4 (79)	(8.0, 10.7)	20%	10.6 (92)
30%	8.9 (74)	(7.6, 10.2)	30%	9.8 (84)
40%	8.4 (68)	(7.1, 9.7)	40%	9.0 (75)
50%	7.9 (63)	(6.6, 9.2)	50%	8.3 (67)
60%	7.4 (57)	(6.1, 8.8)	60%	7.5 (59)
70%	7.0 (53)	(5.6, 8.3)	70%	6.7 (50)
80%	6.5 (48)	(5.2, 7.8)	80%	5.9 (42)
90%	6.0 (42)	(4.7, 7.3)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

TIR during the second and third trimesters is associated with decreased risk of LGA and neonatal outcomes including macrosomia, shoulder dystocia, neonatal hypoglycemia, and neonatal intensive care admissions. More data are needed to define the clinical CGM targets for pregnant women with type 2 diabetes, who spend one-third less time hyperglycemic than women with type 1 diabetes and achieve TIR of 90% (58). Because of the lack of evidence on CGM targets for women with gestational diabetes mellitus (GDM) or type 2 diabetes in pregnancy, percentages of time spent in range, below range, and above range have not been included in this report. Recent data suggest that even more stringent targets (66) and greater attention to overnight glucose profiles may be required to normalize outcomes in pregnant women with GDM (63).

Older and/or High-Risk Individuals With Diabetes

Older and/or high-risk individuals with diabetes are at notably higher risk for severe hypoglycemia due to age, duration of diabetes, duration of insulin therapy, and greater prevalence of hypoglycemia unawareness (51–55). The increased risk of severe hypoglycemia is compounded by cognitive and physical impairments and other comorbidities (53,56). High-risk individuals include those with a higher risk of complications, comorbid conditions (e.g., cognitive deficits, renal disease, joint disease, osteoporosis, fracture, and/or cardiovascular disease), and those requiring

assisted care, which can complicate treatment regimens (56). Therefore, when setting glycemic targets for high-risk and/or elderly people, it is important to individualize and be conservative, with a strong focus on reducing the percentage of time spent > 70 mg/dL (> 3.9 mmol/L) and preventing excessive hyperglycemia.

STANDARDIZATION OF CGM DATA PRESENTATION

As noted above, in 2013 a panel of clinicians with expertise in CGM published recommendations for use of the Ambulatory Glucose Profile (AGP) as a template for data presentation and visualization. Originally created by Mazze et al. (67), the standardized AGP report was further developed by the International Diabetes Center and now incorporates all the core CGM metrics and targets along with a 14-day composite glucose profile as an integral component of clinical decision making (24). This recommendation was later endorsed at the aforementioned international consensus conference on CGM metrics (18) and is referenced as an example in the American Diabetes Association 2019 “Standards of Medical Care in Diabetes” (16) and in an update to the American Association of Clinical Endocrinologists consensus on use of CGM (68). The AGP report, in slightly modified formats, has been adopted by most of the CGM device manufacturers in their download software. An example of the AGP report, updated to incorporate targets, is presented in Fig. 2. In the AGP

report, glucose ranges are defined as “Very High” (Level 2), “High” (Level 1), “Low” (Level 1), and “Very Low” (Level 2). An “mmol/L” version is provided in Supplementary Fig. 1.

There is a general consensus that a useful CGM report is one that can be understood by clinicians and people with diabetes. While there may be some terms (e.g., glucose variability) that are less familiar to many people with diabetes, a single-page report that the medical team can review and file in the electronic medical record and that can be used as a shared decision-making tool with people with diabetes was considered to be of value (69–72). More detailed reports (e.g., adjustable data ranges, detailed daily reports) should remain available for individualized review by or with people with diabetes.

Clinical Application of Time in Ranges
Despite its demonstrated value, clinical utilization of CGM data has remained suboptimal. Although time constraints and reimbursement issues are clearly obstacles, clinician inexperience in data interpretation and lack of standardization software for visualization of CGM data have also played a role (73). The proposed standardized report enables clinicians to readily identify important metrics such as the percentage of time spent within, below, and above each individual's target range, allowing for greater personalization of therapy through shared decision making.

Using the standardized report, the clinician can also address glucose variability (e.g., the coefficient of variation

AGP Report

Name _____

MRN _____

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019–10 Mar 2019**13 days****% Time CGM is Active****99.9%****Glucose Ranges****Targets [% of Readings (Time/Day)]**

Target Range 70–180 mg/dL Greater than 70% (16h 48min)

Below 70 mg/dL Less than 4% (58min)

Below 54 mg/dL Less than 1% (14min)

Above 180 mg/dL Less than 25% (6h)

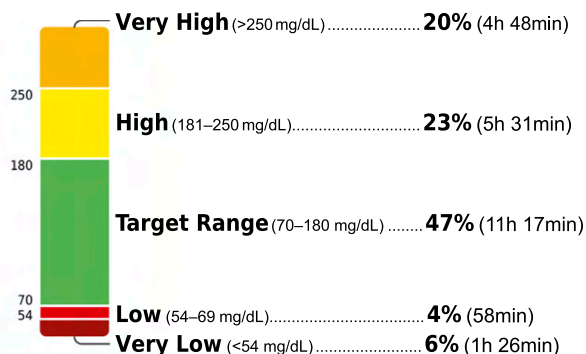
Above 250 mg/dL Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose**173 mg/dL****Glucose Management Indicator (GMI)****7.6%****Glucose Variability****49.5%**

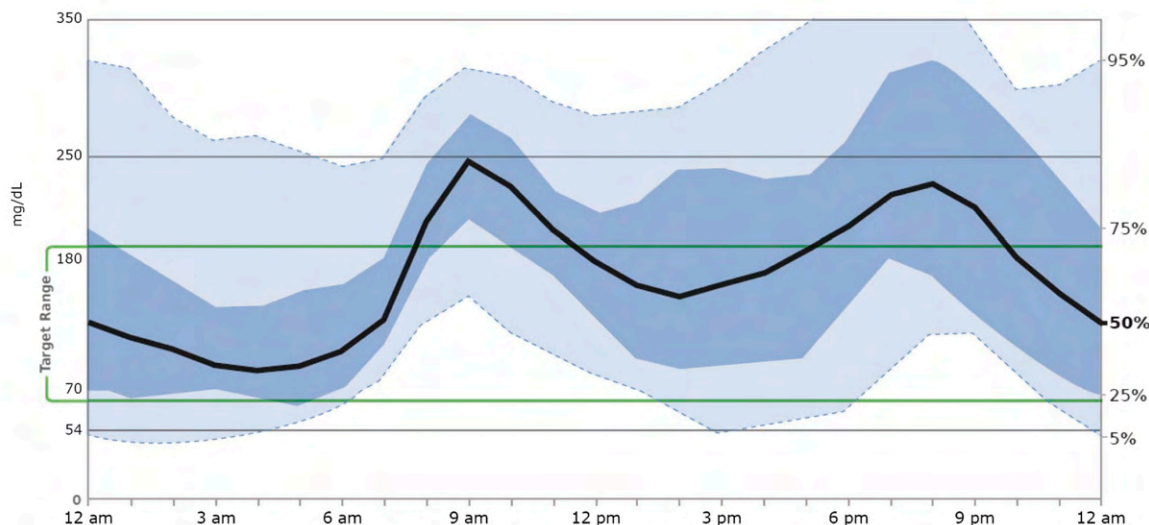
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

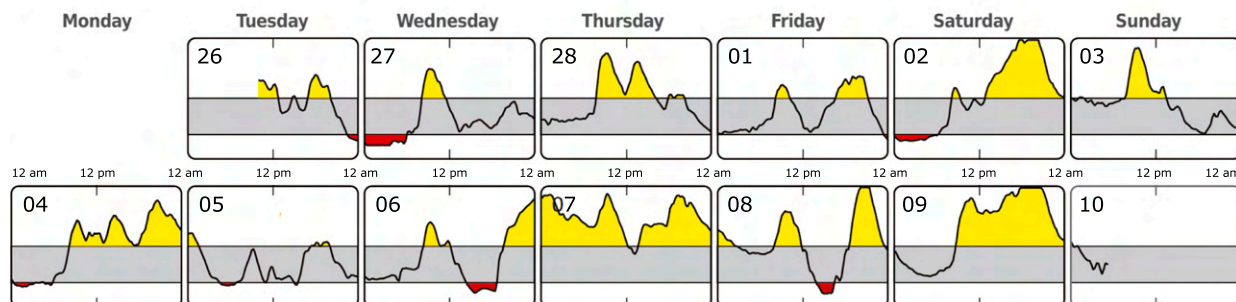


AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES



Each daily profile represents a midnight-to-midnight period.

Figure 2—Ambulatory Glucose Profile.

[%CV] metric) (74) or use the glucose management indicator (GMI) metric (75) to discuss the possible discrepancies noted in glucose exposure derived from CGM data versus the individual's laboratory-measured A1C (41,76). With appropriate educational materials, time, and experience, clinicians will develop a systematic approach to CGM data analysis and the most effective ways to discuss the data with patients in person or remotely.

Goal Setting

Numerous studies have demonstrated the clinical benefits of early achievement of near-normal glycemic control in individuals with type 1 diabetes and type 2 diabetes (77–83). However, when advising people with diabetes, goal-setting must be collaborative and take into account the individual needs/capabilities of each patient and start with the goals that are most achievable. An early study by DeWalt et al. (84) found that setting small, achievable goals not only enhances people's ability to cope with their diabetes, but that people with diabetes who set and achieved their goals often initiated additional behavioral changes on their own. One approach to consider is the SMART goal (Specific, Measurable, Achievable, Relevant, Time-bound) intervention, which is directly applicable to setting targets for time in ranges. First described by Lawlor and Hornyak in 2012 (85), this approach incorporates four key components of behavioral change relevant to goal setting: 1) the goal is specific and defines exactly what is to be achieved, 2) the goal is measurable and there is tangible evidence when it has been achieved, 3) the goal is achievable but stretches the patient slightly so that he/she feels challenged, and 4) the goal should be attainable over a short period of time.

Effective goals should utilize CGM data to identify specific instances for the patient to take measurable action to prevent hypoglycemia. Although analysis of the AGP reports provides an opportunity for meaningful discussion, individuals should be counseled to look at patterns throughout the day to see when low glucose events are occurring and make adjustments in their therapy to reduce these events.

When applying the CGM metrics in clinical practice, it may be more meaningful and motivating to communicate to people with diabetes the importance

of working to reduce the time spent , 70 mg/dL (, 3.9 mmol/L) to less than 1 h per day and time spent , 54 mg/dL (, 3.0 mmol/L) to less than 15 min per day, rather than using , 4% and , 1%, respectively, as the goal. However, as discussed earlier, targets must be personalized to meet the needs and capabilities of each person, focusing on small steps and small successes. Individuals with diabetes should work with their provider and/or educator to develop a SMART goal to reduce TBR.

Individualized goals are particularly important for pediatric and young adult populations. The International Society for Pediatric and Adolescent Diabetes recommends that targets for individuals #25 years of age aim for the lowest achievable A1C without undue exposure to severe hypoglycemia or negative effects on quality of life and burden of care (86). An A1C target of 7.0% (53 mmol/mol) can be used in children, adolescents, and adults #25 years old who have access to comprehensive care (86). However, a higher A1C goal (e.g., , 7.5% [, 58 mmol/mol]) may be more appropriate in the following situations: inability to articulate hypoglycemia symptoms, hypoglycemia unawareness, history of severe hypoglycemia, lack of access to analog insulins and/or advanced insulin delivery technology, or inability to regularly check glucose (86). This would equate to a TIR target of ~60% (Table 4).

The consensus group recognized that achieving the targets for the various time in ranges is aspirational in some situations, and many individuals will require ongoing support, both educational and technological, from their health care team. Importantly, as demonstrated by Beck et al. (26), Vigersky and McMahon (27), and Feig et al. (59), even small, incremental improvements yield significant glycemic benefits. Therefore, when advising individuals with diabetes (particularly children, adolescents, and high-risk individuals) about their glycemic goals, it is important to take a stepwise approach, emphasizing that what may appear to be small, incremental successes (e.g., 5% increase in TIR) are, in fact, clinically significant in improving their glycemia (26,27,59). However, when counseling women planning pregnancy and pregnant women, greater emphasis should be placed on getting to goal as soon as possible (59,60).

CONCLUSIONS

Use of CGM continues to expand in clinical practice. As a component of diabetes self-management, daily use of CGM provides the ability to obtain immediate feedback on current glucose levels as well as direction and rate of change in glucose levels. This information allows people with diabetes to optimize dietary intake and exercise, make informed therapy decisions regarding mealtime and correction of insulin dosing, and, importantly, react immediately and appropriately to mitigate or prevent acute glycemic events (87–89). Retrospective analysis of CGM data, using standardized data management tools such as the AGP, enables clinicians and people with diabetes to work collaboratively in identifying problem areas and then set achievable goals (70–72). We conclude that, in clinical practice, time in ranges (within target range, below range, above range) are both appropriate and useful as clinical targets and outcome measurements that complement A1C for a wide range of people with diabetes and that the target values specified in this article should be considered an integral component of CGM data analysis and day-to-day treatment decision making.

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Boehringer Ingelheim, MannKind, Sanofi, Zealand Pharma, and UNEEG. L.H. is a consultant for companies developing novel diagnostic and therapeutic options for diabetes. He is a shareholder of Profil Institut für Stoffwechselforschung GmbH and ProSciento. I.B.H. receives research funding from Medtronic Diabetes and has received consulting fees from Abbott Diabetes Care, Bigfoot, Roche, and Becton Dickinson. R.H. reports having received speaker honoraria from Eli Lilly and Company, Novo Nordisk, and AstraZeneca, serving on an advisory panel for Eli Lilly and Company and Novo Nordisk, and receiving license fees from B. Braun and Medtronic. O.K. received honoraria from Amring, Eli Lilly and Company, Novo Nordisk, and Sanofi and owns shares from DreaMed Diabetes. B.K. declares research support handled by the University of Virginia from Dexcom, Roche, Sanofi, and Tandem; patent royalties handled by the University of Virginia from Johnson & Johnson, Sanofi, and Dexcom; and has served as a consultant for Sanofi and Tandem and on a speakers' bureau for Dexcom. B.L. is an employee of Close Concerns and The diaTribe Foundation, which receive funding from CGM manufacturers, including Medtronic, Dexcom, and Abbott Diabetes Care. C.M. serves or has served on the advisory panel or speakers' bureau for Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Dianax, and UCB. Financial compensation for these activities has been received by KU Leuven. H.R.M. received honoraria from participation on advisory boards for Medtronic and research support from Dexcom, Medtronic, Abbott Diabetes Care, and Johnson & Johnson. R.N. received honoraria for participation on the speakers' bureau of Novo Nordisk, Pfizer, Eli Lilly and Company, and Sanofi. R.N. owns DreaMed stock and reports two patent applications. K.N. owns shares in Novo Nordisk and has received consulting fees from Medtronic, Abbott Diabetes Care, and Novo Nordisk; speaker honoraria from Medtronic, Roche Diabetes Care, Rubin Medical, Sanofi, Novo Nordisk, Zealand Pharma, and Bayer; and research support from Novo Nordisk, Zealand Pharma, Medtronic, and Roche Diabetes Care. C.G.P. has received consulting fees from Dexcom, Diasome, Onduo, Proteus, Roche Diabetes Care, and Senseonics. E.R. has received consulting fees from A. Menarini Diagnostics, Abbott Diabetes Care, Air Liquide SI, Becton Dickinson, Cellnovo, Dexcom, Eli Lilly and Company, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, and Sanofi and research support from Abbott Diabetes Care, Dexcom, Insulet, Tandem, and Roche. D.R. has received consulting fees from Eli Lilly and Company and Better Therapeutics. K.S. is an employee of dQ&A Market Research, Inc., whose clients include several device and pharmaceutical companies in the diabetes field. S.A.W. has received consulting fees from Eli Lilly and Company, Sanofi, and Zealand and speaker honoraria from Medtronic, Insulet, and Tandem. M.P. is a member of the advisory board of AstraZeneca, Sanofi, Medtronic, Eli Lilly and Company, Novo Nordisk, and Insulet and is a consultant to RSP Systems A/S, Qulab Medical, and Pfizer. The institute headed

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7. Diabetes Technology: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc21-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc21-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to help manage their condition, from lifestyle to blood glucose levels. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump, and blood glucose monitoring as assessed by meter or continuous glucose monitor. More recently, diabetes technology has expanded to include hybrid devices that both monitor glucose and deliver insulin, some automatically, as well as software that serves as a medical device, providing diabetes self-management support. Diabetes technology, when coupled with education and follow-up, can improve the lives and health of people with diabetes; however, the complexity and rapid change of the diabetes technology landscape can also be a barrier to patient and provider implementation.

Recommendation

- 7.1 Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices. **E**

Technology is rapidly changing, but there is no “one-size-fits-all” approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, patient interest in devices and willingness to change can vary, and providers may have trouble keeping up with newly released technology. Not-for-profit websites can help providers and patients make decisions as to the initial choice of devices. Other sources, including health care providers and device manufacturers, can help people troubleshoot when difficulties arise.

SELF-MONITORING OF BLOOD GLUCOSE

Recommendations

- 7.2 People who are on insulin using self-monitoring of blood glucose should be encouraged to test when appropriate based on their insulin regimen. This may

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include testing when fasting, prior to meals and snacks, at bedtime, prior to exercise, when low blood glucose is suspected, after treating low blood glucose until they are normoglycemic, and prior to and while performing critical tasks such as driving. **B**

- 7.3 Providers should be aware of the differences in accuracy among glucose meters—only U.S. Food and Drug Administration–approved meters with proven accuracy should be used, with unexpired strips, purchased from a pharmacy or licensed distributor. **E**

- 7.4 When prescribed as part of a diabetes self-management education and support program, self-monitoring of blood glucose may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections. **B**

- 7.5 Although self-monitoring of blood glucose in patients on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering diet, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**

- 7.6 When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of technique, results, and their ability to use data, including uploading/sharing data (if applicable), from self-monitoring of blood glucose devices to adjust therapy. **E**

- 7.7 Health care providers should be aware of medications and other factors, such as high-dose vitamin C and hypoxemia, that can interfere with glucose meter accuracy and provide clinical management as indicated. **E**

Major clinical trials of insulin-treated patients have included self-monitoring of blood glucose (SMBG) as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (1). SMBG is thus an integral component of effective

therapy of patients taking insulin. In recent years, continuous glucose monitoring (CGM) has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly prandial insulin doses). The patient's specific needs and goals should dictate SMBG frequency and timing or the consideration of CGM use.

Meter Standards

Glucose meters meeting U.S. Food and Drug Administration (FDA) guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for accuracy of blood glucose monitors, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in Table 7.1. In Europe, currently marketed monitors must meet current ISO standards. In the U.S., currently marketed monitors must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy is left to the manufacturer and not routinely checked by an independent source.

Patients assume their glucose monitor is accurate because it is FDA cleared, but often that is not the case. There is substantial variation in the accuracy of widely used blood glucose monitoring systems (2,3). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for SMBG (<https://diabetestechnology.org/surveillance>). In one analysis, only 6 of the top 18 glucose meters met the accuracy standard (4).

There are single-meter studies in which benefits have been found with individual meter systems, but few that compare meters in a head-to-head manner. Certain meter system characteristics, such as the use of lancing devices that are less painful (5) and the ability to reapply blood to a strip with an insufficient initial sample, may also be beneficial to patients (6) and may make SMBG less burdensome for patients to perform.

Counterfeit Strips

Patients should be advised against purchasing or reselling preowned or second-hand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure SMBG accuracy.

Optimizing SMBG Monitor Use

SMBG accuracy is dependent on the instrument and user, so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, by both the patient and the provider, to ensure that data are used in an effective and timely manner. In patients with type 1 diabetes, there is a correlation between greater SMBG frequency and lower A1C (7). Among patients who check their blood glucose at least once daily, many report taking no action when results are high or low (8). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacologic therapy to achieve specific goals. Some meters now provide advice to the user in real time, when monitoring glucose levels (9), while others can be used as a part of integrated health platforms (10).

The ongoing need for and frequency of SMBG should be reevaluated at each routine visit to avoid overuse, particularly if SMBG is not being used effectively for self-management (8,11,12).

Patients on Intensive Insulin Regimens

SMBG is especially important for insulin-treated patients to monitor for and prevent hypoglycemia and hyperglycemia. Most patients using intensive insulin regimens (multiple daily injections or insulin pump therapy) should be encouraged to assess glucose levels using SMBG (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many patients using SMBG, this will require checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjustment for multiple confounders, increased daily frequency of SMBG was significantly associated with lower A1C

Table 7.1—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA (206,207)	ISO 15197:2013 (208)
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	95% within 15% for BG ≥ 100 mg/dL 95% within 15 mg/dL for BG < 100 mg/dL 99% in A or B region of consensus error grid‡
Hospital use	95% within 12% for BG ≥ 75 mg/dL 95% within 12 mg/dL for BG < 75 mg/dL 98% within 15% for BG ≥ 75 mg/dL 98% within 15 mg/dL for BG < 75 mg/dL	

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see <http://endmemo.com/medical/unitconvert/Glucose.php>. †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the “clinically acceptable” A and B regions are considered “outlier” readings and may be dangerous to use for therapeutic decisions (209).

(20.2% per additional check per day) and with fewer acute complications (13).

Patients Using Basal Insulin and/or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often monitoring is needed for insulin-treated patients who do not use intensive insulin regimens, such as those with type 2 diabetes using basal insulin with or without oral agents. However, for patients using basal insulin, assessing fasting glucose with SMBG to inform dose adjustments to achieve blood glucose targets results in lower A1C (14,15).

In people with type 2 diabetes not using insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, it has showed limited improvement in outcomes (16–19). However, for some individuals, glucose monitoring can provide insight into the impact of diet, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naïve patients with suboptimal initial glycemic stability, a group trained in structured SMBG (a paper tool was used at least quarterly to collect and interpret seven-point SMBG profiles taken on 3 consecutive days) reduced their A1C by 0.3% more than the control group (20). A trial of once-daily SMBG that included enhanced patient feedback through messaging found no clinically or statistically significant change in A1C at 1 year (19). Meta-analyses have suggested that

SMBG can reduce A1C by 0.25–0.3% at 6 months (21–23), but the effect was attenuated at 12 months in one analysis (21). Reductions in A1C were greater (20.3%) in trials where structured SMBG data were used to adjust medications, but A1C was not changed significantly without such structured diabetes therapy adjustment (23). A key consideration is that performing SMBG alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Glucose Meter Inaccuracy

Although many meters function well under a variety of circumstances, providers and people with diabetes need to be aware of factors that can impair meter accuracy. A meter reading that seems discordant with clinical reality needs to be retested or tested in a laboratory. Providers in intensive care unit settings need to be particularly aware of the potential for abnormal meter readings, and laboratory-based values should be used if there is any doubt. Some meters give error messages if meter readings are likely to be false (24).

Oxygen. Currently available glucose monitors utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (25). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in patients with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to false high glucose readings. Glucose dehydrogenase-based monitors are not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (25). Most will show an error if the temperature is unacceptable, but a few will provide a

reading and a message indicating that the value may be incorrect.

Interfering Substances. There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems (25). They are listed in Table 7.2.

Table 7.2—Interfering substances for glucose readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA
Ascorbic acid
Glucose dehydrogenase monitors
Icodextrin (used in peritoneal dialysis)

CONTINUOUS GLUCOSE MONITORING DEVICES

See Table 7.3 for definitions of types of CGM devices.

Recommendations

- 7.8 When prescribing continuous glucose monitoring (CGM) devices, robust diabetes education, training, and support are required for optimal CGM device implementation and ongoing use. People using CGM devices need to have the ability to perform self-monitoring of blood glucose in order to calibrate their monitor and/or verify readings if discordant from their symptoms. **B**
- 7.9 When used properly, real-time continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **A** and other forms of insulin therapy **C** are a useful tool to lower and/or maintain A1C levels and/or reduce

- hypoglycemia in adults and youth with diabetes.
- 7.10 When used properly, intermittently scanned continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **B** and other forms of insulin therapy **C** can be useful and may lower A1C levels and/or reduce hypoglycemia in adults and youth with diabetes to replace self-monitoring of blood glucose.
- 7.11 In patients on multiple daily injections and continuous subcutaneous insulin infusion, real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. **A** Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h.
- 7.12 When used as an adjunct to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**
- 7.13 Use of professional continuous glucose monitoring (CGM) and/or intermittent real-time or intermittently scanned CGM can be helpful in identifying and correcting patterns of hyper- and hypoglycemia and improving A1C levels in people with diabetes on noninsulin as well as basal insulin regimens. **C**
- 7.14 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**
- 7.15 People who have been using continuous glucose monitors should have continued access across third-party payers. **E**

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times can lag if glucose levels are rising or falling rapidly). There are two basic types of CGM devices: those that are owned by the user, unblinded, and intended for frequent/continuous use (real-time [rt]CGM and intermittently scanned [is]CGM) and those that are owned and applied in/by the clinic, which provide data that is blinded or unblinded for a discrete period of time (professional CGM). Table 7.3 provides the definitions for the types of CGM devices. For devices that provide patients unblinded data, most of the published randomized controlled trials (RCTs) have been performed using rtCGM devices that have alarms and alerts. The RCT results have largely been positive, in terms of reducing either A1C levels and/or episodes of hypoglycemia, as long as participants regularly wear the devices (26–29). These devices provide glucose readings continuously to a smartphone or reader that can be viewed by the patient and/or a caregiver. It is difficult to determine how much the need to swipe a device to obtain a result, combined with a lack of alarms and alerts, matters in terms of outcomes, although results from these devices (isCGM) have not shown consistent improvements in glycemic outcomes (30). However, data from longitudinal trials (without a control group for comparison) show improvement in A1C levels (31). There is one small study in patients at risk for hypoglycemia that compared rtCGM with isCGM (32). The study showed improvement in time spent in hypoglycemia with rtCGM compared with isCGM. The newest version of the isCGM system has an optional alert for a high or low glucose value (without the capacity for providing predictive alerts), but it still requires that the device be swiped to reveal the glucose level and trend arrows, and RCT data are lacking in terms of

added benefit. This device (FreeStyle Libre 2) and one rtCGM (Dexcom G6) have both been designated as integrated continuous glucose monitoring (iCGM) devices (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/classification.cfm?id=5682>). This is a higher standard, set by the FDA, so these devices can be reliably integrated with other digitally connected devices, including automated insulin dosing systems.

Some real-time systems require calibration by the user, which varies in frequency depending on the device. Additionally, for some CGM systems, the FDA suggests SMBG for making treatment decisions. Devices that require SMBG confirmation are called “adjunctive,” while those that do not are called “nonadjunctive.” An RCT of 226 adults suggested that a CGM device could be used safely and effectively without regular confirmatory SMBG in patients with well-controlled type 1 diabetes at low risk of severe hypoglycemia (33). Two CGM devices are approved by the FDA for making treatment decisions without SMBG calibration or confirmation (34,35). For patients with type 1 diabetes using rtCGM, an important predictor of A1C lowering for all age-groups was frequency of sensor use (26). In this study, overall use was highest in those aged ≥25 years (who had the most improvement in A1C) and lower in younger age-groups.

The abundance of data provided by CGM offers opportunities to analyze patient data more granularly than was previously possible, providing additional information to aid in achieving glycemic targets. A variety of metrics have been proposed (27) and are discussed in Section 6 “Glycemic Targets” (<https://doi.org/10.2337/dc21-S006>). CGM is essential for creating the ambulatory glucose profile (AGP) and providing data on time in range, percentage of time spent above and below range, and variability

Table 7.3—Continuous glucose monitoring (CGM) devices

Type of CGM	Description
Real-time CGM (rtCGM)	CGM systems that measure and display glucose levels continuously
Intermittently scanned CGM (isCGM)	CGM systems that measure glucose levels continuously but only display glucose values when swiped by a reader or a smartphone
Professional CGM	CGM devices that are placed on the patient in the provider's office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. These devices are not fully owned by the patient—they are a clinic-based device, as opposed to the patient-owned rtCGM/isCGM devices.

(36). Access to CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (37,38). This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent SMBG monitoring. Interruption of access to CGM is associated with a worsening of outcomes (39); therefore, it is important for individuals on CGM to have consistent access to the devices.

Education and Training

In general, no device used in diabetes management works optimally without education, training, and follow-up. Device companies offer online tutorials and training videos as well as written material on their use. Patients vary in terms of comfort level with technology, and some prefer in-person training and support. Programs that involve training and support have been shown to improve outcomes in both adults and children using isCGM (40–42). Individuals using CGM should also be trained on how to use SMBG, for use with devices that require calibration, for testing if CGM values seem incongruent with the patient's sense of their glucose levels, and if the CGM device fails or is not available.

Real-time CGM Device Use in Adults and Children With Diabetes

Data exist to support the use of real-time CGM in adults and children, both those on multiple daily injections (MDI) and those on continuous subcutaneous insulin infusion (CSII). This is true in studies both in people with type 1 diabetes and those with type 2 diabetes, although data in individuals with type 2 diabetes is primarily in adults.

In terms of RCTs in people with type 1 diabetes, there are four studies in adults with A1C as the primary outcome (28,29,43–45), three studies in adults with hypoglycemia as the primary outcome (46–48), four studies in adults and children with A1C as the primary outcome (26,49–51), and three studies in adults and children with hypoglycemia as a primary outcome (52–54).

Primary Outcome: A1C Reduction—Adults

In general, A1C reduction was shown in studies where the baseline A1C was higher. In two larger studies in adults with type 1 diabetes that assessed the

benefit of rtCGM in patients on MDI, there were significant reductions in A1C: 2.0.6% in one (28,43) and 2.0.43% in the other (29). No reduction in A1C was seen in a small study performed in underserved, less well-educated adults with type 1 diabetes (44). In the adult subset of the JDRF CGM study, there was a significant reduction in A1C of 2.0.53% (55) in patients who were primarily treated with insulin pump therapy. Better adherence in wearing the rtCGM device resulted in a greater likelihood of an improvement in glycemic control (26,45).

Primary Outcome: Hypoglycemia—Adults

In studies in adults where reduction in episodes of hypoglycemia was the primary end point, significant reductions were seen in individuals with type 1 diabetes on MDI or CSII (46–48). In one study in patients who were at higher risk for episodes of hypoglycemia (48), there was a reduction in rates of all levels of hypoglycemia (see Section 6 “Glycemic Targets,” <https://doi.org/10.2337/dc21-S006>, for hypoglycemia definitions). rtCGM may be particularly useful in insulin-treated patients with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not been powered to show consistent reductions in severe (level 3) hypoglycemia (26,49,50).

Impact on Glycemic Control—Children

When data from adult and pediatric participants are analyzed together, rtCGM use in RCTs has been associated with reduction in A1C levels (49–51). Yet, in the JDRF CGM trial, when youth were analyzed by age-group (8- to 14-year-olds and 15- to 24-year-olds), no change in A1C was seen, likely due to poor rtCGM adherence (26). Indeed, in a secondary analysis of that RCT's data in both pediatric cohorts, those who used the sensor \$6 days/week had an improvement in their glycemic control (56). One critical component to success with CGM is near-daily wearing of the device (49,55, 57–59). One RCT showed no improvement in glycemic outcomes in children aged 4–10 years of age, regardless of how often it was worn (60).

Though data from small observational studies demonstrate that rtCGM can be worn by patients , 8 years old and the use of rtCGM provides insight to glycemic patterns (61,62), an RCT in children aged 4–9 years did not demonstrate improvements

in glycemic control following 6 months of rtCGM use (60). However, observational feasibility studies of toddlers demonstrated a high degree of parental satisfaction and sustained use of the devices despite the inability to change the degree of glycemic control attained (63).

Registry data have also shown an association between rtCGM use and lower A1C levels (55,64), even when limiting assessment of rtCGM use to participants on injection therapy (64).

Impact on Hypoglycemia—Children

There are no studies solely including pediatric patients that assess rates of hypoglycemia as the primary outcome. Some of the studies where pediatric and adult patients were combined together did show potential reductions in hypoglycemia (16,65,66).

Real-time CGM Use in Type 2 Diabetes

Studies in people with type 2 diabetes are heterogeneous in design: in two, participants were using basal insulin with oral agents or oral agents alone (67,68); in one, individuals were on MDI alone (69). The findings in studies with MDI alone (69) and in two studies in people using oral agents with or without insulin (67,68) showed significant reductions in A1C levels. The Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) study in people with type 2 diabetes on MDI showed a reduction in A1C but no reduction in hypoglycemia (69). Studies in individuals with type 2 diabetes on oral agents with or without insulin did not show reductions in rates of hypoglycemia (67,68).

Intermittently Scanned CGM Device Use in Adults and Children With Diabetes

The original isCGM device (to which the majority of the published data applies) did not provide alarms and alerts but is an option used by many patients. There are relatively few RCT data proving benefit in people with diabetes, but there are multiple longitudinal and observational studies. One RCT, designed to show a reduction in episodes of hypoglycemia in patients with type 1 diabetes at higher risk for hypoglycemia, showed a significant benefit in terms of time spent in a hypoglycemic range ($P < 0.0001$) (46). Another RCT, assessing the ability of

isCGM to prevent episodes of recurrent, severe hypoglycemia, showed no benefit (70). In one RCT of isCGM in people with type 2 diabetes on a variety of insulin regimens and with an initial A1C of $\sim 8.8\%$, no reduction in A1C was seen; however, the time spent in a hypoglycemic range was reduced by 43% (71). In a study of isCGM in individuals with type 2 diabetes on MDI, the A1C was reduced by 0.82% in the intervention group and 0.33% in the control group ($P = 0.005$) with no change in rates of hypoglycemia (72). Multiple observational studies have shown benefit in terms of A1C reduction, reductions in hypoglycemia, and/or improvements in quality of life in both children and adults (31,41,73–78). An observational study from Belgium showed no improvements in A1C or quality of life after a year of isCGM use, with a reduction in episodes of severe hypoglycemia and time absent from work compared with patient recall of events during the 6 months prior to starting CGM (79).

There are several published reviews of data available on isCGM (80–83). The Norwegian Institute of Public Health conducted an assessment of isCGM clinical effectiveness, cost-effectiveness, and safety for individuals with type 1 and type 2 diabetes, based on data available to January 2017 (80). The authors concluded that, although there were few quality data available at the time of the report, isCGM may increase treatment satisfaction, increase time in range, and reduce frequency of nocturnal hypoglycemia, without differences in A1C or quality of life or serious adverse events. The Canadian Agency for Drugs and Technologies in Health reviewed existing data on isCGM performance and accuracy, hypoglycemia, effect on A1C, and patient satisfaction and quality of life and concluded that the system could replace SMBG, particularly in patients who require frequent monitoring (81). A 2020 systematic review of RCTs assessing efficacy and patient satisfaction with isCGM revealed improvements in A1C levels in some subgroups of patients (e.g., those with type 2 diabetes) but concluded that additional benefit in terms of time in range, glycemic variability, and hypoglycemia was unclear (30). Benefit was enhanced in individuals with type 1 diabetes when combined with a structured education

program. Another review showed some benefits in terms of A1C reduction as well as improvement in quality of life (84). A review that included studies conducted using a variety of trial designs, including prospective and retrospective cohort studies, showed overall a reduction in A1C (2.026%) in people with type 1 and type 2 diabetes, but there was no difference in time in range or hypoglycemic episodes (83).

Other benefits are discussed in a review (82) that supported the use of isCGM as a more affordable alternative to rtCGM systems for individuals with diabetes who are on intensive insulin therapy. In many cases, isCGM is the preferred alternative compared with SMBG (85,86). It can also improve adherence to monitoring in patients who are in extremely poor control (87).

Real-time CGM Device Use in Pregnancy

One well-designed RCT showed a reduction in A1C levels in adult women with type 1 diabetes on MDI or CSII who were pregnant using CGM in addition to standard care, including optimization of pre- and postprandial glucose targets (88). It demonstrated the value of CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia as well as reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (88). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (89). Use of the CGM-reported mean glucose is superior to use of estimated A1C, glucose management indicator, and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (90). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in women with type 1 diabetes (91) or gestational diabetes mellitus (92).

Use of Professional and Intermittent CGM

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis, can be used to

identify patterns of hypo- and hyperglycemia (93). Professional CGM can be helpful to evaluate patients when either rtCGM or isCGM is not available to the patient or the patient prefers a blinded analysis or a shorter experience with unblinded data. It can be particularly useful to evaluate periods of hypoglycemia in patients on agents that can cause hypoglycemia in order to make medication dose adjustments. It can also be useful to evaluate patients for periods of hyperglycemia.

There are some data showing benefit of intermittent use of CGM (rtCGM or isCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (68,94). In these RCTs, patients with type 2 diabetes not on intensive insulin regimens used CGM intermittently compared with patients randomized to SMBG. Both early (68) and late improvements in A1C were found (68,94).

Use of professional or intermittent CGM should always be coupled with analysis and interpretation for the patient, along with education as needed to adjust medication and change lifestyle behaviors.

Side Effects of CGM Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (95–97). In some cases this has been linked to the presence of isobornyl acrylate, which is a skin sensitizer and can cause an additional spreading allergic reaction (98–100). Patch testing can be done to identify the cause of the contact dermatitis in some cases (101). Identifying and eliminating tape allergens is important to ensure comfortable use of devices and enhance patient adherence (102–105). In some instances, use of an implanted sensor can help avoid skin reactions in those who are sensitive to tape (106,107).

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.16 For people with diabetes who require insulin, insulin syringes or insulin pens may be used for insulin delivery with consideration of patient preference, insulin type and dosing regimen,

cost, and self-management capabilities. **B**

7.17 Insulin pens or insulin injection aids may be considered for patients with dexterity issues or vision impairment to facilitate the administration of accurate insulin doses. **C**

7.18 Smart pens may be useful for some patients to help with dose capture and dosing recommendations. **E**

7.19 U.S. Food and Drug Administration–approved insulin dose calculators/decision support systems may be helpful for titrating insulin doses. **E**

Injecting insulin with a syringe or pen is the insulin delivery method used by most people with diabetes (108,109), although inhaled insulin is also available. Others use insulin pumps or automated insulin delivery devices (see sections on those topics below). For patients with diabetes who use insulin, insulin syringes and pens are both able to deliver insulin safely and effectively for the achievement of glycemic targets. When choosing among delivery systems, patient preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered. It is important to note that while many insulin types are available for purchase as either pens or vials, others may only be available in one form or the other and there may be significant cost differences between pens and vials (see Table 9.3 for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (110–112), while insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see <http://main.diabetes.org/dforg/pdfs/2018/2018-cg-injection-aids.pdf>.) Inhaled insulin can be useful in people who have an aversion to injections.

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units of U-100 insulin, respectively. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited

settings with appropriate storage and cleansing (113).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, which can range from half-unit doses to 2-unit dose increments. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. “Smart” pens that can be programmed to calculate insulin doses and provide downloadable data reports are also available. These pens are useful to assist patient insulin dosing in real time as well as for allowing clinicians to retrospectively review the insulin doses that were given and make insulin dose adjustments (114).

Needle thickness (gauge) and length is another consideration. Needle gauges range from 22 to 33, with higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting shorter needles may lower the risk of intramuscular injection. When reused, needles may be duller and thus injection more painful. Proper insulin injection technique is a requisite for obtaining the full benefits of insulin therapy. Concerns with technique and use of the proper technique are outlined in Section 9 “Pharmacologic Approaches to Glycemic Treatment” (<https://doi.org/10.2337/dc21-S009>).

Bolus calculators have been developed to aid in dosing decisions (115–119). These are subject to FDA approval to ensure safety in terms of dosing recommendations. People who are interested in using these systems should be encouraged to use those that are FDA approved. Provider input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps

Recommendations

7.20 Insulin pump therapy may be considered as an option for all adults and youth with type 1 diabetes who are able to safely manage the device. **A**

7.21 Insulin pump therapy may be considered as an option for adults and youth with type 2 diabetes and other forms of diabetes who are on multiple daily injections who are able to safely manage the device. **B**

7.22 Individuals with diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access across third-party payers. **E**

CSII, or insulin pumps, have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage blood glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin, without tubing.

Most studies comparing MDI with CSII have been relatively small and of short duration. However, a recent systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (2.0.30% [95% CI 2.0.58 to 2.0.02]) and for reducing severe hypoglycemia rates in children and adults (120). There is no consensus to guide choosing which form of insulin administration is best for a given patient, and research to guide this decision-making is needed (121). Thus, the choice of MDI or an insulin pump is often based upon the individual characteristics of the patient and which is most likely to benefit them. Newer systems, such as sensor-augmented pumps and automatic insulin delivery systems, are discussed elsewhere in this section.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to provider preference or center characteristics (122,123) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education (123,124). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (125), addressing the differences in access to insulin pumps and other diabetes technology may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (126,127). Practical aspects of pump therapy initiation include assessment of patient and family

readiness (although there is no consensus on which factors to consider in adults [128] or pediatric patients), selection of pump type and initial pump settings, patient/family education of potential pump complications (e.g., diabetic ketoacidosis [DKA] with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates, extended/square/dual wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (129,130). Additionally, frequency of follow-up does not influence outcomes. Access to insulin pump therapy should be allowed/continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement, occlusion), which place patients at risk for ketosis and DKA and thus must be recognized and managed early (131); lipohypertrophy or, less frequently, lipoatrophy (132,133); and pump site infection (134). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (134,135). Current reasons for attrition are problems with cost, wearability, dislike for the pump, suboptimal glycemic control, or mood disorders (e.g., anxiety or depression) (136).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (137). Studying the effectiveness of CSII in lowering A1C has been challenging because of the potential selection bias of observational studies. Participants on CSII may have a higher socioeconomic status that may facilitate better glycemic control (138) versus MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs comparing CSII and MDI with insulin analogs demonstrate a modest improvement in A1C in participants on CSII (139,140). Observational studies, registry data, and meta-analysis have also suggested an improvement of glycemic control in participants on CSII (141–143). Although hypoglycemia was a major adverse effect of intensified insulin regimen in the

Diabetes Control and Complications Trial (DCCT) (144), data suggest that CSII may reduce the rates of severe hypoglycemia compared with MDI (143,145–147).

There is also evidence that CSII may reduce DKA risk (143,148) and diabetes complications, in particular, retinopathy and peripheral neuropathy in youth, compared with MDI (65). Finally, treatment satisfaction and quality-of-life measures improved on CSII compared with MDI (149,150). Therefore, CSII can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic control while reducing the risk of hypoglycemia and DKA, improving quality of life, and preventing long-term complications. Based on patient–provider shared decision-making, insulin pumps may be considered in all pediatric patients with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (66). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (141,151).

Insulin Pumps in Patients With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (152–156). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels are not consistently seen in individuals with type 2 diabetes when compared with MDI, although they have been in some studies (154,157). Use of insulin pumps in insulin-requiring patients with any type of diabetes may improve patient satisfaction and simplify therapy (130,152).

For patients judged to be clinically insulin deficient who are treated with an intensive insulin regimen, the presence or absence of measurable C-peptide levels does not correlate with response to

therapy (130). Another pump option in people with type 2 diabetes is a disposable patchlike device, which provides a continuous, subcutaneous infusion of rapid-acting insulin (basal) as well as 2-unit increments of bolus insulin at the press of a button (153,155,158). Use of an insulin pump as a means for insulin delivery is an individual choice for people with diabetes and should be considered an option in patients who are capable of safely using the device.

Combined Insulin Pump and Sensor Systems

Recommendations

- 7.23 Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and youth with diabetes to prevent/mitigate episodes of hypoglycemia. **B**
- 7.24 Automated insulin delivery systems may be considered in youth and adults with type 1 diabetes to improve glycemic control. **A**
- 7.25 Individual patients may be using systems not approved by the U.S. Food and Drug Administration, such as do-it-yourself closed-loop systems and others; providers cannot prescribe these systems but should provide safety information/troubleshooting/backup advice for the individual devices to enhance patient safety. **E**

Sensor-Augmented Pumps

Sensor-augmented pumps that suspend insulin when glucose is low or predicted to go low within the next 30 min have been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 patients with type 1 diabetes and documented nocturnal hypoglycemia showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (51). In a different sensor-augmented pump, predictive low glucose suspend reduced time spent with glucose > 70 mg/dL from 3.6% at baseline to 2.6% (3.2% with sensor-augmented pump therapy without predictive low glucose suspend) without rebound hyperglycemia during a 6-week randomized crossover trial (159). These devices may offer

the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. Additional studies have been performed, in adults and children, showing the benefits of this technology (160–162).

Automated Insulin Delivery Systems

Automated insulin delivery systems increase and decrease insulin delivery based on sensor-derived glucose level to begin to approximate physiologic insulin delivery. These systems consist of three components: an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery. With these systems, insulin delivery can not only be suspended but also increased or decreased based on sensor glucose values. While eventually insulin delivery in closed-loop systems may be truly automated, currently meals must be announced. A so-called hybrid approach, hybrid closed-loop, has been adopted in first-generation closed-loop systems and requires users to bolus for meals and snacks. Multiple studies, using a variety of systems with varying algorithms, pump, and sensors, have been performed in adults and children (163–173). Evidence suggests such systems may reduce A1C levels and improve time in range (174–178). They may lower the risk of exercise-related hypoglycemia (179) and may have psychosocial benefits (180–183). Use of these systems depends on patient preference and selection of patients (and/or caregivers) who are capable of safely and effectively using the devices.

Some people with type 1 diabetes have been using “do-it-yourself” (DIY) systems that combine a pump and an rtCGM with a controller and an algorithm designed to automate insulin delivery (184–187). These systems are not approved by the FDA, although there are efforts underway to obtain regulatory approval for them. The information on how to set up and manage these systems is freely available on the internet, and there are internet groups where people inform each other as to how to set up and use them. Although these systems cannot be prescribed by providers, it is important to keep patients safe if they are using these methods for automated insulin delivery. Part of this entails making sure people have a “backup plan” in case of pump failure. Additionally, in most DIY systems, insulin doses are adjusted based on the pump settings for basal rates,

carbohydrate ratios, correction doses, and insulin activity. Therefore, these settings can be evaluated and changed based on the patient’s insulin requirements.

Digital Health Technology

Recommendation

7.26 Systems that combine technology and online coaching can be beneficial in treating prediabetes and diabetes for some individuals. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, in part because it is both common and numeric, lends itself to the development of apps and online programs. The FDA approves and monitors clinically validated, digital, usually online, health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics or “digiceuticals” (188). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes.

An area of particular importance is that of online privacy and security. There are established cloud-based data collection programs, such as Tidepool, Glooko, and others, that have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can be useful for monitoring patients, both by the patients themselves as well as their health care team (189). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can control the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

There are many online programs that offer lifestyle counseling to aid with weight loss and increase physical activity (190). Many of these include a health coach and can create small groups of similar patients in social networks. There are programs that aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program

(191,192). Others assist in improving diabetes outcomes by remotely monitoring patient clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (193–198). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment programs, which vary in terms of their effectiveness (199,200). For many of these interventions, there are limited RCT data and long-term follow-up is lacking. But for an individual patient, opting into one of these programs can be helpful and, for many, is an attractive option.

Inpatient Care

Recommendation

7.27 Patients using diabetes devices should be allowed to use them in an inpatient setting when proper supervision is available. **E**

Patients who are comfortable using their diabetes devices, such as insulin pumps and sensors, should be given the chance to use them in an inpatient setting if they are competent to do so (201,202). Patients who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgeably than inpatient staff who do not personally know the patient or their management style. However, this should occur based on the hospital’s policies for diabetes management, and there should be supervision to be sure that the individual can adjust their insulin doses in a hospitalized setting where factors such as infection, certain medications, immobility, changes in diet, and other factors can impact insulin sensitivity and the response to insulin.

With the advent of the coronavirus disease 2019 pandemic, the FDA has allowed CGM use in the hospital for patient monitoring (203). This approach has been employed to reduce the use of personal protective equipment and more closely monitor patients, so that medical personnel do not have to go into a patient room solely for the purpose of measuring a glucose level. Studies are underway to assess the effectiveness of this approach, which may ultimately lead to the routine use of CGM for monitoring hospitalized patients (204,205).

The Future

The pace of development in diabetes technology is extremely rapid. New

approaches and tools are available each year. It is hard for research to keep up with these advances because by the time a study is completed, newer versions of the devices are already on the market. The most important component in all of these systems is the patient. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist the patient in device/program selection and to support its use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for treating diabetes, but the tools described in this section can make it easier to manage.

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ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies

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1 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Continuous subcutaneous insulin infusion (CSII) pump therapy can be used safely and effectively in youth with type 1 diabetes (T1D) to assist with achieving targeted glycemic control (B).
- Insulin pump therapy can assist with reducing episodes of hypoglycemia (B).
- Insulin pumps reduce chronic complications of T1D in youth, even when compared to those with similar hemoglobin A1c (HbA1c) levels on multiple daily injection (MDI) therapy (B).
- Insulin pump therapy is appropriate for youth with diabetes, regardless of age (B).
- Infusion set failures are common and must be recognized early so as to avoid episodes of diabetic ketoacidosis (DKA) (B).
- Real-time continuous glucose monitors (CGM) can be used effectively for lowering HbA1c, reaching target HbA1c, reducing glucose variability (both for insulin pumps and MDIs), and increasing time in range (TIR) in the pediatric population with T1D (A).
- Assessing clinically meaningful outcomes beyond HbA1c is possible through the use of CGM technologies to determine both glycemic variability and TIR, which encompasses time in target (often defined as 70–180 mg/dL [3.9–10.0 mmol/L]), as well as time spent hypoglycemic (level 1: <70–54 mg/dL [<3.9–3.0 mmol/L] and level 2: <54 mg/dL [<3.0 mmol/L]) and time spent with hyperglycemia (levels 1: >180 mg/dL [>10 mmol/L] and level 2: >250 mg/dL [>13.9 mmol/L]) (E).
- Real-time CGM can be used effectively for reducing mild to moderate hypoglycemia and shortening the time spent in hypoglycemia in the pediatric population with T1D (B).
- The effectiveness of CGM in children and adolescents with T1D is significantly related to the amount of sensor use (A).
- Intermittent, retrospective or real-time CGM use may be useful for diagnostic purposes and in evaluating the effects of major changes in treatment regimens (C).
- Use of intermittently scanned/viewed CGM (isCGM), also known as flash glucose monitoring, in the pediatric population is safe (C).
- Sensor augmented pump (SAP) therapy is superior in children and adolescents over MDI with self-monitoring of blood glucose (SMBG) in reduction of HbA1c without an increase in hypoglycemia or severe hypoglycemia (A). However, this benefit is mediated by adherence to sensor therapy, with at least 60% use being associated with these findings.
- Low glucose suspend (LGS) systems reduce the severity and duration of hypoglycemia while not leading to deterioration of glycemic control, as measured by HbA1c (A).

- Predictive low glucose suspend (PLGS) systems can prevent episodes of hypoglycemia and have been shown to reduce hypoglycemia exposure (B).
- Automated insulin delivery (closed loop) systems improve TIR, including minimizing hypoglycemia and hyperglycemia (A). Commercial availability of automated insulin delivery systems is currently limited, but patient access to these systems is anticipated to improve in the near future.
- Automated insulin delivery systems have proven to be especially beneficial in attaining targeted control in the overnight period (A).
- There exists a wide spectrum of cell phone apps to aid patients with diabetes. Use of evidence-based apps has shown glycemic benefit for adult patients with type 2, but not T1D (A).
- Bolus calculators, either on insulin pumps or as phone apps for MDI users, aid patients with diabetes in determining carbohydrate and correction dosing. Their use is associated with improved glycemic control in patients with T1D and should be encouraged for all patients (B).
- Automated algorithmic adjustment of open-loop pump settings and insulin dosing parameters is an emerging area of research and clinical care in diabetes technology (E). The first system for automated dosing adjustment with health care provider approval has just received regulatory approval.
- Routine downloading of diabetes devices (blood glucose monitors, pumps, or CGM) is associated with better glycemic control, though overall rates of patients downloading their devices are extremely low (C).
- Telemedicine, whereby patients or providers, receive care from a specialist remotely through video conferencing may assist with improving glycemic control and increase the frequency of visits for patients with diabetes living in remote or rural locations (C).
- Setting realistic expectations for the integration of diabetes technologies is paramount to the success of patients as they adopt new technologies (B).
- Identification and counseling of potential barriers to adoption of new technologies or continued use of devices is critical (B).

2 | INTRODUCTION

Numerous milestones mark the advance of diabetes care since the discovery of insulin in 1921. Glucose monitoring has progressed from urine to blood to interstitial fluid measurements every 5 to 15 minutes with continuous glucose monitors (CGM). Similarly, advances in insulin formulations and their delivery include rapid acting and basal insulins as well as insulin pumps to more effectively dose insulin.

While progress has been made in glycemic control, most youth with type 1 diabetes (T1D) do not meet ISPAD targets for hemoglobin A1c (HbA1c) based on data from international diabetes registries.^{1–5} Additionally, hypoglycemia and severe hypoglycemia continue to plague youth with T1D and prevent optimal glycemic control.^{2,6–8} Early advances in diabetes treatment may have inadvertently increased the burden of diabetes care, which for some people may impair quality of life and psychosocial health.^{9–12} Thus, a body of research has explored

how the burdens of these technologies can be offset by the benefits they may provide, determining how to set realistic expectations for what assistance new therapies may provide, and informing the development of the next generation of technologies to minimize the burden they may cause. Therefore, diabetes technology presents an opportunity to improve glycemic control by lowering HbA1c, reducing hypoglycemia, and lowering the burden of care for T1D on children, adolescents, young adults, and their families.¹³

Since the 2014 ISPAD guidelines, numerous advances have been made in diabetes technology. The purpose of this new chapter is to review evidence on diabetes technology in children, adolescents, and young adults and to provide practical advice and approaches on their use. Topics include: insulin pumps, CGM, sensor augmented pumps (SAP), closed loop systems, diabetes apps and automated decision support systems, downloading technologies, telehealth, quality of life issues related to diabetes technology, and a consideration of how to use these technologies in resource-limited situations.

3 | INSULIN PUMPS

3.1 | The dawn of technology use in diabetes care

The first application of technology to improve the care of those living with T1D can arguably be traced to the dawn of insulin pump therapy in the late 1970s.^{14–16} However, integration of continuous subcutaneous insulin infusion (CSII) pump therapy into the care of youth with T1D remained minimal until the turn of the century. Since then, a very consistent picture has emerged in the literature supporting the use of pump therapy for youth with T1D, namely mean HbA1c decreased 0.2% to 1.1%,^{17–30} clinically important hypoglycemia was reduced,^{17–22,25–31} and no significant increase in body mass index (BMI) z-score was recorded.^{17,19–30} These data held true regardless of whether the multiple daily injection (MDI) comparator group used Neutral Protamine Hagedorn (NPH)^{17–26,29,32} or glargine insulin.^{33–36} Randomized controlled trials (RCTs) assessing the use of insulin pumps have yielded conflicting results, with some showing improvement of glycemic control with use of the technology.^{33,34} Yet, the RCT studies that have not shown a lowering of HbA1c have highlighted the endorsement of pump therapy as patients randomized to the technology continued its use by the end of the study,^{37–39} had higher reports of treatment satisfaction,⁴⁰ and reported decreased diabetes-related worry.⁴¹ Interestingly, prospective examination of nearly 1000 patients either on pump or MDI therapy found that despite similar HbA1c levels attained, lower rates of retinopathy and peripheral nerve abnormality were noted in the insulin pump treated group.⁴² Furthermore, data from meta-analyses conducted by various groups have depicted similar findings with pump therapy. Namely, this mode of insulin delivery is associated with reductions in the mean HbA1c,^{43–45} lowering of the total daily insulin dose,^{43,44} and decreased rates of severe hypoglycemia.⁴⁵ A meta-analysis by Yeh et al found no difference between insulin pump therapy and MDI in regards to glycemic control attained or rates of severe hypoglycemia.⁴⁶ As these metanalyses are based on clinical trial data obtained prior to 2008, the pumps utilized are at least 10-years older than current technology available;

thus, lacking some more advanced features now available in the newer generation pumps. Additionally, integration of pump therapy into clinical practice may have had implicit issues, as clinicians' comfort in training patients and titrating doses with this "new" technology may have been limited.

With the wealth of participants included and the long-term follow-up they afford, registries provide means to assess real-world use of these technologies. Data from the US-based type 1 diabetes exchange (T1DX) registry focusing on children <6 years demonstrated lower HbA1c levels for those on pumps, with a tendency for lower HbA1c levels prior to pump initiation, suggesting selection of an ideal population for pump use may have occurred.⁴⁷ The SWEET (better control in Pediatric and Adolescent Diabetes: Working to create Centers of Reference) centers found that almost half of the 16 000 registry participants used pumps, and this technology was associated with lower HbA1c and daily insulin dose as compared to MDI.⁴⁸ In a cross-sectional comparison of three large, transatlantic registries, which included the US-based T1DX, the German/Austrian Prospective Diabetes Follow-up Registry (DPV), and the English/Welsh National Pediatric Diabetes Audit (NPDA), a pooled analysis of nearly 55 000 pediatric participants, pump use was associated with lower mean HbA1c (pump $8.0\% \pm 1.2\%$ vs injection: $8.5\% \pm 1.7\%$, $P < 0.001$).⁴⁹ DPV database analysis of almost 10 000 participants on pump therapy matched to those on injections therapy showed lower rates of severe hypoglycemia (pump: 9.55 vs injection: 13.97 per patient-years) and reduced frequency of diabetic ketoacidosis (DKA) (pump 3.64 vs 4.26 per 100patient-years), favoring pump use.⁷ While HbA1c levels were lower in the pump treated group (pump: 8.04% [95% confidence interval, CI]: 8.00–8.07) vs injection: 8.22% (95% CI 8.18 to 8.25), the clinical significance of this difference in glycemic control is unclear.⁷ Additionally, in an observational study of data on those with T1D in Nordic countries, using an insulin pump was associated with a decreased rate of severe hypoglycemia.⁵⁰ Thus, the benefits of pump use have now been echoed in various registry assessments.

3.2 | Advanced pump settings

More advanced features of pump therapy include the ability to set temporary basal rates and alter the pattern of bolus insulin delivery. Temporary basal rates allow for adjustments to the usually programmed basal rate: decreasing the delivery in the case of physical activity or increasing doses for situations like inter-current illness, which may be further exacerbated by steroid therapy as would be used for an asthma exacerbation.⁵¹ Similarly, different preprogrammed basal patterns can be utilized when days of differing insulin sensitivity are predictable, for example, during menstruation in women. Bolus doses of insulin can be delivered: (1) immediately, known as a standard or normal bolus, (2) slowly over a certain duration of time, deemed an extended or square bolus, or (3) a combination of the two, that is, a combo or dual wave bolus.⁵¹ Foods that are higher in fat may lead to the need for an extended or combo bolus as the rise in glucose following the meal will be delayed by the high fat content. Pumps reduce bolus insulin delivery based on the proportion of insulin that is still deemed "active" from the last bolus, which may

TABLE 1 Indications for use of insulin pumps in Pediatrics—adapted from Reference (52)

Conditions under which insulin pumps should be considered
• Recurrent severe hypoglycemia • Wide fluctuations in blood glucose levels regardless of A1c • Suboptimal diabetes control (ie, A1c exceeds target range for age) • Microvascular complications and/or risk factors for macrovascular complications • Good metabolic control but insulin regimen that compromises lifestyle
Circumstances in which insulin pumps may be beneficial
• Young children and especially infants and neonates • Children and adolescents with pronounced dawn phenomenon • Children with needle phobia • Pregnant adolescents, ideally preconception • Ketosis prone individuals • Competitive athletes

be a reason lower rates of severe hypoglycemia are appreciated for those on pump therapy.

3.3 | Spanning childhood: Incorporation of pump therapy regardless of age or disease duration

Consensus guidelines have been developed for use of pump therapy in youth with T1D, which, based on the indications, likely apply to every youngster living with T1D (Table 1).⁵² Recently, an ISPAD Clinical Practice Consensus Guideline has been released entitled "Managing Diabetes in Preschool Children," which states pump therapy is the recommended mode of insulin delivery for those under the age of 7 years.⁵³ In order to overcome the mechanical barrier dictated by the lowest basal and bolus delivery doses feasible with pump therapy, application of diluted insulin to the youngest population has offered the opportunity to more finely tune insulin delivery.^{54–57} While concern is sometimes expressed over how paid care providers will adopt this technology, a study by Weinzimer et al highlighted that children whose parents work outside of home tended to see the largest improvement in glycemic control with transition to pump therapy.³⁰

Immediate incorporation of pump therapy at the time of diagnosis has been shown to be successful in terms of glycemic control achieved.^{58–60} While a theory exists that achieving more targeted control shortly after diagnosis may help to preserve beta cell function, this finding has not been corroborated by these trials.^{60,61}

The long-term benefits of pump therapy have been depicted in some of the initial studies of this insulin delivery modality^{31,62} and more recently, continued improvement in glycemic control was seen over 7-years of treatment.⁶³ Furthermore, those with suboptimal control (HbA1c >8.5%) at pump initiation, were found to have persistent benefits even after 4 years of treatment and those on MDI therapy had higher rates of severe hypoglycemia and DKA.⁶³

3.4 | Barriers to adoption of pump therapy and predictors of success

Despite the literature supporting the benefits of pump therapy in the pediatric population, universal adoption of this technology has not occurred. A T1DX study reported pump use varied widely between centers and concluded health care provider preferences influence the proportion of patients using pumps in a given center, similar to a

Pediatric Diabetes Consortium (PDC) study reporting 18% to 59% use within the first year after diagnosis.^{47,64} In the PDC study, pump therapy was more common in those with private health insurance, non-Hispanic white race, annual family income over \$100 000, and a parent with a college education.⁶⁴ A more recent analysis has echoed these findings showing sociodemographic factors, namely, income and parental education, increased frequency of blood glucose monitoring, and CGM use were predictive of pump use.⁶⁵ The authors also highlight potential barriers to uptake of the technology, which include concerns regarding the physical footprint and interference of the device, therapeutic effectiveness of the technology, and to a lesser extent, financial burdens this mode of insulin delivery may cause.⁶⁵ In some countries, non-coverage of pump therapy by the health care/insurance system likely influences the low adoption rates of this technology.⁴⁹

Distinguishing what makes integration of pump therapy more successful could help guide clinical centers in assuring a smooth transition for patients. Having more preprogrammed basal rates has been found to correlate with more targeted control.⁶⁶ Others have determined that the total number of boluses delivered daily correlates with HbA1c achieved, more frequent bolusing being associated with more targeted control, and that basal insulin delivery <50% was also important.⁶⁷ In the adolescent population, increasing basal rates at the expected time of meals has been used to account for missed meal boluses; yet, if someone does not eat at one of these prespecified time periods they are at increased risk for hypoglycemia, which could be further exacerbated in the setting of an intercurrent illness.

3.5 | Frequency and causes of discontinuation of pump therapy

Generally, discontinuation of pump therapy is uncommon. The DPV registry over the period of 1995 to 2009 found attrition from this technology to be, in general, very low at 4%.⁶⁸ Adolescents aged 10 to 15 years had the highest rate of pump discontinuation, and those who discontinued were more likely to be female⁶⁸ with similar results from the T1DX registry.⁶⁹ Reasons for discontinuing pump therapy cited by participants included problems with wearability (57%), disliking the pump or feeling anxious (44%), and problems with glycemic control (30%).⁶⁹ Higher depressive symptoms, as captured by the Children's Depression Inventory, has also been reported in those who cease pump therapy.⁷⁰ From these findings, it appears targeting support to those who are in suboptimal control and/or exhibiting alterations in psychological well-being would be warranted.⁶⁹

3.6 | Complications of pump therapy: Infusion sets and hypertrophy

Data regarding adverse events, including pump malfunctions, infusion set failures, alarms, and other problems, associated with insulin pump use demonstrate that these issues are not uncommon-with reported frequencies of 40% to 68% of pump users experiencing such events.^{71,72} One of the major complications of pump therapy remains issues with infusions sets.^{71,73–75} Questions remain regarding whether steel cannulas or flexible Teflon are ideal and whether certain

infusions sets are better based on the age of the patient using the pump. The major concern is occlusion, whether it be full or partial, or dislodgement of the site thereby interrupting the rapid-acting analog being delivered subcutaneously and putting the patient at risk for developing ketoacidosis. Some have explored the use of a small dose of basal insulin, like glargine, to help minimize this complication.⁷⁶ Widespread adoption of this has not occurred, and many groups continue to explore how to develop improved infusion sets⁷⁷ or fault detection algorithms to advise a user of when insulin delivery may be interrupted.^{78,79}

Some studies have documented between a 2- and a 5-fold higher risk of DKA in those on pump therapy.^{80,81} Yet, a cornerstone to avoiding such increased rates of DKA is adequate education on the risk of DKA and how to manage persistent hyperglycemia in pump-treated patients. For those on pump therapy, the most common cause of DKA, per ISPAD Clinical Practice Consensus Guidelines on Diabetic Ketoacidosis and hyperglycemia hyperosmolar state, is failure to inject insulin, with either a syringe or pen, when hyperglycemia and hyperketonemia/ketonuria occur.⁸²

Lipohypertrophy, or local fat accumulation, at the site of insulin administration, is another issue that is frequently encountered with pump therapy.⁸³ Fat loss at the site of prior insulin infusion sites, lipatrophy, is less common and has been seen more frequently in those with multiple autoimmune diseases.⁸⁴ Both of these findings are categorized as lipodystrophy and earlier studies have shown a greater risk of these issues in those with higher insulin autoantibodies.⁸⁵ Lipodystrophy can impact how insulin is absorbed and thus lead to deterioration in glycemic control. Interestingly, use of lipohypertrophied tissues for placement of a CGM was found to not impact the sensor accuracy.⁸⁶ Thus, while resting the impacted tissue from continued insulin infusion, the hypertrophied space for diabetes-related devices may still be utilized for sensor placement.

3.7 | Practical considerations

When preparing to transition patients from MDI to insulin pump therapy, one of the first steps is to have the patient select the pump model they would like to utilize, if insurance coverage does not dictate the decision. To accomplish this, charts and literature describing the differences among the models is helpful, with the annual consumer guide published by Diabetes Forecast being an easily accessible, useful online reference (<http://www.diabetesforecast.org>). The selection of a pump should be based on features desired by the patient and their family with guidance provided by the multidisciplinary team members.

In determining initial pump settings, oftentimes the total daily insulin dose is used for initial calculations. Table 2 provides some suggestions to determine initial pump settings. Critical to success with the adoption of pump therapy is advising patients on risks of infusion set failure, which if unrecognized can lead to metabolic decompensation and potentially DKA.⁸⁷ A useful framework to review these issues and optimize the transition are presented by Diess et al.⁸⁸ As steel cannulas are less likely to kink or dislodge they may be the ideal infusion set for the youngest patients adopting pump therapy.

Introducing patients to advanced pump features should be done over time as they show proficiency with the basic skills for success with

TABLE 2 Basic guidelines for starting insulin pump therapy

Total daily dose (TDD) prior to pump initiation • May be used to determine initial pump settings • Consider reducing total daily dose in those at targeted glycemic control or patients with frequent or severe hypoglycemia. Proportion basal vs bolus insulin delivery • In older children and adolescents expect a 50/50 split • In children <7 years, basal insulin delivery may make up ~30% to 35% of the TDD⁵¹ Determination of basal rates • Take the amount to be delivered as basal (ie, 50% of the TDD) and divide by 24 for the number of hours in a day (if basal insulin per day will be 20 units then hourly rate would be set at 0.8 units/h) • Increases in basal rates in early morning hours are often needed in adolescents who experience the dawn phenomenon^{311,312} • Pre-school aged children may have higher basal insulin requirements between 9 PM and 12 AM and then lower basal rates during early morning hours³¹² Determination of correction factors/insulin sensitivity factors • If using a correction factor prior to transition to the pump, start with the usual factor. • Otherwise, a correction factor can be determined by dividing 1800 by the TDD if glucose readings are in mg/dL (or dividing 100 by the TDD if glucose readings are in mmol/L). Depending on insulin sensitivity, the 1800 rule can be adjusted upward (2000/TDD) for those who are insulin sensitive or downward (1500/TDD) for those who are more insulin resistant. Determination of insulin to carbohydrate ratios • If using a carbohydrate ratio prior to transition to the pump, start with the usual factor. • Otherwise, carbohydrate ratio can be determined by dividing 500 by the TDD • Young children may need more aggressive meal coverage^{313,314} and a 350 rule may be employed Close monitoring following initiation • Consider frequent blood glucose checks prior to and 2-hours postmeals to help inform insulin dose titrations • Consider overnight checks at midnight and 3 AM to assess overnight basal rates • CGM readings may be used in place of SMBG

Abbreviations: CGM, continuous glucose monitor; SMBG, self-monitoring of blood glucose.

the pump: changing the site every 3 days, bolusing for all carbohydrate intake prior to eating, and correction of hyperglycemia. Temporary basal rates, including complete suspension of basal insulin delivery, have been tested and shown to help mitigate hypoglycemia associated with exercise.⁸⁹ Incorporation of advanced boluses includes the use of an extended/square wave bolus, which administers insulin slowly over a certain duration of time or a combination/dual wave bolus, which administers some of the insulin immediately with another portion of that bolus extended over time and may be of benefit when consuming a high fat food. For the extended bolus, the user sets the duration of the extension; whereas, for combo boluses they not only choose the duration to extend but also the amount to be delivered upfront (eg, 40% of the bolus immediately and the remaining 60% over 4 hours-time).

By uploading pump data, clinic visits become more nuanced in regards to the alterations in the medical regimen that can be prescribed and the data download provides a portal by which clinicians can initiate a conversation on behavioral factors, including frequency of infusion set changes and timing of meal boluses.

4 | CONTINUOUS GLUCOSE MONITORS

Self-monitoring of capillary blood glucose (SMBG) is an essential tool in the optimal management of diabetes in children and adolescents

with T1D as established by the landmark Diabetes Control and Complications Trial (DCCT).⁹⁰ Early methods of measurement for SMBG relied upon reflectance assays coupled with oxidation of glucose allowing for a colorimetric readout; whereas more recent glucometers utilize a electrochemical assay that couples glucose oxidation to the generation of a current that is proportional to the glucose concentration. Prior to the advent of SMBG, patients with diabetes relied upon urinary glucose measurements, thus the ability to conduct a rapid, capillary assessment afforded by SMBG has been instrumental in achievement of target control. In fact, it has been well documented the frequency of SMBG correlates with improved HBA1c levels and reduced acute complications.^{91–93} SMBG should be prescribed at a frequency to optimize each child's diabetes control, usually six to ten times a day, though the actual number should be individualized.⁹⁴ However, SMBG has limitations: it only provides single snapshots of glucose concentrations. Consequently, episodes of hyper- and hypoglycemia, in particular nocturnal and asymptomatic episodes, as well as dynamics in blood glucose concentrations may be missed and not factored into treatment decisions.

CGM devices provide patients, caregivers, and health care professionals a broad spectrum of information on real-time glucose trends. Currently available CGM devices measure interstitial glucose concentrations subcutaneously at 5 to 15 minute intervals utilizing enzyme-tipped electrodes or fluorescence technology. When interpreting historic data on CGM use, it is critical to take the results in context of the older technology utilized, especially when considering the pediatric age group. Recent advances in these systems have led to improved system performance, accuracy, and user experience; thus, limiting extrapolation of studies conducted with first generation technologies.

4.1 | Categories of sensors

CGM can be divided into three categories: blinded/retrospective CGM, real time CGM, and intermittently scanned/viewed CGM (isCGM).

Blinded CGM is usually applied intermittently over a short period of time providing health care professionals with sufficient information on glucose excursions and patterns to aid with diagnosis, facilitate changes in therapy, and might serve as an educational tool to improve glycemic control.

Real-time CGMs utilize real-time alarms for thresholds and predictions of hypo- and hyperglycemia, as well as rate of change alarms for rapid glycemic excursion. In addition, new technological developments now enable some CGM sensors to transmit signals to the "cloud," and allow for digital remote monitoring, through which caregivers are able to view a patient's CGM tracing and receive alerts on their own devices, including smartphones, tablets, and smart watches.⁹⁵

Recently, introduced isCGM systems, also known as flash glucose monitoring (FreeStyle Libre, Abbott Diabetes Care, Alameda, California), do not automatically display glucose readings at regular intervals, but report glucose levels only when the user scans the sensor by holding a reader, or a cell phone, close to the sensor. Real-time interstitial glucose levels and glucose trend arrows as well as a graph of current and stored glucose readings are provided on demand. However, these systems do not alarm. While current CGMs for blinded and real-time

use still require calibration using fingerstick blood glucose monitoring results, isCGM systems are factory calibrated, thus eliminating the need for recalibration and increase ease of use and economic feasibility.⁹⁶

Most sensors are self-inserted transcutaneously, and have a life-time of 6 to 14 days. A new type of long-term implantable sensor for real-time use (Eversense, Senseonics Inc, Germantown, Maryland) is available as an alternative for transcutaneous CGM, with approval in Europe for up to 6-months use while in the United States up to 3-months of use has been approved.

4.2 | CGM use and uptake

The concept of interstitial continuous glucose monitoring has existed since the 1990s with the first system being released by Medtronic in 1999 (CGMS Gold; Medtronic, Inc., Northridge, California). A niche product in the past, CGM use has now become standard of care in many countries. Along with substantial advancement of CGM technology over the past 5 years, CGM uptake has increased as supported by data from big western diabetes registries. In 2012, an analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria showed that CGM was used in 4.8% of all patients and in 2.3% of all pediatric patients.⁹⁷ In 2014, the T1DX registry in the United States reported CGM was used by 6% of children <13 years, 4% of adolescents, and 6% of young adults aged 18 to 25 years.⁹⁸ Recent data from both registries suggests that overall CGM use is growing exponentially with usage in pediatric age groups reported at 18.4% (DPV) and 21.7% (T1D), respectively, with highest use among preschool-aged and early school-aged children (28.2% DPV; 44.5% T1DX).⁹⁹ Higher use in younger children might be due to better hypoglycemia detection even in children who are unable to express symptoms of hypoglycemia. Furthermore, these youngsters may benefit from reduced number of painful fingersticks and remote monitoring features of the latest system. Apart from technological advances and higher patient satisfaction, greater overall uptake might reflect changes in insurance coverage, provider beliefs, and CGM training practices.

4.3 | Efficacy of CGM

4.3.1 | Impact on metabolic control

Following its market launch, CGM was widely advocated as a great advance, despite limited accuracy, limited duration of use, and limited usability of early generation systems. However, early clinical studies and meta-analysis have demonstrated mixed results demonstrating only limited overall benefit of CGM, particularly in pediatric age groups with use of these early-generation systems.^{46,100–102} The Juvenile Diabetes Research Foundation (JDRF) landmark trial, performed in 2008, and its follow-up studies evaluated the benefit of third-generation CGM compared with SMBG for T1D management.^{103–106} In adults, CGM use for 26 weeks significantly reduced HbA1c by 0.5% without any increase in hypoglycemia. However, in the younger age groups (8–14 years and 14–25 years) there was no benefit in overall glycemic control associated with CGM use, likely related to <50% adherence in these groups. A secondary

analysis of the JDRF cohort demonstrated a benefit across all age groups when the sensor was used ≥ 6 days/week.¹⁰⁵ Furthermore, when restricting the analysis to those already in optimal glycemic control (HbA1c <7.0%), the same group showed that CGM is of benefit, in terms of sustaining HbA1c and reduction in hypoglycemia.¹⁰⁴

Studies and analyses conducted since 2010, utilizing fourth and fifth generation CGM systems, have more consistently shown that use of real-time CGM improves glycemic control in both children and adults with T1D in terms of improved HbA1c levels and reduced glucose variability.^{98,100,106–113} Clearly, the benefit of CGM is seen primarily in those patients with near daily use.^{100,106,111,114} However, evidence regarding positive impact of CGM on glycemic control in younger children is still limited. Although data from small observational studies suggest that CGM can be used successfully in patients <8 years,^{115,116} an RCT in children aged 4 to 9 years did not demonstrate improvements in glycemic control even over extended CGM use.¹¹⁷ In toddlers <4 years, there was no difference in HbA1c after 6 months of use; however, there was a high degree of parental satisfaction and sustained use of the devices.¹¹⁸

While earlier analysis and guidelines were favoring CGM use in combination with pump therapy,^{46,94,101,119} there is now emerging evidence that improvement in glycemic control is equivalent in users of insulin pump therapy and MDI therapy.^{112,120–122}

4.3.2 | Impact on hypoglycemia

RCTs evaluating the benefit of CGM mainly focused on HbA1c as the primary outcome. Apart from the SWITCH study showing a significant effect of adding CGM to insulin pump therapy on time spent in hypoglycemia,¹¹¹ most studies failed to demonstrate a significant, or relevant reduction, in mild hypoglycemia.^{103,107,117,123–127} Notably, RCTs primarily aimed at hypoglycemia prevention did demonstrate a significant reduction in mild hypoglycemia in terms of reducing the time spent in hypoglycemia by approximately 40%, and reducing the number of mild hypoglycemic events per day.^{104,110} Clear evidence on the positive impact of CGM on severe hypoglycemia is missing. Only one RCT reported a significant increase in severe hypoglycemic events using CGM as compared with SMBG.¹²⁴ Notably, one RCT in pediatric patients reported a significant decrease in severe hypoglycemia using CGM.¹²⁸ However, data from meta-analysis published in 2011 and 2012 suggest that there is no significant difference in incidence rates of severe hypoglycemia between CGM and SMBG; yet, this likely represented what was capable with older generation CGM systems.^{100,101} In adult patients with T1D and impaired hypoglycemia awareness, data from a recent RCT¹²⁹ and from an observational study¹³⁰ suggest reduced severe hypoglycemia using CGM compared with SMBG; thus, supporting the concept of using CGM in this high-risk population.

4.3.3 | Intermittent use of real-time and retrospective CGM

Although intermittent application of retrospective or real time CGM may be of use in children and adolescents with T1D to detect postprandial hyperglycemia, the dawn phenomenon, asymptomatic and nocturnal hypoglycemia, and in evaluating the effect of major changes

in treatment regimens,^{131–133} there are no data that support long-lasting clinical benefits of short-term applications of CGM.¹³⁴

4.4 | Accuracy of CGM

The accuracy and precision of first generation CGM systems were notably inferior to those of capillary blood glucose monitors. Over the past 5 years, however, there has been continuing improvement in the accuracy of CGM sensors. Overall accuracy of the latest sensor generations measured as the mean absolute relative difference (MARD) vs a given laboratory standard is in the 8% to 14% range,^{96,135–138} with some sensors reaching the proposed mark sufficient to permit self-adjustment of insulin dosage without confirmatory capillary blood glucose measurements (MARD, <10%).¹³⁹ Sensor accuracy depends on the glucose level and rate of change, with lower accuracy in the hypoglycemic range and at rapidly changing blood glucose (BG) concentrations.^{140,141} In the REPLACE BG study, Aleppo et al recently demonstrated that non-adjunctive use of CGM (ie, adjustment of insulin dosage without confirmatory capillary glucose measurement) is as safe and effective as using CGM and confirmatory blood glucose readings in adults with T1D.¹⁴²

4.5 | Non-adjunct use

Real-time CGM systems were originally approved for adjunctive use, meaning the sensor glucose results needed to be verified by capillary SMBG before taking action. The latest generation of Dexcom sensors (G5 and G6 Mobile CGM, Dexcom, San Diego, California) has received Food and Drug Administration (FDA) and CE approval for non-adjunct use in persons aged 2 years and older.¹⁴³ Outside the United States, FreeStyle Navigator II (Abbott Diabetes Care, Alameda, California) is approved for diabetes management including insulin dosing when glucose is not changing rapidly. The Abbott Libre Flash Glucose Monitor (Abbott Diabetes Care) is approved for treatment decisions if the person is not hypoglycemic, if glucose is not changing rapidly, and if symptoms are concordant with the system readings. Some have called into question whether this approval for non-adjunctive use of sensors was based on patient testimonials and not clinical evidence. It is noted that nearly 40 000 instances of device inaccuracy have been reported, with some leading to deleterious consequences including loss of consciousness, seizures, motor vehicle accidents, hospitalizations, intensive care unit stays, and deaths.¹⁴⁴ Yet, the presumption here is that the accuracy of blood glucose meters exceeds what is achieved by sensor therapy.¹⁴⁵ Ekhlaspour et al recently assessed 17 commercially available glucometers and found MARD to be quite variable, ranging from 5.6% to 20.8%.¹⁴⁶ Indeed, only one-third of the meters assessed met the latest International Organization for Standardization standard (IWO 15197-2013).¹⁴⁶ Furthermore, the T1DX REPLACE BG study provided evidence of the safety and effectiveness of non-adjunctive sensor use and registry data indicates only 26% of participants using CGM always verified the sensor glucose by performing SMBG.¹⁴² Practical guidelines for non-adjunctive use are being developed.^{147–154}

However, research and clinical experience on non-adjunctive use of CGM systems are limited in pediatric populations.¹⁵⁵

4.6 | Intermittently scanned/viewed CGM

Recently introduced isCGM systems are factory calibrated, small in size, light weight, have good user acceptance and satisfactory accuracy with an overall MARD of 11% to 14%.^{122,156,157} Outside of the United States, the device is approved for 2-week wear, as compared to the 10-day approval granted by the FDA. Results of a large multicenter RCT, known as IMPACT, demonstrated that use of a isCGM system statistically reduced the time adults with well controlled T1D spent in hypoglycemia, reduced glucose variability, and improved time in range (TIR) (3.9–10.0 mmol/L, 70 to 180 mg/dL) when compared to self-monitoring of blood glucose with capillary strips.^{122,158} Benefits were identical for users of MDI and insulin pump therapy. This is supported by a range of non-controlled observational studies highlighting the potential of isCGM technology to improve clinical outcomes including HbA1c in adults with diabetes.^{158–160} Limited evidence in terms of effectiveness of isCGM systems is available in the pediatric population. As of February 2018, this system is CE marked for use by adults and by children (age 4–17 years). The FDA has approved the device in those aged 18 and over, but has required a longer start-up time (12 vs 1 hour) and a shorter duration of use per sensor (10 vs 14 days). Differences in Consensus error grid accuracy have been noted on the first day as compared to other days of wear (zone A day 1 = 72.0% vs day 2 = 88.4%), which may have led to the decision for the longer duration prior to availability of sensor glucose data for the device in the United States.⁹⁶

4.7 | Implantable sensors

A new type of long-term implantable sensor (Eversense, Senseonics Inc, Germantown, Maryland) is available as an alternative for transcutaneous CGM. In Europe, this sensor has been approved for up to 6-months of wear, while in the United States it has been approved for up to 3-month duration. Safety and accuracy (MARD = 11.1%) of this implantable system was demonstrated in a prospective multicenter pivotal trial,¹³⁸ with a subsequent study demonstrating improved accuracy with a MARD of 8.8%.¹⁶¹ Implantable sensors may provide additional ease of use over standard transcutaneous CGM systems, since frequent sensor insertions through the skin are not needed. However, the need for implantation and removal through a minor in-clinic procedure by a trained health care professional is a significant limitation of the system, particularly in regards to its potential application in the pediatric population where there is no data available yet.

4.8 | Practical considerations

Success with CGM requires detailed education and training in diabetes management coupled with extensive training in the use of CGM and high level of contact during the first months of wear.^{151,155,162} Table 3 provides some components that should be considered as sensor therapy is initiated.

Educational materials should also be provided to teachers at school.¹⁶³ Written individualized health care plans should be provided and agreed upon between parents, school nurses, professional caregivers, teachers, and the child, when appropriate.¹⁶⁴ Decreased

TABLE 3 Basic guidelines for starting sensor therapy

Insertion and adherence - Time spent at initiation of sensor therapy to ensure adequate insertion technique will allow for easier incorporation of the device. - Use of supplementary adhesive products may be required. These include: - Wipes: skin tac IV prep, skin prep - Dressings and barriers: tegaderm, IV-3000, hypafix - External Wraps: Coban, PreWrap - Adhesive removers may be required to help remove the sensor. These may include specialized adhesive removers like unisolve or detachol, or products one may have at home, like baby oil. Calibration - For those sensors requiring calibrations, discussion of frequency of calibrations and ideal times to calibrate should be held. - Consider preemptive calibration schedule. If calibrations are required every 12 hours, encourage patients to calibrate three times a day (eg, prior to breakfast, dinner and bedtime) - Discuss calibrating when glucose is relatively stable (no arrows present, no rapid change on sensor glucose graph) Alerts and alarms - Consider leaving alerts off as patients initiate sensor therapy. This may help prevent alarm fatigue. - When incorporating alerts, personalize them and use wide thresholds at first (ie, 70-250 mg/dL [3.9-13.9 mmol/L]). These can be adjusted over time. - For those with recurrent hypoglycaemia, set low alert first. - For those with sub-optimal control, set high alert first. - In the beginning, do not employ rate of change or predictive alerts. Consider how these additional alerts may be actionable moments prior to incorporating them. This will help prevent alarm fatigue. Retrospective review - Encourage downloading, if this is required to review data. - Encourage retrospective review of data to help inform insulin dose titrations. Real-time data - As appropriate discuss, non-adjunctive use of sensor data - Consider recommendations on adjustments of insulin doses based on sensor glucose values. This may be based off of an individual's correction factor to guide alterations in insulin dosing¹⁵⁵

supervision during school days could be overcome by recently available remote monitoring capabilities of CGM systems and collaborative intensive diabetes management by parents and daytime care-collaborative givers.¹⁶⁵ Additional discussion of the psychosocial elements of CGM sharing are reviewed later, in this chapter.

CGM systems allow a wide variety of alert settings. Many people with diabetes are willing to accept the burden of alarms. However, many also experience alarm fatigue. Hence, when setting up alerts, it may be inappropriate to enable all of the alert types at once. Hirsch et al suggest initial threshold values of 70 and 250 mg/dL (3.9 and 13.9 mmol/L) and further suggest a stepwise introduction of alarms.^{166,167}

Barriers to long-term use of CGM sensors include sensor adhesiveness and skin irritation, particularly in young children where body surface is limited. Supplementary adhesive products (eg, liquid adhesives, adhesive wipes) and external wraps are recommended to help secure the sensor to the skin.¹⁶⁸ The number of reports about (severe) skin reactions to the sensor adhesives is quite limited, but might be under-reported.¹⁶⁹ Skin issues might become more prevalent due to longtime use of sensors and availability of devices with longer wear time. Transparent dressings, special tapes, and barriers could be used in case of allergic reaction to the sensor adhesive or skin irritation from the plastic or metal components of the sensor/transmitter unit. Additionally, regular site rotation to prevent rashes and dry skin due

to frequent application, and removal of sensor adhesives are recommended.¹⁶⁸ Adhesive remover could be used to make the sensor removal less traumatic for both the patient and the skin.¹⁶⁸

5 | SENSOR-AUGMENTED PUMP THERAPY

SAP therapy, defined as combination of the technologies described above (insulin pumps and CGM), represents the first step on the path toward an artificial pancreas.

5.1 | A single platform: The beginnings of SAP therapy

The first RCT comparing SAP to insulin pump therapy in those with T1D showed similar reductions in HbA1c after 6-months, but, this was associated with significantly increased hypoglycemia exposure in the insulin pump with SMBG group.¹²⁴ Reduction in HbA1c was recorded in those who had at least 60% sensor utilization.¹²⁴

The Sensor-Augmented Pump Therapy for A1c Reduction (STAR) 3 study randomized participants to either SAP or maintained them on MDI therapy with conventional SMBG checks for a 1-year study period and reported a greater reduction in HbA1c was associated with an increased frequency of sensor use. Children, defined as those ages 7 to 12, had a $\times 1.5$ higher use of sensors as compared to the adolescent cohort, who were 13 to 18 years old.¹⁷⁰ Those using SAP were more likely to attain the 2010 American Diabetes Association (ADA) age adjusted HbA1c targets, have decreased hyperglycemic exposure, and decreased glycemic variability.^{107,170} While rates of severe hypoglycemia and DKA did not differ among the treatment groups, frequency of these events was relatively low in the entire study cohort.

Glycemic variability, measured as sensor glucose SD and coefficient of variation (CV) in the STAR3 group was assessed.¹⁷¹ Those with HbA1c <8% in the SAP group were found to have lower sensor glucose SD and CV than those in the control group, suggesting that glycemic excursions may be reduced with use of this technology in an HbA1c independent manner.¹⁷¹ At the end of the year-long STAR3 trial, a 6-month continuation phase demonstrated that those participants (including children) initially randomized to SAP-maintained improvements in HbA1c levels at the 18-month mark and those who were in the control arm and crossed over to SAP also achieved significantly decreased HbA1c.^{109,171}

5.2 | Low glucose suspend systems: Reducing the severity and duration of hypoglycemia

With integration of CGM data and insulin pump delivery into one device, the next logical step is to alter insulin delivery based on sensor glucose readings. As fear of hypoglycemia may preclude patients and providers to attain targeted control and knowing that suspension of insulin is less "risky" than automating insulin delivery, investigation into low glucose suspend (LGS) systems began. Feasibility data on the efficacy and safety of LGS from early closed-loop studies demonstrated the ability of insulin suspension to mitigate the risk of hypoglycemia.^{172,173}

Current LGS systems interrupt insulin delivery for 2 hours when sensor glucose reaches a predefined low sensor threshold and automatically resumes insulin delivery regardless of current sensor glucose levels. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) in-clinic study demonstrated that the mean duration of hypoglycemia was shorter with LGS-On and the nadir glucose was slightly higher.¹⁷⁴

Next, the ASPIRE in home study reported a 37.5% reduction in the primary end-point—area under the curve (AUC) <3.9 mmol/L (<70 mg/dL) for nocturnal hypoglycemia—in the SAP with LGS vs SAP.^{174,175} More importantly, percentages of sensor readings <3.9 mmol/L (<70 mg/dL), <3.3 mmol/L (<60 mg/dL), and <2.8 mmol/L (<50 mg/dL) were all significantly reduced in the SAP with LGS as compared to SAP alone; yet, despite this reduction in hypoglycemia there was no deterioration in glycemic control as measured by HbA1c.¹⁷⁵ After 2-hours of nocturnal insulin suspensions, sensor glucose was 92.6 ± 40.7 mg/dL (5.1 ± 2.6 mmol/L) and 168.8 ± 64.6 mg/dL (9.4 ± 3.6 mmol/L) at 4 hours post-initiation of the suspension.¹⁷⁵

The benefits of a LGS system in those with proven impaired hypoglycemia awareness were shown by a reduction in combined severe (seizures/coma) and moderate hypoglycemia favoring the LGS vs pump with SMGB group.¹⁷⁶ There were 0 severe hypoglycemic events in the LGS arm vs 6 events in the pump with SMBG ($P = 0.02$) and significantly less percentage of time was spent in hypoglycemia, particularly during the night.¹⁷⁶

Observational studies have corroborated the results from the two RCTs described above. A pediatric observational study included 21 children and compared a 2-week run-in period where low sensor glucose alerts were set to sound at 75 mg/dL (4.2 mmol/L) to 6-weeks with the LGS feature on.¹⁷⁷ A full 2-hour suspend most often occurred during the night and AUC <70 mg/dL (<3.9 mmol/L) was significantly smaller during LGS-On vs LGS-Off.¹⁷⁷ Finally, an analysis of uploaded data from 935 patients providing 49 867 patient-days (with LGS used for 82%) was performed,¹⁷⁸ only 11% of the suspensions lasted for >115 minutes, with the mean sensor glucose during these episodes being 59 ± 12 mg/dL (3.3 ± 0.7 mmol/L) at LGS activation, 102 ± 53 mg/dL (5.7 ± 2.9 mmol/L) by the end of the LGS episode, and 150 ± 69 mg/dL (8.3 ± 3.8 mmol/L) 2 hours after insulin delivery resumed.^{177,178} This delayed rise in glucose despite resumption of insulin 2 hours prior represents the pharmacodynamic profile of current rapid acting insulin analogs, as peak insulin action is 1 to 3 hours after administration.¹⁷⁹

To address concerns of what could happen if insulin suspension occurred based off the readings of an inaccurate CGM, random 2-hour preprogrammed insulin suspensions were conducted overnight in a cohort of participants in their home setting as long as pre-bed blood glucose was <300 mg/dL (16.7 mmol/L) and blood beta-hydroxybutyrate (BHB) levels were <0.5 mmol/L.¹⁸⁰ A total of 118 suspend nights were compared to 131 non-suspend nights and showed the morning after suspensions, blood glucose was ~50 mg/dL (2.7 mmol/L) higher but there was no clinically meaningful difference in BHB levels.¹⁸⁰

5.3 | Mitigating hypoglycemia: The benefits of predictive low glucose suspend

Furthering the automation process, predictive low glucose suspend (PLGS) systems suspend insulin delivery in hopes of preventing hypoglycemia. In 45 participants between the ages of 15 and 45 years, the system reduced hypoglycemia exposure by 81% and time spent <60 mg/dL (<3.3 mmol/L) by 70%.¹⁸¹ The same system assessed in a pediatric cohort reduced median time <70 mg/dL (3.9 mmol/L), while not leading to a difference in BHB levels in the morning.¹⁸² The system was found equally efficacious in all groups.¹⁸³

The MiniMed 640G and 670G system (Medtronic, Northridge, California) provide the PLGS feature in clinical practice, which interrupts insulin delivery if the sensor glucose is predicted to reach 20 mg/dL (1.1 mmol/L) above the preset low glucose limit within 30-minutes and automatically resumes basal insulin delivery after recovery from hypoglycemia. An in-clinic assessment utilized basal rate increases to induce hypoglycemia with the system set at 65 mg/dL (3.6 mmol/L); hypoglycemia was avoided in 60% of the 69 experiments.¹⁸⁴ A RCT conducted in 100 children and adolescents with T1D demonstrated that use of the PLGS feature reduced the number of hypoglycemic events.¹⁸⁵ However, the authors note that use of the PLGS feature led to a concomitant rise in the time spent in the hyperglycemic range.¹⁸⁵ More recently, a 6-month multicenter RCT demonstrated the ability of this feature to reduce time spent with sensor glucose <63 mg/dL (<3.5 mmol/L), with no change in HbA1c level at the end of the study.¹⁸⁶ In a real-world assessment, initiation of the PLGS system while at camp was shown to be possible and there was persistence of sensor use, with 74% of the cohort at 3-months and 66% of the cohort achieving sensor wear at least 70% of the time.^{181,187} It was proposed that this continuation of sensor use was due both to adequate education at initiation of therapy as well as the benefits of PLGS feature.¹⁸⁷ More recently, Tandem received FDA approval of its PLGS system, the t:slimX2 insulin pump with Basal IQ Technology (Tandem, San Diego, California), which uses the Dexcom sensor. Supporting approval of this system, a RCT of 102 participants found that the PLGS system led to a 31% relative reduction overall in sensor time <70 mg/dL (<3.9 mmol/L) by 31%.¹⁸⁸

Highlighting the safety of a PLGS system, BHB levels were assessed on 1954 mornings, half of which occurred after an intervention night.¹⁸⁹ Frequency of BHB >0.6 mmol/L was not different between the two study conditions supporting the recommendation that assessing for ketones should not be different regardless of whether a patient is using a PLGS system.¹⁸⁹

5.4 | Practical considerations

Success with SAP, in many ways, hinges on integration and understanding of the system components, namely the CGM and pump. Scaramuzza et al have provided a framework by which to initiate PLGS in children.¹⁹⁰ Topics that should be considered when initiating these therapies may include expected frequency of sensor use, and how treatment may vary when breaks from sensor therapy may occur. This may be especially important in those utilizing systems that

suspend insulin delivery as behavioral changes may be needed to mitigate the risk of hypoglycemia when the system is not actively being used.

Discussion should be held regarding whether alarms should be set for when suspensions occur. Furthermore, patients are usually encouraged to allow LGS systems to work overnight, but should an alert occur while the patient is awake, they can consume carbohydrates. With a PLGS system, should a hypoglycemic event occur despite insulin suspension carbohydrate intake may need to be decreased as compared to usual treatment strategies to prevent rebound hyperglycemia. Analysis of downloads can assist decisions regarding frequency of suspending insulin and whether changes in insulin doses and treatment for low blood glucose values is required.

6 | CLOSED LOOP SYSTEMS

Automated insulin delivery systems consist of three components: an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery. These systems not only suspend insulin delivery, like the LGS and PLGS system discussed above, but also can increase insulin delivery based on sensor glucose values. Single hormone (insulin) and dual hormone systems, which consist of insulin and another hormone like glucagon or pramlintide, have been tested. Several automated insulin delivery platforms exist utilizing various combinations of insulin pumps, CGMs and algorithms. There are three core algorithm constructs: (1) proportional integrative derivative (PID),¹⁹¹ (2) model predictive control (MPC)¹⁹² and (3) fuzzy logic.¹⁹³

6.1 | Adopting a hybrid approach

Early, fully closed loop studies found significant postprandial glycemic excursions compared to a premeal bolus¹⁹⁴ due to the delay of insulin absorption and the delayed onset of action of currently available rapid acting insulin analogs. Now, the majority of automated insulin delivery systems use a “hybrid” approach, where background (or basal) insulin is controlled by the algorithm, but the user needs to manually announce meals with carbohydrate estimation combined with capillary glucose level and deliver an insulin bolus. Nevertheless, the technical evolution in automated insulin delivery systems has been rapid, from proof of concept experiments published in 2006¹⁹⁵ to the first commercial release of a single hormone hybrid system (Minimed Medtronic 670G, approved in the United States only, for those aged 14 years and over in 2016, and by 2018 it has received CE mark and FDA clearance for those 7 years and older), taking just over a decade to see this technology available in clinical care.

6.2 | Controlled studies: From the clinic to transitional settings of camps and hotels

Early studies focused on demonstrating feasibility of automated insulin delivery in carefully controlled in-clinic studies, and were conducted in a range of patients including children,^{196,197} adolescents,^{196–204} adults,^{197,199,201,203–211} and in pregnant women.²¹² These included single hormone,^{196,197,200–202,206,207} dual

hormone systems,^{198,199,205,208,209} and the incorporation of insulin absorption adjuncts.^{203,204,210,211} In-clinic studies that simulated hypothetical real world challenges including exercise,^{209,213–215} alcohol,²⁰⁶ high fat meals,²⁰⁶ and inaccurate continuous glucose sensors²¹³ followed, and demonstrated that the automated insulin delivery systems remained safe and effective. Accordingly, closely supervised outpatient studies at diabetes camps for children and adolescents,^{55,216–222} and hotel studies for adults^{223–226} were conducted. All studies consistently showed safety and a 10% to 20% improved time spent in target glucose sensor range of 70 to 180 mg/dL (3.9–10 mmol/L) with a concomitant reduction in time spent hypoglycemic, in comparison to either conventional insulin pump therapy, or SAP therapy.

6.3 | Free living assessments of automated insulin delivery

“Free-living” outpatient studies, despite heterogeneous design and a range of different automated insulin delivery systems, have invariably demonstrated safety and efficacy. Very young children,²²⁷ adolescents,^{228–237} adolescents with sub-optimal control,²³⁸ and adults^{79,228–230,232–234,236,237,239–245} all demonstrated a 10% to 20% improvement in TIR compared to insulin pumps, SAP or SAP + LGS, and less time spent with hypoglycemia. Some studies used automated insulin delivery overnight only,^{228,230–234,236,237,239,243,245} while others applied automated insulin delivery for 24 hours a day.^{79,227,229,235,237–240,242,244} In the 24-hour use studies, the improvement in overall time spent in range is mainly due to improved overnight glucose levels. In a meta-analysis that included free living, camp and hotel studies, time in target range of 70 to 180 mg/dL (3.9–10 mmol/L) improved by 12.59% using automated insulin delivery compared to insulin pumps or SAP.²⁴⁶ There have been no reports of severe hypoglycemia or DKA during the use of automated insulin delivery.

The longest outpatient RCT published to date by Thabit et al compared a model-predictive-control automated insulin delivery device to SAP for 12 weeks.²³⁷ There were two sub studies included; (1) a cohort of 33 adult participants who used the system 24 hours per day, and (2) a child and adolescent study (n = 25) who used the system only overnight. Adults improved time in target range (3.9–10 mmol/L) by 11%, and the children and adolescents improved overnight glucose time in target range 70 to 145 mg/dL (3.9–8 mmol/L) by 24.7%.²³⁷ A 3 month non-controlled trial using the only commercially available automated insulin delivery system (Minimed Medtronic 670G) (n = 124) demonstrated safety,²⁴⁷ and improved HbA1c in adults (7.3% ± 0.9% to 6.8% ± 0.6%) and adolescents (7.7% ± 0.8% to 7.1% ± 0.6%).¹³⁷ Recently, data on the use of the same system in 105 participants aged 7 to 13 years demonstrated a reduction in HbA1c (7.9%–7.5%, P < 0.001) and an increase in time in target range by ~9%.²⁴⁸ The system has now obtained CE Mark and FDA approval for patients aged 7 and up.

Use of automated insulin delivery systems have been shown to reduce nocturnal hypoglycemia following physical activity occurring in the afternoon²¹⁵ and increase TIR as compared to open-loop therapy.^{222,249} Yet, the ability to mitigate hypoglycemia during exercise

has remained elusive leading to the development of different system announcements, incorporation of heart rate data, dual hormone approaches, and intake of carbohydrates being applied to overcome this obstacle.^{214,250–253}

High user acceptability and improved measures of treatment satisfaction have been shown.^{254–257} However, it should be noted that device alerts and alarms and technical difficulties can negatively affect the overall experience using automated insulin delivery.²⁵⁶

6.4 | Practical considerations

As the first commercially available hybrid closed loop system penetrates the market, clinicians will need to be prepared to assist their patients in adopting this technology. Furthermore, it is expected that in the coming years a number of other companies and academic groups will see regulatory approval of their first-generation systems as their pivotal trials are planned. To ensure success with adoption of this technology, it will be important for clinicians to have a framework to integrate this technology. Use of the acronym CARE, has been suggested as a strategy to help clinicians conceptualize the differences between automated insulin delivery systems.²⁵⁸ This acronym can assist clinicians in answering four fundamental questions related to the patient and device, and include:

- Calculate: How does the system CALCULATE insulin delivery?
- Adjust: How to ADJUST insulin doses—immediately and long term?
- Revert: When to stop automated insulin delivery and REVERT to pump settings; also, when the system automatically REVERTS to pump mode?
- Educate: Where does the user/provider find EDUCATION resources?

It will also be important to reinforce with patients the tasks that will be necessary to utilize automated insulin delivery, which at least will include having a functional CGM and use of a pump, as well as bolusing for carbohydrate intake when using a hybrid closed loop system. Indeed, for many patients currently struggling with diabetes management, education on these foundational skills will be critical to ensure they are afforded equal access to these systems while setting the stage for success. Finally, reviewing with patients how to treat both hyper and hypoglycemia will be important. Carbohydrate intake required for hypoglycemia may need to be reduced with prolonged basal insulin suspension. Conversely, patients will need to be reminded about the risk of infusion set failures that may lead to persistent hyperglycemia and the potential for ketosis. While automated insulin delivery holds the promise of reducing glycemic variability, it will be critical to discuss realistic expectations as patients adopt these technologies to help mitigate the frustration they may feel as early systems will likely require user input and not be a set and forget device. Moreover, how best to expand access to these systems is a top priority that will require exploration of both the economic as well as educational challenges that remain.

7 | DIABETES APPS, AUTOMATED DECISION SUPPORT, AND BOLUS CALCULATORS

7.1 | Diabetes applications

Patients with T1D who are on MDI therapy may seek to obtain some of the benefits of the calculators and bolus wizards of an insulin pump via use of a cell phone based mobile application “app” on their smart phone. In addition, patients on pumps and/or CGM may seek to gather all of their data in one place and receive advice on bolusing, carbohydrate amounts, or device tuning. Apps cover a broad spectrum of self-management activities from simple blood glucose logs and dosing reminders,^{259,260} to carbohydrate counting and bolus calculators²⁶¹; also reaching into the realm of providing incentives to bolus and peer support.²⁶² The challenge for many patients, however, is that there are over 165 000 general health-related apps which may aid in assessment of diet and physical activity, and over 1100 diabetes-specific apps from which to choose.²⁶³ With this wide variety and rapidly changing landscape, little guidance is available to patients on what app may be right for them. Similarly, physicians and educators may find it difficult to be aware of the spectrum of options for their patients. Most available apps are not evidence based,²⁶⁴ and one study concluded that few are informed by either users or professionals during their development.²⁶⁵ A recent cross-sectional survey by Trawley et al investigated demographic, clinical, and psychological variables associated with app use.²⁶³ They found that in Australia, 21% of adolescents reported using an app for diabetes management with 89% of those using it for carbohydrate counting assistance.²⁶³ App usage was associated with shorter duration of T1D, higher socioeconomic status, and more frequent blood sugar testing. Barriers to app use were identified as lack of awareness of suitable products and the belief that the app would not provide benefit.²⁶³

Providing evidence-based recommendations on diabetes apps has been similarly difficult. In 2016, Hou et al conducted a review and meta-analysis of 14 randomized trials on apps and their impact on HbA1c identifying 1360 participants in 14 studies.²⁶⁶ They found that for patients with type 2 diabetes (T2D), there was a significant overall improvement in HbA1c of -0.49 (-0.68 , -0.30)% in the app-use groups compared to the control groups.²⁶⁶ For patients with T1D, however, there was no significant improvement in HbA1c -0.36 (-0.87 , 0.14)%.²⁶⁶ Another review from 2017 by Wu et al attempted to identify functions of apps associated with glycemic efficacy.²⁶⁷ They identified 974 participants across 12 trials, with some trial overlap with the Hou review. They similarly identified significant HbA1c improvement in patients with T2D with HbA1c reduction of -0.52 (-0.85 , -0.18), without significant improvement in patients with T1D.²⁶⁷ App characteristics associated with greater HbA1c improvement included having a complication prevention module and having a structured display. They did not find having a clinical decision-making function to be associated with HbA1c reduction.²⁶⁷

Table 4 provides a good starting point for app recommendation as of this writing in 2018. Some apps such as Calorie King and My Fitness Pal are general health apps that provide information beneficial to patients with T1D. These apps may assist patients with carbohydrate

TABLE 4 Diabetes apps, automated decision support, bolus calculators, and downloading software

App	Category	Website	Phones Supported	Cost	BG Meter Integration	Pump and/or CGM Integration	Decision Support	Evidence Based Research
Bant	Diabetes	www.bantapp.com	iPhone and Android	Free	None	None	No	Yes
Calorie King	General health	www.calorieking.com	iPhone and Android	Free	N/A	N/A	N/A	No
Glooko/Diasend	Diabetes	https://glooko.com	iPhone and Android	\$\$ Subscription	Over 60 BGM's digitally uploadable	Animas, Dexcom G4 or G5, Omnipod, Medtronic, Tandem	No	Yes, FDA cleared, HIPAA compliant
My Fitness Pal	General health	www.myfitnesspal.com	iPhone and Android	Free for Basic \$\$ for Pro	N/A	N/A	No	No
mySugr	Diabetes	https://mysugr.com	iPhone and Android	Free for Basic \$\$ for Pro	Any BGM via photo of number	FreeStyle Libre or Medtronic CGM	In Pro version (EU only)	Yes
One Drop	Diabetes	onedrop.today	iPhone and Android	\$\$ Subscription	Via One Drop BGM, other BGM via Apple Health	Dexcom integration via Apple Health	Via coaching subscription	Yes
Sugar.IQ	Diabetes	none	iPhone	Free for Medtronic users	Via Medtronic Pump	Medtronic pump and CGM	Yes	Yes, FDA Approved
Tidepool	Diabetes	https://tidepool.org	iPhone and Android	Free for user version	Bayer, Abbott, and OneTouch	Animas, Dexcom G4 or G5, Omnipod, Medtronic, Tandem	No	Yes

Abbreviation: BG, blood glucose; BGM, blood glucose meter; CGM, continuous glucose monitor; FDA, Food and Drug Administration; HIPAA, health insurance portability and accountability act; N/A is not applicable.

counting as well as exercise tracking. More diabetes-specific apps such as Bant, Glooko, mySugr, One Drop, and Tidepool enable patients to maintain a digital diabetes log on their phone, often interacting directly or indirectly with their BGM, some even assist with carbohydrate counting and insulin bolus calculations. Indeed, the DREAMED Advisor Pro, which analyzes the volumes of data that fill each patient's life including insulin dosing, blood glucose readings, and other factors such as carbohydrate intake and then suggests alterations in insulin dosing, has recently received regulatory approval in Europe and is currently under review by the FDA. Additionally, the Sugar.IQ diabetes assistant (Medtronic, Inc., Northridge, California) allows those wearing the Guardian 3 sensor to be alerted to patterns in their CGM tracings, which may lead to investigation of whether behavioral changes or insulin dose adjustments would be warranted. For patients on CGM or insulin pumps these apps may allow uploading of their device data to be reviewed by their diabetes health care team.

7.2 | Bolus calculators

Despite advances in other areas of technology, accurately counting carbohydrates and bolusing based on an insulin to carbohydrate (I:C) ratio prior to meals will remain a key to optimal diabetes therapy for the near future. The need to perform calculations for the I:C may also be complicated for some patients and is prone to simple human error. Insulin pumps have long offered bolus calculators which handle the I:C and correction factor calculations and account for active insulin on board (IOB), generally resulting in a positive impact on glycemic control.²⁶⁸ Similar bolus calculators are now available on some commercial blood glucose meters or as cell phone apps.^{269,270} The Automated Bolus Advisor Control and Usability Study (ABACUS) showed that significantly more patients using the bolus calculator achieved an HbA1c reduction of >0.5% compared to the control group (56% vs 34%; $P < 0.01$).²⁷¹ A recent study showed a significant increase in the number of patients achieving HbA1c targets and a reduction in hypoglycemia in the bolus calculator use group compared to the active control group.^{272,273} In patients on insulin pump therapy, the rate of bolus calculator use has been correlated with improved glycemic control in both the adult and pediatric populations.^{268,274,275} Overall, these studies show that for MDI and conventional insulin pump patients, use of a bolus calculator reduces burden, improves glycemic control, and improves quality of life.

7.3 | Automated decision support systems

Beyond the simple arithmetic of calculating insulin dosing for meals is the more complex tuning of insulin dosing parameters. To better aid patients with insulin dosing adjustments between visits, multiple groups are developing automated decision support systems that may be used to algorithmically optimize dosing recommendations. Such adjustments may be beneficial for patients on MDI therapy, conventional pump therapy, and may even help tune emerging artificial pancreas systems. Wang et al conducted a pilot study assessing a learning-type artificial pancreas, which showed significant improvement in the time spent in target range with use of this learning system

vs open loop control ($P = 0.02$).²⁷⁶ Dassau et al conducted a randomized crossover trial where algorithmic adjustment of open-loop settings was conducted prior to artificial pancreas (AP) control and was compared to AP control without algorithmic adjustment, similar TIR was noted between the two groups.²⁷⁷ Recently, DreaMed Diabetes obtained CE Mark clearance and FDA approval for its Advisor Pro (DreamMed Diabetes LTD, Petach Tikva, Israel) which is a decision support tool that aggregates and analyzes data from patient downloads and provides dose adjustment recommendations, which must be signed off by a health care provider prior to distribution. Further work in this area is ongoing with extension to the MDI population in several studies that are ongoing in 2018.

8 | DOWNLOADING TECHNOLOGIES

Insulin pumps, CGMs, and most blood glucose meters have the ability to be downloaded onto either the manufacturer's platform or a uniform secondary service. Downloading of device data enables patients and their caregivers to visualize graphics, see summary statistics and review trends in glycemic data. It also enables clinicians and diabetes educators to review such data remotely between visits and make more frequent dosing adjustments. Wong et al found that routinely downloading and reviewing glycemic data was associated with a significantly lower HbA1c ($7.2\% \pm 1.0\%$ vs $8.1\% \pm 1.6\%$; $P = 0.03$).²⁷⁸ Despite this positive association, they showed that only 31% of adults and 56% of caregivers reported ever downloading data from devices, and even fewer routinely reviewed the downloaded data.²⁷⁸ In a commentary to this article, Beck presented previously unpublished data from the T1DX showing that participants reported rarely or never downloading their devices for BGM (75%), CGM (51%), and insulin pumps (59%).²⁷⁹ To date, there have been no published reports investigating barriers to device downloading, but anecdotal experience suggests that patients have difficulty with the downloading software, do not remember their log in information, do not have the necessary cables, and may not find the downloaded information to be directly beneficial to them. More patient centered platforms such as Glooko/Diasend, Tidepool, and One Drop seek to bridge this divide and empower patients to download and visualize their own data via improved connectivity and user interfaces. In addition, many device manufacturers are working towards perpetually connected devices which utilize cell phone and Wi-Fi connectivity to continually download data; thus, relieving the burden of periodic downloading placed on patients. These efforts may reduce or eliminate user burden associated with device downloads in the future, though review of the data by the patient, or their care provider, will still be necessary for optimal benefit to be seen.

9 | TELEHEALTH

As the vast majority of youth fail to meet glycemic targets, consideration needs to be given to alternative care models to help improve care. Telemedicine is a practice by which video conferencing is utilized to deliver health care to patients in their local region. Telemedicine

has a particularly valuable role in allowing specialized tertiary centers to reach out to patients and health care professionals in rural or remote locations.^{280,281} Typically, video tele-consultation is operated in real-time providing a virtual face-to-face meeting online with a specialized provider. The clinician has access to the patient medical record and provides oral and written advice to the patient. Various consultation models are used, including the patient situated in a primary care medical facility, with or without a trained health worker alongside them, or with consultations provided directly to the patient in his/her home.

9.1 | Telemedicine advantages and limitations

ISPAD guidelines recommend that all patients with T1D have their care reviewed every 3 months.²⁸² The greatest advantage of telemedicine is the ability to provide access to specialized care in remote locations. Reduction in traveling costs and saved working days for parents and school days for children may overcome some of the barriers to adhering to the frequency of follow-up recommended. One method that has been employed previously is having a clinician travel to more remote locations to see patients; yet, in assessing the efficiency of such satellite clinics one would need to consider the travel time and travel cost to the clinician. Thus, telemedicine has the benefit of delivering specialized care while reducing costs of travel to both patients and clinicians, and potentially increasing the likelihood of follow-up visits being completed.

However, telemedicine is limited by access to the required technology at the remote site. Additionally, concerns exist regarding reimbursement for the visits and whether one must hold a license in the location where they practice as well as the location where the patients are being seen. Further, the remote site (either the home, or primary care facility) must have the ability to download glucometers and insulin pumps, when applicable, in order for the specialized team to review clinical data that informs decisions. Body language might be more demonstrative than verbal language and these physical cues may be missed in a teleconference. Additionally, unless the visit is conducted in a medical facility it may not be possible to conduct some recommended components of these quarterly visits including anthropomorphic measures, pubertal staging, and assessment of general health. In a survey of health care providers, the biggest concerns reported in a qualitative assessment of telemedicine were problems with the technology components and a concern about the lack of physical contact with patients.²⁸³ Finally, specifically with respect to adolescents with T1D, discussions regarding risk taking behavior and psychological aspects may be limited due to the challenge of creating a confidential consultation environment. Therefore, consideration should be given to conduct face to face consultations with a specialized service at least annually.

9.2 | Data on telemedicine application to those with diabetes

Data on the use of telehealth in patients with diabetes is encouraging. Telemedicine To Reach, Education, Access, and Treatment is a program that included adults with diabetes residing in rural communities,

which found participants were generally satisfied with this mode of care delivery, had improvement in HbA1c values, and a better understanding of diabetes.²⁸⁴

Assessment on the application of telemedicine in Denmark has been conducted over a 7-year period in those with both T2D and T1D.²⁸⁵ The program has shown good results in diabetes treatment parameters and has been associated with improved cost-effectiveness and patient satisfaction.²⁸⁵

The telemedicine intervention of the Informatics for Diabetes Education and Telemedicine project, offered in-home telemedicine visits with a diabetes educator for elderly rural adults with diabetes. While some noted difficulties related to the use of the computer,²⁸⁶ telemedicine resulted in net improvements in self-management, glyce-mic control, low density lipoprotein (LDL)-cholesterol and blood pressure levels over 1 year,²⁸⁷ and over 5 years of follow-up in an ethnically diverse, elderly, rural population.²⁸⁸

A retrospective analysis of US Army soldiers with T1D who used telemedicine as their mode of care delivery documented clear success based on glycemic parameters with A1c levels trending to targeted control (baseline A1c 9.8%, 3-month 7.3% and end of study 6.9%)²⁸⁹ Use of telemedicine over a 1-year period in a pediatric diabetes clinic has also been conducted at the Barbara Davis Center, which has a large catchment area including neighboring states. While telemedicine resulted in no alteration in HbA1c levels, frequency of annual visits was increased, the frequency of missed school/work was reduced and financial burdens were decreased.²⁹⁰ As there is a tendency for deterioration of glycemic control during adolescence, likely secondary to the increased insulin resistance associated with puberty,²⁹¹ this lack of rise in HbA1c levels is quite compelling. Others have corroborated these findings through their use of telemedicine in rural areas.²⁹²

Telemedicine can also be applied in the school setting. A study run with children 5 to 14 years old showed the benefits of once a month telemedicine communication between the school nurse and the diabetes team in addition to the regular care. Children in the telemedicine group had lower HbA1c, improvements in the Pediatric Diabetes Quality of Life questionnaire, and fewer hospitalizations/emergency department visits.²⁹³

Building on the traditional telemedicine model, Project ECHO (Extension for Community Healthcare Outcomes) employs primary care clinicians who receive “telementoring” from a specialist to guide the management of their own patients with complex medical conditions.²⁹⁴ Ongoing assessment of this model is being conducted in those with diabetes, with the primary clinician working in consort with a multi-disciplinary team, with longitudinal assessment of this approach planned.²⁹⁴

9.3 | Adoption of telemedicine into clinical practice

Telemedicine has the potential to help reduce disparities in diabetes management especially in remote regions, by improving access to care and reducing health care costs as demonstrated in this study of older adults.²⁹⁵ While a recent meta-analysis found a mean reduction in HbA1c of 0.18% with use of telemedicine, given the paucity of data available and heterogeneity of the studies included in the analysis, the findings are limited.²⁹⁶ When impact of telemedicine was investigated

by subpopulation, its use was noted to be successful in adolescents with a mean difference in HbA1c of -0.32% between groups.²⁹⁶ Importantly, those studies with longer duration (>6 months) and those that recruited individuals with higher baseline HbA1c values ($\geq 9\%$) demonstrated greater benefit.²⁹⁶ Thus, a cautious optimism can be used when considering application of this technology in the future.

The immediate cost of implementing telemedicine can be high.²⁹⁷ However, today, less costly smartphones, iPads, and laptop devices are widely available and there are other less well-defined economic benefits due to a positive impact on either the health care system and/or business productivity.

For pediatric patients, one must consider a few important factors in the integration of telemedicine into clinical care. First and foremost, at diabetes onset the initial management and education should be given in person by a multi-disciplinary diabetes team staffed by sub-specialists. In regions with established telemedicine programs, the follow-up appointments could alternate between on-site and remote consultations, as body weight and pubertal staging are important factors to consider when adjusting insulin therapy and provides the opportunity to assess any deviations in normal growth and development.^{298,299} Taking into account the few, encouraging available studies and the comfort level of both the adolescent age group and parents, there is hope that telemedicine could become an option, interspersed with face-to-face visits for children and adolescents from underserved locations.

9.4 | Limited resource settings

Provider availability is critical in improving health care accessibility.²⁸¹ In underserved, undeveloped regions, the first step is to train local health workers to improve diabetes diagnosis and early management. The second step is to encourage health policies, philanthropic organizations and industry to focus on increasing access to insulin, glucose test strips and diabetes education, since advice may be useless if patients do not have the basic supplies need to comply with medical advice. As a third step, telemedicine might be developed to deliver specialized advice in regions with limited access or care.^{287,288,295,297} Nevertheless, electricity, internet and technological devices may not be available in some rural underdeveloped areas where remote consultation may be a challenging goal to achieve.³⁰⁰

10 | QUALITY OF LIFE/PATIENT SATISFACTION/BURDEN WITH USE OF TECHNOLOGIES

Uptake and use of diabetes devices and technologies are associated with psychosocial and family factors. Psychosocial factors are broadly defined as behavioral, emotional, and social variables that characterize an individual across both dimensions of promoting health (eg, resilience) and having negative effects on health (eg, depression). The focus on psychosocial factors in relation to diabetes device and technology use has grown out of the broader interest in understanding how these factors impact diabetes management and health outcomes. For example, it is well established that personal strength and resilience

factors, along with positive family communication, are associated with optimal management and outcomes.^{301,302} Likewise, psychosocial factors such as diabetes distress and depression and family conflict are common in youth with diabetes and often lead to suboptimal management and outcomes.^{303,304} Herein, the current understanding of the association between psychosocial factors and device and technology use will be highlighted.

Prior ISPAD guidelines on the psychosocial care of youth and the recently released American Diabetes Association guidelines for the psychosocial care of people with diabetes¹⁰ highlight that attending to the psychosocial needs of all youth and their families is critical. Similarly, when considering whether diabetes devices and technologies should be recommended or encouraged, understanding the psychosocial aspects of the user and family will help optimize a good fit for the device. The most evidence is available for insulin pumps and CGM. Notably, youth on insulin pumps tend to experience a benefit in health-related quality of life,^{221–223} but factors such as depression lead to discontinuation of insulin pump use.⁷⁰ As noted previously, CGM is linked to optimal glycemic outcomes and many users report greater treatment satisfaction.²²⁵ However, there are reports of heightened worries³⁰⁵ among adolescents and young adults and many discontinue CGM for a variety of reasons including cost, too many alarms, issues with accuracy, and discomfort wearing a device on one's body.¹² Thus, setting realistic expectations for potential users and their families and providing referrals for any psychosocial need that may serve as a barrier to optimal use, are indicated. In addition, the following recommendations are made when considering device and technology use in diabetes care practices:

- Portray the use of diabetes devices and technologies as an option that can be a good fit for many youth and families; provide education and encourage youth and families to review vetted websites and device informational materials.
- Encourage uptake and refrain from having youth and families “earn” the right to use devices (ie, achieve a certain hemoglobin HbA1c before considering starting a device). If payers/insurance companies require logging or other documentation prior to device approval, convey that directly instead of a requirement of the diabetes care practice.
- Conduct a brief assessment of barriers to uptake and use. Common barriers are cost (often noted by parents of youth), wearing multiple devices, sensation of wearing a device on changing and growing body, frequent alarms and maintenance of device.
- Problem solve with the youth and their family on ways to break down barriers. This may require referral to a psychological care provider to teach problem solving skills¹⁰
- If psychosocial needs are reported or identified, refer to psychological care provider.¹⁰

Beyond insulin pumps and CGM, two other areas with psychosocial components and considerations are automated insulin delivery/closed loop technologies and digital health applications. Given the rapidly advancing state of closed loop described earlier, there is a need to understand psychosocial factors leading to the uptake and use of these systems as well as whether they offer psychosocial benefits. As

noted, to maximize benefit from closed loop systems, users will need to wear an insulin pump and CGM continuously. However, rates of uptake of these technologies are lagging. Thus, the above recommendations are relevant for each component of the closed loop system. In a recent report of 284 potential users of closed loop in the United States and United Kingdom,³⁰⁶ three themes were identified as critical for uptake: developing trust in the system and degree of control of it; features of the closed loop systems; and concerns about the everyday barriers to adoption. Children and adolescents differed from parents in that youth primarily identified needs specific to their immediate contexts (eg, school and peers). Parents were most concerned about the accuracy and ensuring that systems stabilize glucose levels and reduce risk for long-term complications. Other reports emphasize these same ideas of setting realistic expectations^{229,230} and potential benefits on quality of life and well-being are already being realized with closed loop systems.^{226,228,231}

In addition to these developments over the past decade, there have been developments in the realm of mobile applications which can serve as adjunct strategies for improving diabetes management and outcomes. Several thousand diabetes-related applications are available in the Apple iTunes store and Android Play store.³⁰⁷ Some apps target health behaviors such as physical activity, sleep, and nutrition, while others target blood glucose monitoring, provide diabetes education, and/or enable users to share their diabetes data with others. For example, applications such as “bant” (www.bantapp.com), which enables users to link their blood glucose meter directly to an application that synthesizes data, has been shown to increase rates of glucose checking in adolescents.²⁶² While promising and exciting, the documentation of the effectiveness of these applications to facilitate behavior change lags behind the pace that these applications hit the marketplace. Research has shown the utility of a mobile and web-based program called YourWay³⁰⁸ to improve the management and glycemic outcomes of adolescents with T1D. Further, another study found that for adolescents with T1D, use of technology (eg, social networking, websites, pump/glucose meter software) was associated with better diabetes self-management behaviors.³⁰⁹

In sum, the current evidence base points to psychosocial and quality of life benefits from using insulin pumps, and growing evidence of benefits with CGM, closed loop, and digital health. Interventions to reduce barriers to technology use are actively being investigated.¹² However, more clinically translatable research, specifically conducted in the pediatric population is needed on the best ways to break down barriers to device and technology use and prevent discontinuation. This likely rests in setting realistic expectations, teaching effective problem-solving skills (general and technology specific), and viewing digital health applications as a scaffolding for youth to internalize the salience and routine of specific health behaviors.

11 | CONCLUSION

Just as our everyday lives have vastly changed with integration of new technologies including computers, smartphones, and the increased connectivity of devices, the management of diabetes is in the midst of a technological revolution. It is likely that the years ahead

will see significant growth in this realm of diabetes care with the hopes that these mechanical solutions may afford patients, and their families, the ability to achieve glycemic targets while reducing the burden of this chronic medical condition. Furthermore, as both diabetes care providers and patients now recognize the importance of not just relying on HbA1c to determine adequacy of control, a shift is occurring to define clinically meaningful outcomes such as TIR (defined as 70–180 mg/dL [3.9–10 mmol/L]), measures of hypoglycemia, and glycemic variability.³¹⁰ Through the use of CGM this data can be collected in both research and clinical settings, and the true test of new technologies will be to see how they can reduce glycemic variability by achieving a greater proportion of TIR. Paramount in the integration of technology into clinical care will be the need for a better understanding of the cost-benefit analysis that may help justify coverage of such innovations in the future. Indeed, as many of these technologies are quite expensive, further understanding of the health economics will provide valuable information for clinicians, their patients, as well as payors. This chapter has reviewed evidence on diabetes technology in children, adolescents, and young adults with the aim of providing practical advice and approaches on their use. Further updates are anticipated in this rapidly evolving area of research and practice.

Conflict of interest

J.L.S. reports having receiving speaker honoraria from Medtronic. J.L.S. also serves on advisory boards of Bigfoot Biomedical, Eli Lilly (Nasal Glucagon), and Insulet Corporation. J.L.S.'s institution received research grant support from JDRF, Medtronic and Insulet. M.T. reports having received speaker honoraria from Medtronic and Novo Nordisk. T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, DreaMed Diabetes and Bayer Health Care. T.B.'s Institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T.B. received honoraria for participating on the speaker's bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. T.B. owns stocks of DreamMed. M.D. has received honorarium from Medtronic. G.F. reports grants from NIH NIDDK; grants and personal fees from Medtronic, grants and personal fees from Tandem, grants and personal fees from Dexcom, grants from Insulet, grants and personal fees from Abbott, grants from Bigfoot, and grants from NovoNordisk. R.R. reports no conflicts of interest. K.H. serves as a consultant to J&J Diabetes Institute, Bigfoot Biomedical, Lilly Innovation Center, and Insulet. Receives research support for investigator-initiated study from Dexcom, Inc. D.M. has research support from the NIH, JDRF, NSF, and the Helmsley Charitable Trust and his institution has research support from Medtronic, Dexcom, Insulet, Bigfoot Biomedical, and Roche. D.M. has consulted for Abbott, the Helmsley Charitable Trust, Sanofi, and Eli Lilly and has served on an advisory board for Insulet.

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Minimising hypoglycaemia in the real world: the challenge of insulin

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Abstract

Insulin therapy has been a life saver for people with type 1 diabetes and has been an essential tool in the therapy of people with type 2 diabetes, but the risk for hypoglycaemia has been a major hurdle to achieving good glycaemic control for most. Insulin analogues, the availability of novel technologies for the administration of insulin, like insulin pumps, and, in particular, tools to measure glucose levels, evolving from capillary measurements to continuous glucose monitoring, have revolutionised the way in which people living with diabetes use insulin. Novel insulin concepts, like once-weekly or oral insulin administration, will have to demonstrate safety on the side of hypoglycaemia before they will be able to move into the clinic.

Keywords Hypoglycaemia · Insulin · Insulin analogues · Real world · Review

Abbreviations

CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
GLP-1	Glucagon-like peptide-1
rtCGM	Real-time CGM
SGLT2	Sodium–glucose cotransporter 2
TIR	Time in range

Introduction

Since its first clinical application in 1921, insulin has become a widely prescribed glucose-lowering agent in people with diabetes. The purpose of using insulin is quite different depending on the situation: in people with type 1 diabetes or those who have lost pancreatic beta cells due to other causes, insulin is a life-saving therapy, where the goal is to mimic the physiological profile of insulin secretion of the original beta cells. Typically, beta cells would provide a variable basal insulin secretion, with the goal of keeping the body in an anabolic state. Intricate glucose sensing in the beta cells and neural mechanisms continuously feed back to the beta cell, thus allowing adaptation of basal insulin

secretion to the body's needs. Thus, in periods of low glucose supply or increased peripheral glucose use, insulin secretion would shut down, eventually being accompanied by increased counter-regulatory hormone (e.g. glucagon) secretion to prevent blood glucose levels from falling and to avoid hypoglycaemia. In addition, feedback signals from the brain and gut, together with rising blood glucose levels, would stimulate insulin secretion at mealtimes, leading to disposal of glucose in the liver, muscle and adipose tissue [1].

In type 2 diabetes, insulin therapy can also be given to replace failing insulin secretion by the beta cell, but often it is given as a supplement in severely insulin-resistant individuals where non-insulin therapies do not suffice to achieve tight glycaemic control [2].

The needs of the insulin formulations used in these different situations will, thus, differ. However, a major challenge common to all people using insulin is the fact that, to date, insulin is administered peripherally, whereas endogenous insulin is secreted directly in the portal system, ideally for targeting the liver, the primary target organ of insulin action. In most patients, this leads to over-insulinisation of peripheral organs (muscle and adipose tissue) while trying to achieve the desired hepatic insulin effect. Typically, this leads to undesired weight gain, both in people with type 1 diabetes and type 2 diabetes. The biggest challenge of present-day insulin formulations is, however, the risk of hypoglycaemia due to lack of feedback of ambient glucose levels for the amount of insulin released from the site of injection into the blood.

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Hypoglycaemia: what it means

Defining hypoglycaemia proved to be a challenge, with learned societies issuing different descriptions, some using absolute glucose values, others symptoms to define levels of hypoglycaemia. In 2017, the International Hypoglycaemia Study Group proposed a workable definition, with three different levels of hypoglycaemia [3]. Levels 1 and 2 are linked to specific blood glucose cut offs, whereas level 3, severe hypoglycaemia, is defined just by clinical presentation and not linked to a blood glucose level. Level 1 (<3.9 mmol/l glucose) is to be considered an alert value for patients and clinicians and can prompt action, eventually including alterations in insulin dose or type. In contrast to level 1, where symptoms may not be present, level 2 (<3 mmol/l glucose) denotes impaired cognitive function and is considered serious, requiring immediate action to resolve the hypoglycaemic event. Level 3, or severe hypoglycaemia, is a severe event characterised by altered mental and/or physical functioning, coma or seizure that requires assistance from another person for recovery. These cut offs and definitions have been incorporated since their publication in clinical guidance documents worldwide. They have been used for defining the time(s) below range(s) in the metrics for continuous glucose monitoring (CGM) and have appeared, for instance, in the ADA standards of care since 2019 [4].

A major clinical problem is the phenomenon of ‘hypoglycaemia unawareness’, whereby the person experiencing the hypoglycaemic attack does not feel that hypoglycaemia is happening. This brings the person treated with insulin into a dangerous situation, in particular into level 2, where cognitive function is impaired and impacts, for instance, driving skills or other intellectual capacities, without the person being aware of the limitations, thus endangering the patient and even others. The frequency of these asymptomatic hypoglycaemic periods has been revealed by the use of CGM [5].

The impact of hypoglycaemia on the life of people living with diabetes is not to be underestimated. In both type 1 and type 2 diabetes, severe hypoglycaemia is linked to increased risk of mortality and morbidity [6] and is associated with an increased societal cost due to hospital and emergency room (ER) admissions, but also due to work absenteeism [7]. However, minor hypoglycaemia and, in particular, hypoglycaemia unawareness also has an impact on quality of life of people with diabetes [8], leads to fear of hypoglycaemia and contributes to insufficient glucose control by defensive down-titration of insulin doses [9, 10].

Striking the right balance between tight glycaemic control and hypoglycaemia prevention

During the past decades, insulin preparations have evolved from purified animal insulins to human insulins (produced by genetically modified organisms) and then insulin analogues, with each approach being better than the last with regard to the desired physiological profile of insulin secretion by the beta cell. However, the ideal insulin preparation that caters for all remains elusive [11].

Therefore, people treated with insulin have had to learn to live with the limitations of the resulting insulin profiles, which do not completely fit mealtime glucose curves or fail to cover basal insulin needs in a stable way. Thus, education and motivation through patient empowerment have been central to diabetes care for those on insulin. The advent of novel insulin analogues or new formulations of existing ones, with profiles better suited for the clinical demands, as well as novel technologies for insulin delivery, have improved the lives of those treated with insulin. In particular, the use of insulin analogues has allowed better personalisation of insulin therapy and more flexibility in lifestyle for many living with diabetes. Still, the ideal insulin replacement strategy has not been realised yet, and searches for adjunct therapies, added on to insulin, to limit side effects of our present insulin administration regimens, are being tested.

Education and motivation

Central to avoidance of insulin-induced hypoglycaemia in day-to-day life is education and motivation in those using insulin. Education for those using mealtime insulins should cover, for instance, a clear representation of the profile of the insulin, so that the person using the insulin can understand the need for proper timing of injection and the need to wait in between successive injections. Basal or premix insulin users should understand the duration of action of their insulin and learn how to adapt the dose to changing insulin needs, for example, when exercising. Also, emphasis on the need to collect information on glucose profiles is essential in people using insulin, and use of capillary blood glucose measurements or CGM is crucial, but it is only of value when it is linked to education on what to do with the collected glucose values. Intensive education on how to adapt mealtime insulin doses to glucose values, meal content, exercise or to changing day-to-day life should be available to all people using mealtime insulin. Also, practical tips and tricks are essential, like frequent injection needle change, avoidance of lipodystrophy and correct preservation of insulin preparations. These educational interventions are essential both in people with type 2 and type 1 diabetes, from young to old age [12, 13].

In people using insulin pumps (continuous subcutaneous insulin infusion [CSII]), specific attention should be given to the use of different bolus and basal profiles to allow adaptation of the insulin profile to the content or style of the meal (e.g., rich in protein and fat vs pure refined carbohydrates) or to the planned exercise (e.g., temporary basal rates) [14].

Even as progress in systems for automated insulin delivery through a combination of CSII with CGM reduce the burden of these insulin dose calculations, education, as well as motivation and support of the person needing treatment of insulin by a member of the medical team, will remain important.

Successful examples of educational programmes are the US blood glucose awareness training (BGAT) and the UK-originated Dose Adjustment for Normal Eating-Hypoglycaemia Awareness Restoration Training (DAFNE-HART) programme. These have demonstrated that hypoglycaemia rates in the real world can be reduced, even in those in whom hypoglycaemia awareness is impaired [15, 16].

Mastering the match between insulin profiles and insulin needs requires an enormous effort from the person treated with insulin and a complex set of skills for guessing the changes in insulin needs as a consequence of food intake, exercise, stress and many other factors, which has been mastered by few. Any minor error, such as failing to anticipate physical activity or miscounting carbohydrate intake, can lead to hypoglycaemic episodes, which are distressing to the person involved and, occasionally, dangerous. The margin for error is small, particularly if those affected are aiming for tight glucose targets and/or are affected by hypoglycaemia unawareness.

Insulin analogues

The purpose of manufacturing insulin analogues was to create insulin formulations that would better mimic the insulin profiles of the beta cell in normal physiology while administering the insulin preparations subcutaneously. The primary clinical aim of analogues was, thus, the avoidance of hyperglycaemia and to allow more people to achieve lower HbA_{1c} levels. However, the major benefit of the introduction of insulin analogues actually lies in the reduction of hypoglycaemic events and greater flexibility in lifestyle for people treated with insulin [11].

Sadly, these insulin analogues come at a higher price than human insulins and are not affordable to all. Biosimilar insulin analogues have been manufactured, somewhat reducing the price. For each individual patient, the advantages (more stable glycaemic profiles, lower risk of hypoglycaemia, more flexibility, often higher quality of life) will have to be weighed against the higher cost of these analogues. Clinicians should discuss value in terms of benefits with their patients, rather than pure cost of therapy.

Rapid-acting insulin analogues With the advent of lispro, aspart and glulisin insulin, a revolution happened in the life of people with type 1 diabetes [17]. Until then, clinicians urged them to take in-between meal snacks and, in particular, bedtime snacks to avoid late hypoglycaemic attacks, which occurred due to the action of subcutaneously administered human regular (conventional) insulin being too long (more than 4 h). When using the more rapid- and shorter acting analogues, these snacks became redundant. The biggest benefit of using rapid- and shorter acting insulin analogues both in trials and in the real world was the reduction in night-time hypoglycaemia. The problem, however, with the present-day rapid-acting insulin analogues is that clinicians and patients have overestimated their rapidity of onset and underestimated their variability and duration of action. Many people are, thus, injecting just before meals, or even after meals, leading to inadequate postprandial glucose control, with mealtime glucose peaks and post-meal hypoglycaemic attacks. In addition, use of CGM, with which people are now continuously seeing glucose swings, has led to the phenomenon of repetitive administration of rapid-acting insulin, particularly in pump users, with accumulation of insulin again ensuing in increased hypoglycaemia risk. Education to provide insight into the profile of the insulin used by the patient and guidance on how to use the particular insulin preparation are as important as the profile of the preparation itself.

Still, newer and ‘better’ preparations of insulin analogues are being proposed, resulting in insulins with an even faster onset and shorter duration of action, like the faster acting insulin aspart and the ultra-rapid-acting insulin lispro [18, 19]. These insulin preparations now provide a profile of mealtime insulin that has an onset of action just 5 min after the subcutaneous injection, peaking at 90 min and completely disappearing after 5 h [18, 19]. The impact of these even faster and shorter acting insulins on hypoglycaemia is limited and will depend on how they are used by the patient. In those using CSII, in particular (hybrid) closed-loop systems, these analogues may help to more closely mimic physiological insulin secretion of the beta cell, with more time in target blood glucose range and less time in hypoglycaemia [20, 21]. However, this will most probably depend on the performance of the algorithm in the system more than on the type of analogue used.

Basal insulin analogues The most dramatic impact of the introduction of basal insulin analogues for people with diabetes using insulin was the decrease in nocturnal hypoglycaemia as compared with when using human NPH insulin. This decrease was seen both in people with type 1 and type 2 diabetes and was attributed to the flatter insulin profile in the blood, resulting from more regular release of insulin from the depot injection site due to innovative prolongation techniques (e.g., shifting of isoelectric point and, thus, solubility at

different pH values for glargine, and di-heximerisation and albumin binding due to the presence of a free fatty acid link in detemir). However, perhaps even more important than the flatter insulin profile was the decrease in variability of release [9]. Pharmacokinetic studies showed a clear relationship between decreased variability in insulin release, more reliable insulin profiles and risk of hypoglycaemia, with an advantage of glargine over NPH insulin and, in turn, an advantage of detemir over glargine [22]. In particular, nocturnal hypoglycaemia risk is decreased with basal insulin analogues, with randomised trials reporting a 30% reduction in nocturnal hypoglycaemia in individuals with type 1 diabetes using glargine or detemir compared with NPH users [23, 24]. In people with type 2 diabetes using basal insulin only (a popular way to initiate insulin therapy in this population), considering the fact that mainly nocturnal hepatic glucose output is targeted, the reductions in hypoglycaemia risk with these therapies also stand on the forefront, with the historic Treat-to-Target Trial also reporting 30% reductions in (nocturnal) hypoglycaemia in individuals with type 2 diabetes taking basal insulin analogues vs those on NPH insulin [25]. Real-world studies confirmed these observations, showing that the less variable the insulin profile, the lesser hypoglycaemia risk, with the lower nocturnal hypoglycaemia risk particularly contributing to the rise in status of the basal insulin analogues to the preferred basal insulins [26, 27].

The latest generation of basal insulins, the more concentrated form of glargine (glargine U300) and insulin degludec, with even flatter, less variable and longer duration profiles, have again moved the needle forward with regard to nocturnal hypoglycaemia risk, with further reductions of 30% risk as compared with the first generation analogues being observed in head-to-head studies, and similar observations being reported in real-world studies [28, 29, 30, 31]. Another advantage of these very-long-acting insulin analogues, in particular insulin degludec, is the increased flexibility in the time of injection, again contributing to improved quality of life [32].

Novel technologies for glucose monitoring and insulin administration

The availability of capillary blood glucose measurement techniques was the prerequisite for use of intensive insulin therapy, but it has been the arrival of CGM, under the form of intermittent scanning CGM (isCGM) or real-time CGM (rtCGM), that has revealed the real impact of insulin therapy on glucose profiles in day-to-day life. As demonstrated in a real-world study in Belgium, the biggest impact of the introduction of rtCGM in the country was the reduction in hypoglycaemic events, accompanied by a reduction in hospital admissions and absence from work or school in people with type 1 diabetes using rtCGM vs those not using this system [33]. A worry with the novel technologies, however,

is the false reporting of low blood glucose levels due to underestimation of glucose levels in the lower range, leading to down-titration of insulin doses or defensive snacking. The ‘flat lines’ reported by sensors during the night are also notorious; these are induced, in part, by sleeping on the arm where the sensor is applied, leading to hypoxia at the sensor site and, thus, false reporting of hypoglycaemia. Again, education and instruction of patients using these technologies is of the essence. Still, despite these shortcomings, the availability of CGM systems, in particular the availability of alarm-equipped technologies, have altered the way clinicians and insulin-treated patients are titrating insulin. Presence of alarms and long-distance monitoring systems have, in most patients, installed a confidence to bring glucose levels down and up-titrate insulin, as the systems reduce the fear of hypoglycaemia in the majority of users [33]. Moreover, use of CGM allows prevention of severe hypoglycaemic attacks in people with type 1 diabetes, even in those with hypoglycaemia unawareness [34]. In addition, these technologies have highlighted to patients the shortcomings of even the modern insulins when it comes to covering glucose excursions during meals, and have motivated many patients to adapt the time of injection at meal-times to deal with postprandial hyperglycaemia and late hypoglycaemia risk.

The closed-loop systems, now available in their early stages as sensor-augmented pumps or hybrid closed-loop systems, will be yet another step towards better adaptation of insulin levels to the individual patient’s demands. Clinical trials and, in particular, real-world experience again show an important impact of these systems on the risk of hypoglycaemia, without compromising overall glucose control [35].

Alternative routes of insulin administration have been tested and, in particular, inhaled insulin was brought to market. However, issues of cost, uncertainty of long-term safety and hassle of use have led to most development programmes being stopped. One inhaled preparation (Technosphere insulin) remains available in some areas, with an interestingly rapid onset of action [36].

Reducing insulin needs

An alternative path that has been taken in type 1 diabetes, as well as in type 2 diabetes, is trying to reduce insulin needs or replace insulin altogether. In type 2 diabetes, the availability of other glucose-lowering agents, some of which have proven to go beyond glucose lowering and also have a direct impact on comorbidities, like cardiovascular disease (particularly heart failure) and chronic kidney disease, has changed the place of insulin in treatment algorithms. As such, insulin has been pushed back in priority, with drug classes like glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors moving to the front. Still,

the most recent ADA/EASD consensus highlights the importance of introducing insulin early on in the therapy of people with type 2 diabetes in specific circumstances, such as when in doubt on the diagnosis of type 2 diabetes, when symptoms of hyperglycaemia or catabolism are present or in pregnancy [37]. For the treatment of people with type 2 diabetes, combination preparations of insulin and GLP-1 receptor agonists are now available, allowing combination of these newer agents and insulin, resulting in improved glycaemic control, reduced weight gain and reduced hypoglycaemia risk compared with the use of basal insulin alone [38].

In type 1 diabetes, insulin is the mainstay of therapy, but adjunct therapies have been tested. The purpose of these adjunct therapies is not to replace insulin but to achieve equal or better overall glycaemic control (reduced HbA_{1c}), with more stable glucose curves (higher time in range [TIR]), less weight gain or less risk of hypoglycaemia. In particular, pramlintide, metformin and SGLT2 inhibitors have progressed to acceptance as adjunct therapies for type 1 diabetes by regulators or found their way into guidelines [39]. In particular, SGLT2 inhibitors have shown a clear effect on HbA_{1c} lowering and increased TIR (3.9–10.0 mmol/l [70–180 mg/dl]), while being insulin-dose sparing and resulting in reduced weight and systolic blood pressure in individuals with type 1 diabetes. The European Medicines Agency has approved use of dapagliflozin at low dose (5 mg) in people with type 1 diabetes and a BMI ≥ 27 kg/m² [40].

A major limitation with adjunct therapies is the increased risk of inducing ketosis through their insulin-sparing effect, reaching insulin doses that are insufficient to suppress peripheral lipolysis. This phenomenon, combined with the increase in ketosis directly induced by SGLT2 inhibitors, has hampered widespread use of SGLT2 inhibitors in people with type 1 diabetes, as these agents increase the risk for overt diabetic ketoacidosis by two- to fourfold [41].

Finally, GLP-1 receptor agonists have also been studied and are being used in clinic as adjunct therapies, primarily to induce weight loss. Studies show clear benefits, particularly in overweight type 1 diabetes patients but, to date, no label for use of these agents in type 1 diabetes is available [42].

The future for insulin and hypoglycaemia

One hundred years after the first clinical application of insulin, insulin is still very much alive as a therapy for people with diabetes. No substitution therapy is available and it does not seem that one will be available in the near future. Still, major innovations are to be expected in the manufacturing of insulins in the following years. In the short term, ultra-long-acting, once-weekly insulins will be available [43]. Most patients applaud this evolution, while most clinicians are sceptical, in particular because of fear of hypoglycaemia. It is hard to

envision how a once-weekly administration of a basal insulin would be compatible with the demands of more flexibility of basal insulin delivery in type 1 diabetes, where CSII has clearly been proven to be the answer to avoiding hypoglycaemia, for example, when exercising. There may be a sweet spot in people with type 2 diabetes where this weekly basal insulin could be exploited as a ‘supplement’ to other glucose-lowering therapies. Still, robust clinical trials will be needed to convince clinicians to use this tool in the real world.

However, when an ultra-long-acting insulin could be combined with another pipeline concept, namely glucose-sensing technology, we could be facing a completely new paradigm. For several years, a number of industry players have already begun exploring the potential to apply one or other ‘glucose-sensing’ tool to insulin, making delivery or action of the injected insulin dependent on ambient glucose levels, thus eliminating the risk of hypoglycaemia, as insulin would only be delivered or active when glucose levels rise. The road to this concept has, however, been one with many disappointments to date [44].

Another development in insulin discovery is oral insulin. Here, again, several early reports were encouraging but there was subsequent silence and arrest of programmes. However, no particular benefit on reduction of hypoglycaemia risk is to be expected with this route of administration. In fact, experts even predict an increased risk of hypoglycaemia as the absorption of orally administered insulin in the presence of food could be more fluctuating than that achieved upon subcutaneous administration [44].

There have been attempts to produce liver-preferred insulins, which would preferentially target the liver, thus, not only reducing weight gain, but also reducing hypoglycaemia risk. One product, peglispro, was terminated during a late phase. This product had clear liver-preferred action, with less weight gain and a trend to reduced hypoglycaemia risk, in particular nocturnal hypoglycaemia, as compared with glargine U100. However, the development of this programme was halted due to liver enzyme rises, suggesting direct liver damage [45]. At present, several liver-preferred insulins are still in development.

In addition, combination insulins are currently being further developed. On top of the combinations at hand, such as combining a rapid-acting with a long-acting insulin, or a basal insulin with a GLP-1 receptor agonist for once-daily injection, novel formulations, such as once-weekly basal insulin formulations with once-weekly GLP-1 receptor agonists, are being considered. These could help mitigate the theoretical increased hypoglycaemia risk of using a once-weekly basal insulin in people with type 2 diabetes.

Finally, the future may lie in technology, with the development of connected pens that will reflect time of injection of insulin and link it to CGM reports, allowing both patients and medical teams to track insulin injections and learn from their

effect on glucose excursions. This may help prevent hypoglycaemic events, as suggested by study findings [35]. The biggest hopes, in particular for people living with type 1 diabetes, are placed on the realisation of closed-loop systems. As discussed, present-day smart pumps and hybrid closed-loop systems allow people to more frequently achieve TIR (3.9–10.0 mmol/l [70–180 mg/dl]) and have less time in hypoglycaemia, but they require a lot of work and input by the patients themselves and intensive guidance by the diabetes team. The advent of real full closed-loop systems, with algorithms that can cope with mealtimes and adapt to changing demands for insulin during the life of people living with diabetes, taking into account exercise, emotions, stress, etc., may be the final step to full avoidance of hypoglycaemic risk despite insulin therapy. Again, the discussion of cost and value of such systems will need to involve the person being treated with insulin.

Conclusions

One hundred years after its first clinical application, insulin therapy has come a long way, with novel insulin analogues, adjunct therapies and novel technologies for insulin administration and glucose monitoring all contributing to better glycaemic control. This better glycaemic control not only means avoidance of hyperglycaemia and, thus, in the long run, complications of diabetes, but also avoidance of hypoglycaemia, with its dramatic impact on healthcare budgets and the daily life of people living with diabetes.

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Review

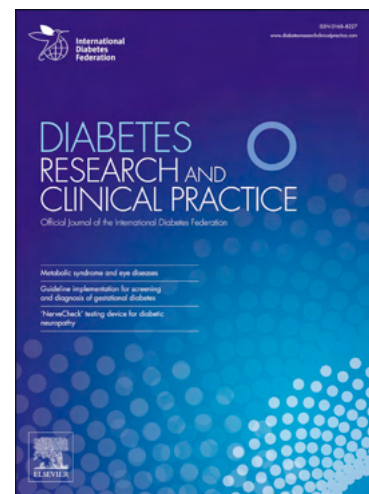
Insulin pump dosing strategies for meals varying in fat, protein or glycaemic index or grazing-style meals in type 1 diabetes: a systematic review

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Insulin pump dosing strategies for meals varying in fat, protein or glycaemic index or grazing-style meals in type 1 diabetes: a systematic review

(Short title: Mealtime Insulin Bolus Strategies in T1D)

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Abstract

Background: Nutritional composition and food patterns influence postprandial glycaemia in type 1 diabetes (T1D). For optimal glycaemic control, insulin dose and delivery pattern must be matched accordingly. This systematic review aimed to compare insulin dosing strategies for meals varying in fat, protein and glycaemic index (GI), and prolonged meals in T1D.

Methods: Studies in adults and/or children with T1D on insulin pump therapy comparing the glycaemic effects of different insulin pump bolus types for these meal types were identified from biomedical databases (MEDLINE, PREMEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials; March 1995-April 2020) and systematically reviewed.

Results: All eleven publications investigating high-fat meals (234 participants) and all seven studies investigating high-protein meals (129 participants) showed a dual-wave bolus was superior. Additional insulin further improved postprandial glycaemia, although increasing risk of hypoglycaemia in 5 of 14 studies. One study investigating GI found a dual-wave bolus reduced postprandial glycaemia and risk of hypoglycaemia. No studies were identified for grazing/degustation-style meals. Due to heterogeneity, meta-analysis was not possible.

Conclusion: Dual-wave boluses improve postprandial glycaemia in high-fat, high-protein and low-GI meals. Further research is needed to identify optimal bolus delivery split, duration and optimal total dose adjustment.

1. Introduction

Continuous insulin infusion systems (CSII; or insulin pump therapy) deliver rapid-acting insulin subcutaneously and offer individuals with type 1 diabetes (T1D) greater mealtime flexibility through advanced bolus settings, which alter how the insulin is administered. A normal (standard) bolus delivers the insulin all at once; an extended (square-wave) bolus delivers the insulin gradually spread over a specified period of time; and a dual-wave (combination; combo or multi-wave) bolus delivers a specified percentage immediately as a normal bolus, and the remaining percentage is delivered as a square wave over a nominated period of time (1).

Several meal types are known to cause delayed and/or prolonged postprandial glycaemic excursions in individuals with T1D, including high fat, high protein, low glycaemic index (GI) and grazing/deglustation-style (termed 'prolonged meals' in this paper) meals and therefore require adjusted insulin dosing (2). Even with identical carbohydrate contents, meals high in fat and/or protein have been shown to increase postprandial glycaemia and delay gastric emptying, leading to a lag in glucose absorption (3). They also increase hepatic glucose release and cause acute postprandial insulin resistance, which further increases postprandial glycaemia in the absence of sufficient insulin (4). Thus high fat/protein meals require additional insulin over low fat/protein meals (4). Indeed, the American Diabetes Association suggests that individuals with T1D who consume high fat and/or high protein meals adjust bolus insulin dose adjustments to improve postprandial glucose control (2). However, the optimal insulin delivery pattern for these meals remains unclear.

GI has also been shown to be an important consideration for postprandial glycaemic control and is frequently recommended as a meal planning approach for individuals with diabetes (5-8). In healthy individuals, low-GI foods produce a reduced glycaemic response, with a reduced blood glucose peak compared with high GI foods (9). This holds true in individuals with T1D, resulting in an increased risk of early hypoglycaemia with low GI foods and a rapid and sustained glucose appearance following high-GI foods (9). Ideal insulin bolus delivery options to match the glycaemic profile of low and high GI meals are unclear (4).

Prolonged meals, such as degustation, cocktail-service, buffet or grazing-style meals, also present a challenge for insulin dosing in T1D. They often come in small, frequent portions, spread over a much longer mealtime. As a result, it would be expected that the appearance of nutrients in the bloodstream would occur over a longer time period, which makes it difficult to match with insulin. Insulin pump companies have suggested that the square-wave or dual-wave bolus types may be better suited to prolonged meals, however there is no review of the evidence to support this recommendation (10, 11).

Given the various postprandial glucose patterns seen (or anticipated) with these meal types, insulin dosing strategies are needed to better match the postprandial glycaemic responses to high-protein, high-fat, low-GI and high-GI, and prolonged meals. This paper therefore aims to systematically review the evidence comparing insulin dosing strategies for meals varying in fat, protein and glycaemic index (GI), high GI and for prolonged meals in T1D.

2. Method

A systematic literature review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (12). MEDLINE, PREMEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials were searched to identify original controlled trials conducted in children, adolescents and adults with T1D using CSII and assessing postprandial glycaemic control following low- vs high-protein meals, OR low- vs high-GI meals, OR low- vs high-fat meals OR prolonged meals with varying insulin bolus strategies. The key search terms employed to identify relevant articles included “type 1 diabetes” AND (“continuous subcutaneous insulin infusion” OR “Insulin pump therapy”) AND bolus types (“normal OR standard” OR “square wave” OR “dual wave”) AND (“glycaemic index” OR “dietary protein OR “dietary fat” OR “prolonged meals”). The full search strategy was developed in consultation with a university research librarian and is available as supplementary material. The search was confined to research articles in English published between March 1995 (date the first rapid-acting insulin analogue Lispro was made available) and April 2020. Control trials, cross-over trials, clinical trials and studies with individuals of any age, sex and race were included. Observational studies and studies conducted in pregnancy, other diabetes types (e.g. type 2 diabetes, gestational diabetes), or in individuals using multiple daily injections (MDI) were excluded. Since insulin bolus type and insulin dose are intrinsically linked to postprandial glycaemia, the insulin dose was also collected and reported on in this review but did not form part of the inclusion/exclusion criteria (i.e. studies that

investigated adjusting the bolus dose only were not included). An expert advisory committee (Dietitians Association of Australia National Diabetes Interest Group) was also consulted to identify any additional studies.

The title and abstract of studies identified by the search strategies was screened by two independent researchers (NC, MM). The full-text of potentially relevant studies were then obtained and independently assessed by two review authors (NC, MM) against the predetermined inclusion criteria. Differences were resolved by discussion, or consultation with the senior researchers (KJB, RS).

Data was extracted independently using a pro-forma. Considering there is no gold standard measure of postprandial glycaemia, a variety of glucose profile metrics available from capillary blood glucose testing and continuous glucose monitoring (CGM) were collected as outcome measures. These included area under a curve (AUC), mean and peak blood glucose level and time in range.

The quality of the evidence for individual studies was assessed using the Cochrane Risk of Bias tool. Quality was assessed against selection bias (random sequence generation, allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete data); reporting bias (selective reporting) and any other biases (13).

Sensitivity analysis and subgroup analyses to assess differences between children (<18 years) vs adults (>18 years) and high vs low-quality studies were planned, however, due to the small number of studies included in this review, were unable to be conducted.

3. Results

The literature search identified 3383 potentially relevant studies. Supplementary hand-searching yielded 4 additional studies. (**Figure 1**). A total of 55 studies remained after removal of duplicates and screening by title and abstract. A further 41 studies did not meet the inclusion criteria and so were excluded after screening the full text, primarily due to not investigating relevant meal types and/or bolus types/insulin dosing (n = 24), were not conducted in CSII (n = 8), were conference abstracts (n = 8) and full text was unavailable (n = 1). The remaining 14 studies were assessed as eligible for the overall review investigating the effect of protein, fat, glycaemic index and prolonged meals. Of these, 11 studies were included for dietary fat, 7 studies investigated dietary protein and 1 study was found investigating GI. No studies were found examining optimal insulin pump dosing strategies for prolonged meals.

3.1 Dietary fat

Eleven studies (14-24) investigated the impact of dietary fat on postprandial glycaemia, including a total of 234 participants (range: 9-42 participants). The majority of studies were conducted in the USA (n=4) and Australia (n=3), with the remainder from Poland (n=1), Germany (n=1), Italy (n=1) and Sweden (n=1). Five studies were conducted in children or adolescents (15, 19-22), four studies were conducted in adults (14, 16, 18, 24) and two studies were conducted in both children and adults (17, 23). Seven trials (17-23) used high fat, high protein test meal, which contained between 14g (18) to 35g (23) of fat or 23% (22) to 36% (17) total energy as fat, respectively. Two trials (15, 24) looked at dietary fat alone, consisted of 17.6 g vs 22.1 g and 0 g vs 20 g vs 40 g vs 60 g fat in the meal, respectively, with controlled contents

of protein and carbohydrate. The remaining two trials investigated dietary fat but simultaneously increased dietary protein (14, 16).

3.1.1 Optimal bolus type for dietary fat

All eleven studies (14-24) investigated the optimal bolus type in high fat meals (**Table 1**). Nine of the 11 studies (14-17, 19-21, 23, 24) reported that a dual-wave bolus provided the best method of managing postprandial glycaemia, however, the optimal split and duration of the delivery varied between studies. Two studies used a 70:30% split over 2 h (17, 19) for meals containing 36% fat and 34% fat respectively and reported reductions in the postprandial blood glucose levels (BGL) compared with using a normal bolus. Four studies used slightly smaller upfront insulin doses 60:40% (15, 20), 63:37% (24), 66:34% (14), but also reported improved postprandial glycaemia compared with a normal bolus despite substantially different bolus durations (1h vs 5h vs 1.25h vs 5.2h respectively). Lopez et al. (23) tested five different dual-wave dosing combinations as 70:30%, 60:40%, 50:50%, 40:60% and 30:70%, and reported that a normal bolus, 70:30% and 60:40% all controlled glycaemia in the first 2 h but only a 30/70% controlled glycaemia from 4-5 h. Similarly, Bell et al. (16) used mathematical modelling to determine individualised optimal doses, with the mean dose being a 30:70% split over 2.4 h. Giving the larger proportion of the dose in the extended wave halved incremental AUC and mean incremental peak plasma glucose compared to a 50:50% split over 2h. Finally, Jones et al. (18) compared running the same dual-wave (50:50%) over 4h vs 8h, and concluded the overall postprandial glycaemic response was significantly lower ($p=0.03$) with the longer

duration. The only study to find a dual-wave was not superior was De Palma et al. (22) who found a normal bolus superior to a 30:70% dual-wave over 6h for pizza margherita meal (50% carbohydrate, 23% fat and 16% protein). This test meal had the lowest fat content (23%) compared to the test meals used in other studies (>34% fat).

3.1.2 Optimal insulin dose for dietary fat

Six studies (14, 16, 19-21, 24) altered both the total insulin dose and the bolus types for high fat meals and reported that additional insulin improved postprandial glycaemia (**Table 1**). However, 3 out of these 6 studies also reported an increased risk of hypoglycaemia (19, 20, 21). In the only included study looking at the addition of dietary fat alone, Bell et al. (24) reported a dose-dependent increase in postprandial glycaemia with 20g, 40g and 60g of dietary fat (with 45g carbohydrate). Using an individualised mathematically-derived Model Predicted Bolus (MPB), only minimal dose increases were needed for the addition of 20-40g fat (6% dose increase) but that the addition of 60g fat meal required a 20% mean increase in the insulin dose over carbohydrate counting (CC: 6.5 ± 0.4 vs MPB: 7.9 ± 0.8 units), which lowered postprandial glycaemia without increasing the risk of hypoglycaemia. Using the same approach in a separate study, Bell et al (16) increased the insulin dose by 65% on average (range 17-124%) for a high fat, high protein meal and reported no hypoglycaemia events. Kordonouri et al (19), Lopez et al (20) and Pankowska et al (21) compared traditional carbohydrate counting with different novel insulin dosing algorithms. The Pankowska Equation (PE) is based on the carbohydrate content and number of fat and protein units (FPU); FPU = 100kcal of fat and/or protein) and the Food Insulin Index (FII). These studies all reported that postprandial glycaemia was reduced but the risk of hypoglycaemia was increased when dosing for fat and protein

(PE: 35.7% vs CC: 9.5% (19), PE: 13 vs FII: 5 vs CC: 2 participants (20) and PE: 4 vs CC: 0 participants (21).

3.2 Dietary protein

Seven trials (14, 16, 20, 21, 23, 25, 26) were identified assessing insulin dosing for high protein meals in 129 participants with T1D (range: 10-58 participants) (**Table 2**). The majority of studies were conducted in Australia (n=3), Poland (n=2) and US (n=2). Four studies were conducted in children and adolescents (20, 21, 23, 26), and 3 were conducted in adults (14, 16, 25), with one study (16) conducted in a relatively older population (mean age 60 ± 11). Three trials looked at protein alone (25) (protein ranging from 12-60g) or controlled for other macronutrients (20, 26) (34g and 36g protein respectively). Four trials investigated dietary protein but simultaneously increased fat (n = 4) (14, 16, 21, 23) and carbohydrate (n=1) (14). Protein-only meals ranged from 24-60g protein (25). Two studies compared low protein vs high protein meals, 14% vs 20% protein (14) and 9 g vs 36 g protein (16), respectively. The remaining studies contained between 25g (21) to 40g (23) of protein in the test meals.

3.2.1 Optimal bolus type for dietary protein

Across all 7 trials, a dual-wave bolus was consistently found to improve postprandial glycaemia compared to a normal bolus. However the optimal bolus split, and duration differed between studies, ranging between 30:70% and 66:34% for 2-6h (14, 16, 20, 21, 23, 25, 26). For example, Pankowska et al. (21) found that a 6 h dual-wave significantly reduced mean blood glucose ($p=0.008$), and significantly reduced the

change in blood glucose from baseline at 120 min, 240 min, and 360 min when compared to a normal bolus ($p < 0.05$ for all). Piechowiak et al. (26) also used the Pankowska equation to determine the insulin dose and dual-wave split and found a 3 h dual-wave reduced glycaemic response compared to the normal bolus, with reduced mean BG (7.25 ± 3.61 vs 9.0 ± 3.37 , $p = 0.004$) and lower iAUC (1452.94 mmol/l/min vs 1515.28 mmol/l/min, $p = 0.430$). Lee et al (14) found a 66:34% dual-wave over ~5 h was able to sustain postprandial BGLs in the early and late postprandial period, significantly reducing the mean glucose from 5 to 14 h after the meal compared to the normal bolus which was only sustained from 1 to 3 h. In contrast, Bell et al. (16) found the a 30:70% dual-wave over 2.4 h optimised postprandial glycaemia compared to a 50:50% dual-wave for 2 h; reducing iAUC ($11,712 \pm 3,172$ mg/dL.min vs $27,092 \pm 1,709$ mg/dL.min, $p = 0.0013$) and incremental change in blood glucose (1.3 ± 0.6 vs 4.1 ± 0.2 mmol/l, $p = 0.001$). Lopez et al (23) did not find any bolus split to be optimal to control postprandial glycaemia in both the early and late postprandial periods when dosing with CIR (carbohydrate-insulin ratio) and instead concluded that at least 60% of the ICR was needed in the upfront portion of the dual-wave, and 70% ICR in the extended portion over 5 h improved glycaemic control. This would translate to an ~50:50% split with an overall dose increase to 130% of the CIR but was not explicitly tested in their study.

3.2.2 Optimal insulin dose for dietary protein

All studies showed that adjusting the insulin dose for protein improved postprandial glycaemia (14, 16, 20, 21, 23, 25, 26), however in 4 out of the 6 studies that increased insulin dose, the risk of hypoglycaemia also increased (14, 21, 25, 26).

Lopez et al (23) and Bell et al (16) showed that insulin dosing for carbohydrate alone could not control postprandial glycaemia over a 5 h postprandial period for high protein meals. One study (20) used 50% CIR to estimate insulin: protein-and- fat ratios, increasing the dose in the extended portion of the dual-wave, which resulted in a significant reduction in mean glucose from 5-14 h ($p=0.01$). Bell et al. (16) increased the insulin dose by $65 \pm 10\%$ using the Model predictive bolus algorithm which significantly improved postprandial glycaemia without increasing the risk of hypoglycaemia over 6 h. Dosing insulin using the FII and Pankowska equation significantly reduced the postprandial response compared to carbohydrate counting but increased the incidence of hypoglycaemia (20, 21, 25, 26). Lopez et al. (20) compared the FII and Pankowska equations head-to-head and found that the Pankowska Equation reduced postprandial hyperglycaemia compared to the FII but at the expense of increased hypoglycaemia.

3.3 Glycaemic index (GI)

Only one study (27) investigated insulin bolus types for high- and low-GI meals (**Table 3**). This trial was conducted in 10 children and adolescents with T1D, aged 9-17 years in Australia. A high- and low-GI meal ($GI = 76$ and 34 respectively) were consumed and tested on different days, with a normal bolus and a 50:50% dual-wave bolus delivered over 2 h, using individual CIR for insulin dosing. Postprandial glycaemia was monitored by CGM for 3 h. Overall, the dual-wave reduced the AUC by 47% compared to the normal bolus in low-GI meals ($p=0.004$), whilst in the high-GI meal, no bolus type was better able to control AUC (27). The dual-wave showed a reduced frequency of hypoglycaemia in both meals compared to the normal bolus, with 4 vs 7 events following the low-GI meal, and 0 vs 2 events following the high-GI meal (27).

3.4 Risk of bias

The risk of bias in the included studies is shown in **Figure 2**. Almost all studies were cross-over trials, with the order of meal types, insulin delivery regimes and/or counting methods randomised. Most studies (13 of 14 studies) could not use blinding due to the nature of the intervention, however this was unlikely to influence the trial outcome. All of the studies were free of detection bias because the test results were objective monitored using either capillary blood or CGM and therefore unlikely to be influenced by the investigator. Studies tended to score lower for ambiguity around blinding and high subject attrition (>50%) without justification (14, 27).

4. Discussion

The present literature review reveals that dual-wave insulin bolusing improves postprandial glycaemic control for high fat, high protein and, likely, low GI meals, however the optimal bolus delivery split and duration is not yet clear. There was substantial variation in the dual-wave splits and durations used in the included trials, ranging from 30:70% to 70:30% over 1-8h, however there were still clinically relevant reductions in mean BGL, BGL peak and AUC. This review did not seek to review all available literature on the optimal total insulin dose adjustments, although the included studies suggest an increased insulin dose improves postprandial glycaemia (16, 19-21, 23, 27), despite being associated with an increased risk of hypoglycaemia in some studies (19-21, 23).

The findings of this literature review are consistent with previous reviews (4, 28) concluding that carbohydrate-based insulin-dosing is inadequate for meals higher in dietary fat and protein. The finding that the dual-wave bolus type is superior is

consistent with the known delayed postprandial glycaemic profiles of meals high in protein and/or fat and low in GI (4).

It is interesting to note that a wide range of dual-wave bolus splits and durations were effective for glycaemic control. The reason for this is not clear but could be due to variations in the amount or sources of carbohydrate, fat and/or protein in the meals. Included studies used both plant and animal protein sources (including meats, eggs, beans, cheese & protein powders), and both saturated & unsaturated fat sources (cheese, fried foods and avocado). However, the type of fat (polyunsaturated, monounsaturated vs saturated fat) was shown to have no significant impact on postprandial glycaemia in one study (24). Bell et al (24), also showed that the optimal dual-wave split changed as the amount of fat changed, with a high proportion needed in the extended wave with higher fat amounts. Furthermore, higher carbohydrate meals would theoretically need larger proportions of insulin upfront compared with low- or no-carbohydrate meals. In addition, participants' basal rates and basal: bolus insulin ratios, which would have impacted participant ICR (and thus total dose) and late postprandial glycaemia.

4.1 Clinical implications

Our findings support the use of the dual-wave bolus for high fat, high protein and low GI meals in clinical practice. Just as insulin doses need to be titrated to the individual to account for inter-individual differences in insulin and macronutrient sensitivities, the optimal bolus split and duration also needs to be individualised. For high protein and/or high fat or low GI meals, it would be reasonable to start with a 50:50% split over 2-3h and adjust the dose, split and duration based on review of the postprandial glycaemic

profile. As always, the balance needs to be struck between controlling postprandial hyperglycaemia, preventing hypoglycaemia and maintaining quality of life and the pleasure of eating.

Importantly, before adjusting insulin dosing and bolusing for meal composition, other reasons for postprandial hyperglycaemia must be addressed, such as missed boluses, inaccuracies in carbohydrate counting and inaccurate insulin ratios, including non-optimised basal rates. Healthy eating principles should be emphasised, given the cardiometabolic benefits (29). Bolus timing is important, with Scaramuzza et al (30) has previously reported that rapid-acting insulin administration either 15 mins or immediately before a meal high in carbohydrate, fat and protein (95g, 40g and 28g respectively) improves postprandial glycaemia when compared to post-meal delivery. In this review, 4 studies dosed insulin preprandially for high fat and/or protein meals (19, 20, 22, 26). De Palma et al (22) directly examined the impact of dose timing, while maintaining the total insulin dose and delivery pattern, for a high fat meal in children. They found that dosing 15 minutes preprandially did not significantly impact postprandial glycaemia over 6 hours compared with dosing at the time of the meal. Lastly, carbohydrate counting is already burdensome for individuals with T1D, and further decision-making surrounding fat, protein and GI bolusing amplifies the challenges associated with living with T1D. Rather than recommending individuals count grams of fat and protein, it may be simpler to identify 'high' vs 'low' fat and protein meals and plan insulin adjustments for these scenarios. Alternatively, food database apps could be integrated with insulin dosing calculators to convert the users' selected meal into the nutrient compositions and automatically determine the insulin dose based on the individuals' insulin ratios (31). Irrespective of the approach, it will be important that simplified education and additional support is offered and

technological decision-support tools, such as smartphone apps, continue to be investigated (31, 32). More studies on the closed loop pump system are also needed to automatically regulate blood glucose to match different meal types. Current hybrid closed-loop systems still require individuals to enter carbohydrate and don't allow for dual-wave bolus options. This may be problematic in clinical practice since this review has shown normal boluses are inferior for high fat and/or protein meals in both the early and late postprandial period.

This review specifically addressed insulin bolusing using insulin pumps, however further research and clinical solutions are also needed for individuals using MDI. One of the only studies in MDI found a 30% dose increase given 3 h after a meal containing: 55 g fat, 26 g protein and 68 g carbohydrate was the most effective adjustment for controlling postprandial glycaemia (33).

4.2 Strengths and limitations

This is the first review that summarised the evidence of mealtime insulin dosing for dietary fat, protein, GI and prolonged meals, specifically in insulin pump therapy. The advantage of insulin pumps is the increased flexibility in bolus delivery options, which can be better tailored to different meal types. The strengths of the study are the adherence to the PRISMA guidelines (12), the broad inclusion criteria and search across five databases in addition to grey literature searching and consultation with a research librarian and an expert advisory committee was designed to capture all relevant studies. Additionally, most included trials were assessed as high quality using a valid methodological tool (34).

Several limitations of this review must be acknowledged. There were a relatively small number of studies identified for fat and protein and a paucity of evidence for GI and

prolonged meals. Of the studies included, the sample sizes were relatively small and the studies included were highly heterogeneous, with substantial variations in the participants, meal compositions, insulin adjustments (doses, bolus types, splits and durations), glycaemia monitoring methods and durations and outcomes metrics. As a result, the planned meta-analyses and sub-group analyses could not be undertaken nor could definitive clinical guidelines be recommended. Standardisation of methodology, including the metrics of measuring postprandial glycaemia will ensure trials can directly compared. Studies should monitor glycaemia for a minimum of 5 h to ensure the full postprandial profile is identified, as fat and protein have been shown to have a delayed impact on glycaemia (3h onwards) (20), yet 4 studies only monitored blood glucose for 3h postprandial (15, 25-27).

Furthermore, fat and protein were often co-existing and simultaneously altered in test meals, which confounded the results for both high-fat and high-protein meals (14, 16, 19, 21, 22, 25), as the effect of fat and protein are additive (35). Further systematic research is needed on these individual nutritional properties alone and in combination, so that clearer clinical guidance can be given to patients and clinicians alike. Similarly, the paucity of evidence around GI and prolonged meals in T1D needs addressing to provide practical, real-world solutions.

5. Conclusion

In conclusion, dual-wave insulin boluses improve postprandial glycaemic control following high fat, high protein and low GI meals compared with normal boluses in individuals with T1D using insulin pump therapy. The optimal dual-wave split and

duration is not yet clear and additional studies, with greater standardisation are needed as well as investigation dosing strategies for GI and prolonged meals.

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Table 1: Included studies on optimal insulin boluses and dosing strategies for dietary fat (n=11), protein (n=7) and glycaemic index (n=1)^c

Source	Dietary fat/protein/GI	Study population and design	Intervention & Insulin dose/duration	Glucose monitoring & method duration	Outcome
Lee et al 2004 (14)	Dietary fat/protein	USA n=10 Adults Non-randomised, crossover trial	A) LFLP, NW: 100%; 8.1 ± 3.5 U (CIR) B) HFHP, NW: 100%; 9.2 ± 3.4 U (+50% CIR for fat) C) HFHP, DW: 65.9:34.1% over 5.2 ± 1.4h; 13.4 ± 5.6 U (8.7 ± 3.4 U:4.7 ± 2.2 U; 150% of CIR for fat)	CGM, 16h	Peak BGL (mmol/L): B: 3.0 ± 1.9 for 8h, C: 0.7 ± 0.1 for 2h Mean Glucose (mmol/L): Mean glucose values were similar in each of the three combinations of meal and bolus type (p=0.64 NS, p=0.84 NS, p=.99 NS)
Lindholm Olinder et al 2009 (15)	Dietary fat	Sweden n=15 Adolescents Randomised, parallel trial	A) LF, NW: 100%, 5.0 ± 1.2 U (CIR) B) HF, NW: 100%, 5.0 ± 1.2 U (CIR) C) LF, DW: 60:40% over 1h, 5.0 ± 1.2 U (CIR) D) HF, DW: 60:40% over 1h, 5.0 ± 1.2 U (CIR) E) LF, SW: 100% over 1h, 5.0 ± 1.2 U (CIR) F) HF, SW: 100% over 1h, 5.0 ± 1.2 U (CIR)	Capillary and CGM, 3h	AUC (mmol/L): A: 1631 (NS), B: 1451 (NS), C: 1548*, D: 1312*, E: 1704*, F:1515* Change in peak glucose (mmol/L): A: 4*, B: 2.4 (NS), C: 3.8 (NS), D: 3(NS), E: 5*, F: 3.7 (NS)
Bell et al 2016 (16)	Dietary fat/protein	USA n= 10 Adults Randomised, crossover trial	A) LFLP, DW: 50:50% over 2h; 4.7 U (CIR) B) HFHP, DW: 50:50% over 2h; 4.7 U (CIR) C) HFHP, DW: 30:70% over 2.4h; 7.9 U (MPB)	Venous, 6h	iAUC (mg/dL): A is more than double that of B, p=0.0013*, significant from 180min+ Mean incremental plasma glucose (mmol/L): A: 1.28 ± 0.61, B: 4.1 ± 0.22, C: 1.33 ± 0.61

Chase et al 2002 (17)	Dietary fat	USA n=9 Adults Randomised, crossover trial	A) HF, NW: 100%, given at t= -10 min; mean dose 9.6 U (CIR) B) HF, 2 NW: 50%, given at t= -10 min, 50%, given at t= 1.5 h; mean 9.6 U (CIR) C) HF, SW: 100% over 2 h, given at t= -10 min; mean 9.6 U (CIR) D) HF, DW: 70:30% over 2 h, given at t= -10 min; mean 9.6 U (CIR)	Capillary, 6h	AUC (mmol/L): P=0.834 NS A: 2.5 ± 0.3 , B: 2.9 ± 0.4 , C: 2.3 ± 0.2 , D: 2.3 ± 0.19 , p = 0.83 Mean change in BGL from baseline (mmol/L): p=0.014* A: 1.9 ± 1.0 , B: 3.7 ± 1.4 , C: 4.4 ± 1.3 , D: 0.5 ± 0.9
Jones et al 2005 (18)	Dietary fat	USA n=24 Adults Randomised, parallel trial	A) HF, DW: 50:50% over 4h, CIR B) HF, DW: 50:50% over 8h, CIR C) HF, NW: 100%, CIR	CGM, 12h	Mean BGL 8-12h (mmol/L): A: 8.1 ± 3.8 (NS different to C, but p=0.03* for A vs B) B: 5.8 ± 2.3 (NS different to C) C: 7.4 ± 3.0 (NS different to A)
Kordonouri et al 2012 (19)	Dietary fat	Germany n=42 Children Randomised, crossover trial	A) HF, NW: 100%, CIR B) HF, NW: 100%, PE C) HF, DW: 70:30% over 2h, CIR D) HF, DW: 70:30% over 2h, PE	CGM and Capillary, 6h	AUC (mg/dL): A: 953 ± 299 , B: 784 ± 235 , C: 898 ± 270 , D: 725 ± 286 A & B: P<0.001*, C & D: p=0.045* CFP counting: 805 ± 261 mg/dL x 6h CC counting: 926 ± 285 mg/dL x 6h
Lopez et al 2018 (20)	Dietary fat/protein	Australia n=25 Children Randomised, crossover trial	A) HFHP, DW: 60:40% over 4h, 5.9 ± 3.2 U, CIR B) HFHP, DW: 60:40 over 4h, 6.1 ± 2.9 U, FII C) HFHP, DW: 60:40 over 5h, given at t= -15 min; 6.9 ± 3.9 U, PE	CGM, 5h	Peak BGL excursion (mmol/l): A: 2.45 at 180min, B: 2.34 at 120min, C: 1.54 at 150min Peak glucose excursion was higher for CC, FII compared to PE (p<0.02*)
Pankowska et al 2012 (21)	Dietary fat/protein	Poland n=23 Children Randomised, parallel trial	A) HFHP, DW: split NR; 9.6 ± 2.5 U over 6 h, PE B) HFHP, NW: 100%, 5.9 ± 1.9 U, CIR	Capillary, 6h	Change in BGL from baseline: Increased for Group B compared to Group A at 120 (p=0.003*), 240 (p=0.004*) and 360 (p=0.003*) min

De Palma et al 2011 (22)	Dietary fat	Italy n=38 Children Randomised, parallel trial	A) HFHP, NW: 100%, given at t= -15 min, CIR B) HFHP, NW: 100%, given at t= 0 min, CIR C) HFHP, DW: 30:70 over 6 h, given at t= -15 min, CIR D) HFHP, DW: 30:70 over 6 h, given at t= 0 min, CIR	Capillary, 6h	AUC (mmol/L): A: 0.1 ± 1.2 (NS), B: $0.7 \pm 0.9^*$, C: 0.4 ± 0.8 (NS), D: 0.2 ± 1.4 (NS) Mean BGL (mmol/L)– 6 hr A: $6.2 \pm 3.5^*$, B: 7.0 ± 3.7 (NS), C: 7.9 ± 3.9 (NS), D: $9.5 \pm 3.4^*$
Lopez et al 2017 (23)	Dietary fat/protein	Australia N=19 Children Randomised, crossover trial	A) HFHP, DW: 30:70% over 2 h, CIR B) HFHP, DW: 40:60% over 2 h, CIR C) HFHP, DW: 50:50% over 2 h, CIR D) HFHP, DW: 60:40% over 2 h, CIR E) HFHP, DW: 70:30% over 2 h, CIR F) HFHP, NW: 100%, CIR (all $1.0 \pm 0.7/10$ g CHO)	CGM, 5h	Glucose excursion AUC at 240-300 min (mmol/l) A: $36.8 \pm 5.0^*$, B: 54.0 ± 6.7 , C: 50.3 ± 7.3 , D: 43.7 ± 4.6 , E: 49.9 ± 5.8 , F: $51.2 \pm 5.3^*$; A & F: p=0.004* Glucose AUC at 60-120 min (mmol/l) B: 50.7^* , C: 65.7^* , F: 39.7 Glucose AUC at 240-300 min (mmol/l) A: 36.8*. F: 51.2
Bell et al 2020 (24)	Dietary fat	USA N=19 Adults Randomised, crossover trial	A) 20g fat, 50:50% over 120 min; 6.5 ± 0.4 U, CIR B) 20g fat, 74:26% over 73 min; 7.0 ± 0.8 U, MPB C) 40g fat, 50:50% over 120 min; 6.5 ± 0.4 U, CIR D) 40g fat, 63:37% over 75 min; 6.9 ± 0.5 U, MPB E) 60g fat, 50:50% over 120 min; 6.5 ± 0.4 U, CIR F) 60g fat, 49:51% over 105 min; 7.9 ± 0.8 U, MPB	Capillary, 5h	Incremental mean BGL (mmol/l) A: 1.5 ± 0.4 , B: 0.5 ± 0.3 , C: 1.1 ± 0.2 , D: 0.6 ± 0.2 , E: 2.1 ± 0.5 , F: 0.7 ± 0.3 Fat amount p= 0.089 (NS), dosing algorithm p=0.001* Incremental AUC at 0-120min (mmol/l) A: 305 ± 59 , B: 160 ± 38 , C: 210 ± 39 , D: 123 ± 27 , E: 229 ± 56 , F: 126 ± 36 Fat amount p= 0.078 (NS), dosing algorithm p<0.001*
Piechowiak et al 2017 (26)	Dietary protein	Poland n=58 Children	A) LFHP, NW: 100%, given at t= -15 min, CIR	BG, 3h	iAUC (mmol/l/min) DW vs SW: 1452.94 vs 1515.28 (p=0.430) Mean BG (mmol/l)

		Randomised, crossover trial	B) LFHP. DW: split NR; 3h. given at t= -15 min, PE		DW v SW: 7.25 ± 3.61 vs 9.0 ± 3.37 (p=0.004)
Bell et al 2014 (25)	Dietary protein (high protein test foods)	Australia n=11 Adults Randomised, crossover trial	A i) HP (60g); NW: 100%; 0 U (CIR) A ii) HP (60g); NW:100%; 3.7 U (FII) B i) HP (12g); NW: 100%; 1.6 U (CIR) B ii) HP (12g); NW: 100%; 3.7 U (FII) C i) HP (24g); NW: 100%; 0.1 U (CIR) C ii) HP (24g); NW: 100%; 1.8 U (FII) D i) HP (14g); NW: 100%; 4.4 U (CIR) D ii) HP (14g); NW: 100%; 6.9 U (FII) E i) HP (15g); NW: 100%; 4.3 U (CIR) E ii) HP (15g); NW: 100%; 5.9 U (CIR) F i) HP (40g); NW: 100%; 2.4 U (CIR) F ii) HP (40g); NW: 100%; 4.2 U (FII)	BG, 3h	Mean BGL (mmol/L): FII vs CC 5.7 ± 0.2 vs 6.5 ± 0.2 (p=0.003) Peak BG (mmol/l): FII v CC: -0.7 ± 0.2 v 0.1 ± 0.2 (p=0.001)
O'Connell et al 2008 (27)	Glycaemic index	Australia n= 10 Children, Randomised, crossover trial	A) LGI, NW: dose NR; 100%, CIR B) LGI, DW: dose NR; split NR; 50:50%, CIR C) HGI, NW: dose NR; 100%, CIR D) HGI, DW: dose NR; split NR; 50:50%, CIR	CGM, 3h	AUC (mmol/l) B vs D: 31% reduction with LGI (p <0.05) LGI (A, B): DW 47% reduction vs NW (p=0.004) HGI (C, D): NS difference between normal and DW

Legend: NW, Normal Wave; SW, Square Wave; DW, Dual Wave;

LF, Low Fat; HF, High Fat; LFLP, Low Fat Low Protein; HFHP, High Fat High Protein; CHO, Carbohydrate; LGI, low glycaemic index; HGI, high glycaemic index; CIR, Carbohydrate-to-Insulin Ratio; FII, Food Insulin Index; PE: Pankowska Equation; MPB: Model Predictive Bolus; AUC, Area Under the Curve; iAUC, incremental Area Under the Curve; BGL, Blood Glucose Level; Hypo, Hypoglycaemia;

p-value: *Significant; NS, Not Significant; NR, not reported

τ For more information, see online supplementary material

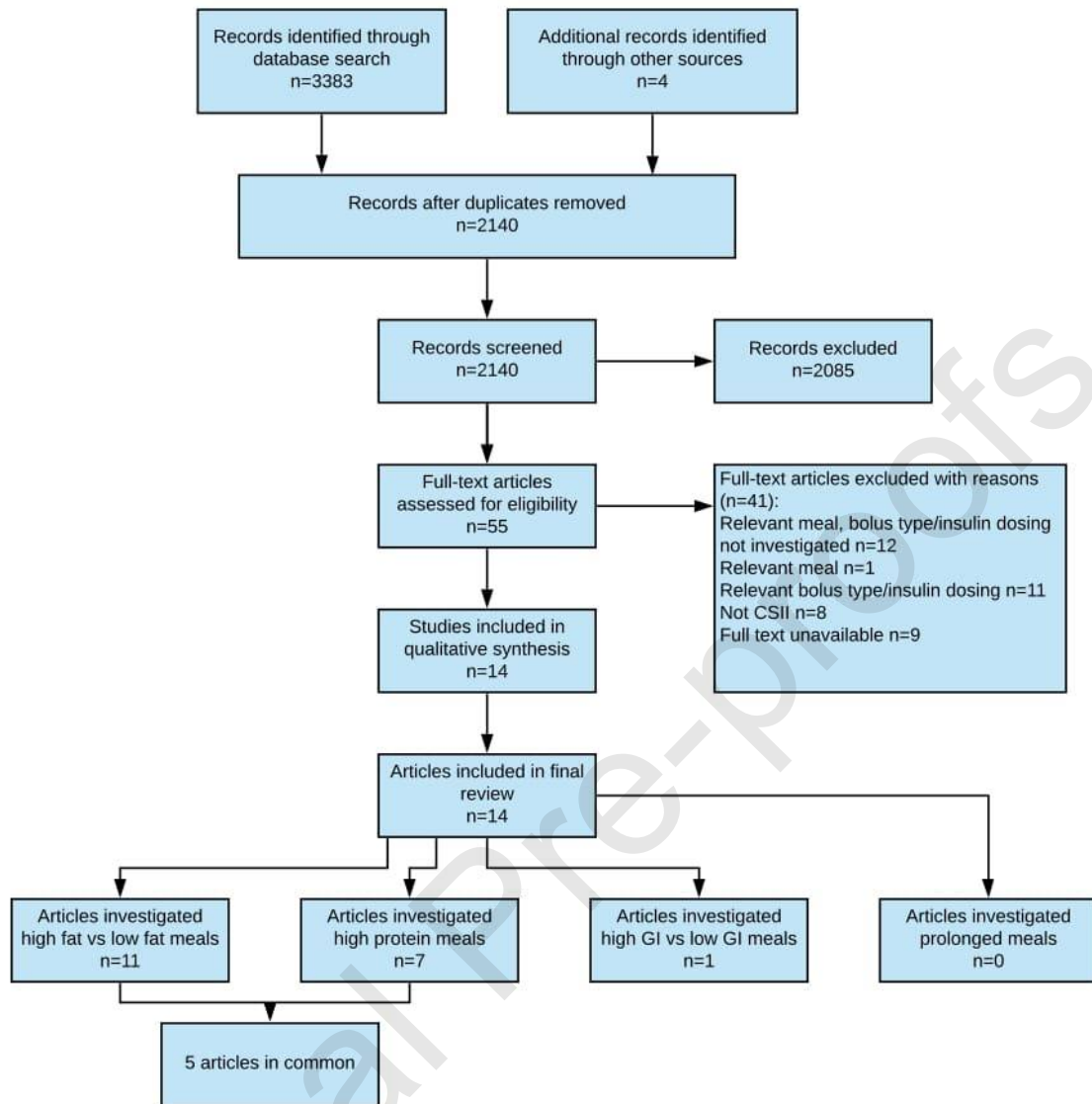


Figure 1: Flow diagram for study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (in colour)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Bell et al 2014	+	+	+	+	+	+
Chase et al 2002	+	+	+	+	+	?
Jones et al 2005	+	+	+	+	+	?
Kordonouri et al 2012	+	+	+	+	?	+
Lee et al 2004	?	+	+	+	+	+
Lopez et al 2018	+	+	+	+	+	+
O'Connell et al 2008	+	+	+	+	-	+
Pankowska et al 2012	+	+	+	+	+	+
Piechowiak et al 2017	+	+	+	+	+	+
De Palma et al 2011	+	+	+	+	?	+
Lindholm Olinder et al 2009	+	+	+	+	+	?
Bell et al 2016	+	+	+	+	+	+
Lopez et al 2017	+	+	+	+	+	+
Bell et al 2020	+	+	+	+	+	+

Figure 2: Risk of bias summary (in colour)



The Evolution of Hemoglobin A_{1c} Targets for Youth With Type 1 Diabetes: Rationale and Supporting Evidence

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The American Diabetes Association 2020 *Standards of Medical Care in Diabetes* (Standards of Care) recommends a hemoglobin A_{1c} (A1C) of <7% (53 mmol/mol) for many children with type 1 diabetes (T1D), with an emphasis on target personalization. A higher A1C target of <7.5% may be more suitable for youth who cannot articulate symptoms of hypoglycemia or have hypoglycemia unawareness and for those who do not have access to analog insulins or advanced diabetes technologies or who cannot monitor blood glucose regularly. Even less stringent A1C targets (e.g., <8%) may be warranted for children with a history of severe hypoglycemia, severe morbidities, or short life expectancy. During the “honeymoon” period and in situations where lower mean glycemia is achievable without excessive hypoglycemia or reduced quality of life, an A1C <6.5% may be safe and effective. Here, we provide a historical perspective of A1C targets in pediatrics and highlight evidence demonstrating detrimental effects of hyperglycemia in children and adolescents, including increased likelihood of brain structure and neurocognitive abnormalities, microvascular and macrovascular complications, long-term effects, and increased mortality. We also review data supporting a decrease over time in overall severe hypoglycemia risk for youth with T1D, partly associated with the use of newer insulins and devices, and weakened association between lower A1C and severe hypoglycemia risk. We present common barriers to achieving glycemic targets in pediatric diabetes and discuss some strategies to address them. We aim to raise awareness within the community on Standards of Care updates that impact this crucial goal in pediatric diabetes management.

Twenty-seven years ago, the Diabetes Control and Complications Trial (DCCT) first demonstrated in a randomized clinical trial that intensive insulin treatment aiming to lower glucose levels closer to the normal range, beyond that necessary to control symptoms of hyperglycemia, reduced the risk of microvascular (1) and long-term (2) diabetes complications. Increased severe hypoglycemia risk was an adverse effect of intensive therapy. In addition, there was fear that intensive treatment could increase the risk of macrovascular complications due to hyperinsulinemia, and significant real-world impediments to feasibility of and accessibility to the diabetes care required to achieve the study results were noted in the initial report almost three decades ago (3).

Since its 1993 landmark publication, the DCCT and many other studies have progressively provided overwhelming evidence that near-normal glucose control diminishes the risks of retinopathy, nephropathy, neuropathy, and macrovascular complications (4). The development of insulin analogs, more sophisticated insulin delivery systems (e.g., insulin pumps), continuous glucose monitoring (CGM), and,

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more recently, integrated systems (e.g., sensor-augmented insulin pumps, predictive low-glucose suspend systems, and closed-loop control systems) greatly enhanced the feasibility of maintaining glucose levels within a prespecified target range. These advances have also contributed to lessening hypoglycemia risk and have diminished the relationship of significant or severe hypoglycemia with lower glycemic targets in people with T1D. Consideration of emerging evidence relevant to pediatrics has prompted the American Diabetes Association (ADA) to revise its hemoglobin A_{1c} (A1C) targets in pediatric T1D several times through the years.

The ADA's Professional Practice Committee updates the Standards of Medical Care in Diabetes (Standards of Care) (5) annually "to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care" (6). With the 2020 Standards of Care (5), the ADA issued a new recommendation for children with T1D: "A1C goals must be individualized and reassessed over time. An A1C of , 7% (53 mmol/mol) is appropriate for many children" (recommendation 13.21, evidence grade B) (7). The previous version, published in January 2019, had recommended a goal of 7.5% for most children (8).

In this Perspective, we review the history of pediatric A1C targets and the evidence supporting the 2020 revision. Barriers to achieving pediatric A1C targets are discussed, as are proposed strategies to address them. With this article, we aim to raise awareness within the diabetes community of the updated 2020 A1C recommendations to the Standards of Care.

HISTORICAL PERSPECTIVE OF A1C GOALS IN PEDIATRIC T1D

The 2003 Standards of Care established that, while the general A1C goal for individuals with diabetes was , 7%, a "less stringent treatment goal may be appropriate for . . . very young children." In 2005, the ADA issued a statement with age-specific A1C goals for pediatric T1D. A range of 7.5% to 8.5% was recommended for children , 6 years of age, , 8% for children 6–12 years old (#8 stated in the narrative), and , 7.5% for adolescents 13–19 years old. The 2011 Standards of Care introduced the concept that lower A1C targets for children with T1D were

reasonable if achievable without significant hypoglycemia (see Table 1 for goals). In 2015, the Standards of Care recommended a goal of , 7.5% across all pediatric age-groups, , 7% if achievable without excessive hypoglycemia, with premeal and bedtime/overnight plasma blood glucose ranges also recommended. The 2020 Standards of Care recommends an A1C goal of , 7% for many children with T1D (recommendation 13.21, evidence grade B). A higher target of , 7.5% may be more appropriate for youth who cannot articulate symptoms of hypoglycemia or have hypoglycemia unawareness, as well as those who do not have access to analog insulins, cannot monitor their blood glucose regularly, or do not have access to advanced diabetes technologies, including insulin pumps and CGM (recommendation 13.22, evidence grade B). Individuals who have nonglycemic factors that increase A1C, such as higher erythrocyte life span, or are high glycaters (i.e., those who, for the same level of glucose, have consistently higher A1C) may also need a higher target such as , 7.5% (recommendation 13.22, evidence grade B). Similar to that for adults with diabetes, a target of , 8% is recommended for youth with a history of severe hypoglycemia, severe morbidities, or short life expectancy (recommendation 13.23, evidence grade B). A lower A1C target, such as , 6.5%, may be appropriate during the partial remission period (or "honeymoon") or in persons with longstanding T1D if achievable without excessive hypoglycemia, poor quality of life, or undue burden of care (recommendation 13.24, evidence grade B).

The 2020 revision aligns the A1C goals in pediatric T1D and type 2 diabetes (T2D). Table 1 illustrates a summary of the history of ADA's guidelines for A1C targets in youth with T1D or T2D since 2000. Supplementary Table 1 provides significant narrative information on goals and additional details such as specific changes from year to year, whether guidance was labeled as a recommendation, and level of evidence as graded by the ADA.

The emphasis on glycemic target individualization has been a constant through the years in the ADA clinical guidelines. Age-specific goals were recommended between 2005 and 2015. The 2020 Standards of Care recommends considering a less stringent A1C goal if, based on the individual's circumstances, the risks (such as increased risk of hypoglycemia, increased burden of care,

or decreased feasibility) exceed potential benefits or when A1C is not a reliable indicator of mean glucose concentrations (recommendation 13.22, evidence grade B, and recommendation 13.23, evidence grade B). On the other hand, in selected children, a lower target (e.g., , 6.5%) is reasonable (recommendation 13.24, evidence grade B).

Besides A1C goals, the premeal/bedtime/overnight glucose targets have also been adjusted empirically through the years to reflect A1C goal changes. Yet specific evidence on ways to achieve A1C goals is currently sparse, reflecting a need for more data.

EVIDENCE SUGGESTING DETRIMENTAL EFFECTS OF HYPERGLYCEMIA IN CHILDREN AND ADOLESCENTS

Structural and Neurocognitive Effects on the Central Nervous System

The negative effects of hypoglycemia on the brain have long been established, with those of chronic hyperglycemia appreciated more recently. Reported relationships between dysglycemia-associated neurocognitive and brain structure changes have varied by study design and differing clinical populations. Barnea-Goraly et al. (9) studied 127 children aged 4 to , 10 years with T1D and 67 age-matched control subjects and found abnormalities in axial diffusivity (a measure that reflects fiber coherence), reduced radial diffusivity (a measure of fiber integrity and myelination), and fractional anisotropy (reflecting the degree of diffusion anisotropy, which is determined by fiber diameter and density, myelination, extracellular diffusion, interaxonal spacing, and fiber tract coherence). These changes correlated with earlier onset of diabetes, longer diabetes duration, and higher A1C. A Diabetes Research in Children Network (DirecNet) longitudinal study (10) in 142 children with T1D and 65 age-matched control subjects (4–10 years of age at study entry) observed slower hippocampal growth in the span of 18 months associated with higher A1C and greater glycemic variability, as assessed by CGM. A separate analysis from this DirecNet study pediatric population (11) incorporated high-resolution structural MRI combined with neurocognitive testing, finding that both hyperglycemia and glucose variability (but not hypoglycemia), were associated with slower growth in specific

Table 1—History of ADA guidance for A1C targets for youth with diabetes since 2000. Years when glycemic target changed are illustrated. Specific changes from the previous goal are indicated in boldface type. A more detailed version of this table is provided as Supplementary Table 1.

Date and publication	Type 1 diabetes	Type 2 diabetes
2000: Type 2 Diabetes in Children and Adolescents (Consensus Statement)(70)		All children: <7%
2003: Standards of Medical Care for Patients With Diabetes Mellitus (71)	Very young children: less stringent treatment goals than the <7% recommended for other individuals	
2005: Care of Children and Adolescents With Type 1 Diabetes: A Statement of the American Diabetes Association (72)	Children <6 years: between 7.5% and 8.5% Children 6–12 years: <8% (≤8 in the narrative) Adolescents (13–19 years): <7.5%	
2005: Standards of Medical Care in Diabetes (73)	<u>Plasma blood glucose and A1C goals:</u> Toddlers and preschoolers (<6 years) Before meals: 100–180 mg/dL Bedtime/overnight: 110–200 mg/dL A1C: ≤8.5 (but ≥7.5%) School age (6–12 years) Before meals: 90–180 mg/dL Bedtime/overnight: 100–180 mg/dL A1C: <8% Adolescents and young adults (13–19 years) Before meals: 90–130 mg/dL Bedtime/overnight: 90–150 mg/dL A1C: <7.5% (a lower goal [<7%] is reasonable if it can be achieved without excessive hypoglycemia)	
2006: Standards of Medical Care in Diabetes (74)	<u>Plasma blood glucose and A1C goals:</u> Toddlers and preschoolers (0–6 years) Before meals: 100–180 mg/dL Bedtime/overnight: 110–200 mg/dL A1C: <8.5% (but >7.5%) School age (6–12 years) Before meals: 90–180 mg/dL Bedtime/overnight: 100–180 mg/dL A1C: , 8% Adolescents & young adults (13–19 years) Before meals: 90–130 mg/dL Bedtime/overnight: 90–150 mg/dL A1C: , 8% (a lower goal [, 7.0%] is reasonable if it can be achieved without excessive hypoglycemia)	
2007: Standards of Medical Care in Diabetes (75)	<u>Plasma blood glucose and A1C goals:</u> Toddlers and preschoolers (0–6 years) Before meals: 100–180 mg/dL Bedtime/overnight: 110–200 mg/dL A1C: , 8.5% (but . 7.5%) School age (6–12 years) Before meals: 90–180 mg/dL Bedtime/overnight: 100–180 mg/dL A1C: , 8% Adolescents & young adults (13–19 years) Before meals: 90–130 mg/dL Bedtime/overnight: 90–150 mg/dL A1C: <7.5% (a lower goal [, 7.0%] is reasonable if it can be achieved without excessive hypoglycemia)	

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Table 1—Continued

Date and publication	Type 1 diabetes	Type 2 diabetes
2011: Standards of Medical Care in Diabetes (76)	<u>Plasma blood glucose and A1C goals:</u> Toddlers and preschoolers (0–6 years) Before meals: 100–180 mg/dL Bedtime/overnight: 110–200 mg/dL A1C: , 8.5% (a lower goal [<8.0%] is reasonable if it can be achieved without excessive hypoglycemia) School age (6–12 years) Before meals: 90–180 mg/dL Bedtime/overnight: 100–180 mg/dL A1C: , 8% (a lower goal [<7.5%] is reasonable if it can be achieved without excessive hypoglycemia) Adolescents and young adults (13–19 years) Before meals: 90–130 mg/dL Bedtime/overnight: 90–150 mg/dL A1C: , 7.5% (a lower goal [, 7.0%] is reasonable if it can be achieved without excessive hypoglycemia)	
2015: Standards of Medical Care in Diabetes (77)	An A1C goal of <7.5% is recommended across all pediatric age-groups. Plasma blood glucose and A1C goals across all pediatric age-groups: Before meals: 90–130 mg/dL (5.0–7.2 mmol/L) Bedtime/overnight: 90–150 mg/dL (5.0–8.3 mmol/L) A1C: <7.5% (a lower goal [<7.0%] is reasonable if it can be achieved without excessive hypoglycemia)	
2016: Standards of Medical Care in Diabetes (78)	An A1C goal of , 7.5% (58 mmol/mol) is recommended across all pediatric age-groups. Blood glucose across all pediatric age-groups: Before meals: 90–130 mg/dL (5.0–7.2 mmol/L) Bedtime/overnight: 90–150 mg/dL (5.0–8.3 mmol/L) A1C: , 7.5% (58 mmol/mol) (a lower goal [, 7.0%] is reasonable if it can be achieved without excessive hypoglycemia)	
2018: Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association (79)		, 7% (most youth). More stringent A1C goals (such as <6.5%) may be appropriate for selected individual patients if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes and lesser degrees of β-cell dysfunction and patients treated with lifestyle or metformin only who achieve significant weight improvement. E
2019: Standards of Medical Care in Diabetes (8)		Incorporated the recommendations in the 2018 Position Statement

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Table 1—Continued

Date and publication	Type 1 diabetes	Type 2 diabetes
2020: Standards of Medical Care in Diabetes (7)	Recommendation 13.21: A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children. B Recommendation 13.22: Less stringent A1C goals (such as <7.5% [58 mmol/mol]) may be appropriate for patients who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or continuous glucose monitors; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). B Recommendation 13.23: Even less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or extensive comorbid conditions. B Recommendation 13.24: Providers may reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if they can be achieved without significant hypoglycemia, negative impacts on well-being, or undue burden of care, or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower targets may also be appropriate during the honeymoon phase. B	, 7% (53 mmol/mol) (most youth); , 6.5% (48 mmol/mol) (selected youth as specified in 2019 Standards of Care). Less stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is increased risk of hypoglycemia.

regions of gray (left precuneus, right temporal, frontal, and parietal lobes and right medial-frontal cortex) and white (splenium of the corpus callosum, bilateral superior-parietal lobe, bilateral anterior forceps, and inferior-frontal fasciculus) matter areas over the 18 months of the study. However, no differences in cognitive and executive function scores between groups were observed. Perantie et al. (12) analyzed a cohort of 108 children 7–17 years old with T1D and 51 healthy sibling control subjects; hyperglycemia was associated with smaller gray matter volume in the right cuneus and precuneus, smaller white matter volume in a right posterior parietal region, and larger gray matter volume in a right prefrontal region, while a history of severe hypoglycemia was associated with smaller gray matter volume in the left superior temporal region. A further study (13) in a subset of the DirecNet cohort of children aged 3 to , 10 years with T1D (n = 22) and age- and sex-matched healthy control subjects (n = 14) demonstrated that

higher time-weighted A1C values were significantly correlated with lower overall intellectual functioning measured by the full-scale intelligence quotient and, within the diabetes group, there was a significant, positive correlation between time-weighted A1C and radial diffusivity. In a recent study, children with T1D performed worse on visuospatial working memory tasks and showed greater increase in activation with higher working memory load (i.e., compensatory modulation of activation) as measured by functional MRI (14).

A meta-analysis on executive function in T1D, including 17 studies and 1,619 pooled participants, determined that inhibition, working memory, set shifting, and overall executive function were lower in adolescents and young adults with T1D than in control subjects (15). A systematic review of 500 youth concluded that repeated episodes of acute hyperglycemia, e.g., diabetic ketoacidosis (DKA), is detrimental to the brain in children and adolescents (16).

Overall, evidence indicates that both hyperglycemia (chronic and acute) and hypoglycemia are associated with structural brain changes, brain function adaptation, and neurocognitive dysfunction in children. More studies are needed on the underlying pathophysiology that can be leveraged for preventive and treatment purposes as well as on optimal glycemic range/glucose variability targets for brain development and growth.

Microvascular and Macrovascular Complications

The DCCT demonstrated that intensive diabetes treatment diminished the risk and rate of development of diabetic complications in individuals with T1D aged 13 to 39 years (1,2). In a subanalysis of the adolescents between the ages of 13 and 17 years at DCCT study entry (n = 125), who were followed for a mean of 7.4 years (range 4–9 years), those in the intensive treatment group attained a mean A1C of 8.06% (SE 0.13) and had significantly lower risk of microalbuminuria as well

as retinopathy appearance or progression compared with participants in the conventional treatment group with a mean A1C of 9.76% (SE 0.12). These results were consistent with the risk reduction observed in adults.

In a longitudinal Australian cohort of adolescents with T1D, a mean decrease in A1C from 9.1% to 8.5% was associated with lower rate of retinopathy (17). The Vascular Diabetic Complications in Southeast Sweden (VISS) study observed 451 individuals diagnosed with T1D before age 35 years and found that no one with long-term weighted mean A1C < 7.6% (60 mmol/mol) developed proliferative retinopathy or persistent macroalbuminuria, compared with 51% of individuals with long-term weighted mean A1C > 9.5% (60 mmol/mol) (18). A population-based Swedish National Diabetes Registry cohort study of 10,398 children and adults with T1D between 1998 and 2017 observed that, while A1C under 6.5% increased the risk of hypoglycemia, the risk of any retinopathy and nephropathy progressively increased with A1C above 6.5% (19) (Fig. 1).

Data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, including 658 subjects with childhood-onset (< 17 years old) T1D diagnosed between 1950 and 1980, evaluated at baseline between 1986 and 1988 and then followed biennially, showed that A1C was an independent risk factor for fatal coronary artery disease (20). Moreover, the longitudinal A1C trajectory was associated with 25-year cardiovascular disease incidence in this cohort; associations were similar across the specific manifestations of cardiovascular disease (21).

Long-term Effects on the Risk of Complications (“Metabolic Memory”)
The Epidemiology of Diabetes Interventions and Complications (EDIC) study was launched to follow adult and pediatric participants after conclusion of the DCCT and evaluate the long-term effects of the DCCT interventions. Over 90% of DCCT participants participated in the EDIC study. After 30 years of diabetes, the cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were much lower (21%, 9%, and 9%) in the DCCT intensive therapy group compared with 50%, 25%, and 14% in the DCCT in the conventional

group (22) despite similar A1C after the DCCT concluded. An analysis restricted to pediatric participants ($n = 175$) observed that, although the mean A1C trajectories of the intensive and conventional groups converged, the risk of retinopathy progression decreased by 74–78% over the next 4 years in the intensive treatment group compared with the conventional group (23). Longitudinal observation of this cohort of adolescents aged 13–18 years at randomization demonstrated that, although none developed diabetic retinopathy requiring treatment while < 18 years of age, there were three cases of proliferative diabetic retinopathy in participants > 21 years of age, all females in the conventional therapy arm (24). More long-term DCCT/EDIC outcome studies are needed, especially for the pediatric cohort.

Early good glycemic control may also beget long-term improved control. Glucose control tracking has been demonstrated in a longitudinal study (25) of 1,146 children and adolescents in Austria and Germany where prepubertal A1C predicted metabolic control in young adulthood after adjustment for confounders. Similarly, the Swedish pediatric diabetes quality registry and the Swedish National Diabetes Register analyzed data from 1,543 youth and found that higher A1C close to diagnosis was associated with higher A1C in adult life as well as risk of microalbuminuria and retinopathy (26). Although more research is needed in this area, it is clear that achieving the best glucose control possible as early as feasible after diagnosis is an important pediatric goal.

Mortality

Mortality is increased for persons diagnosed with T1D during childhood and is associated with glycemic control. The Swedish National Diabetes Register studied 27,195 individuals with T1D registered between 1998 and 2012 and 135,178 matched general population control subjects. This study found the highest excess risks compared with the control subjects of both all-cause mortality and cardiovascular disease in individuals who were diagnosed with T1D at < 10 years of age, adjusting for diabetes duration, with risk over fourfold for all-cause mortality, over sevenfold for cardiovascular mortality, and over elevenfold for cardiovascular disease. In comparison, the corresponding hazard ratios in individuals diagnosed

with T1D between 26 and 30 years of age were 2.83, 3.64, and 3.85 (27). Therefore, earlier age at T1D diagnosis is associated with higher risk of mortality and cardiovascular disease, suggesting the importance of early risk factor control. These findings are in direct contradiction to the historical wisdom that the clock determining risk of complications does not start until puberty. An analysis of 12,652 individuals in the Swedish pediatric diabetes quality registry from 2006 to 2014 showed that higher mortality in young people (< 30 years of age) was associated with higher A1C during childhood (28).

EVIDENCE OF DECREASE IN HYPOGLYCEMIA RISK—AN EVOLUTION SINCE DCCT

Historically, the increased risk of hypoglycemia associated with lower A1C led to establishing guidelines with higher glycemic targets for youth. At the individual level, fear of hypoglycemia leads persons with T1D, caregivers of children with T1D, and diabetes care providers to adopt strategies to maintain hyperglycemia to mitigate this risk (29). While increased risk of hypoglycemia was a major adverse effect in the intensive treatment group in the DCCT study, this study started recruitment in 1983 and concluded follow-up of participants in 1993. The incidence of hypoglycemia has been declining over the almost three decades since then.

The Danish Adult Diabetes Database (DADD) documented an annual decrease of 8.4% in the incidence rate of severe hypoglycemia (30). An analysis of temporal trends in children diagnosed with T1D < 15 years of age from 1995 to 2016 from the longitudinal, prospective, population-based German/Austrian Diabetes Patient History Documentation (Diabetes Patienten Verlaufsdokumentation, DPV) ($N = 59,883$) and Western Australian Children's Diabetes Database (WACDD) ($N = 2,595$) diabetes registries demonstrated concurrent improvements in A1C and decreasing severe hypoglycemia rates (31) between 1995 and 2016. The relationship of A1C and severe hypoglycemia has also changed in the 27 years that have elapsed since the DCCT report. In children and adolescent participants in the U.S. T1D Exchange ($N = 7,102$), German/Austrian DPV ($N = 18,887$), or WACDD ($N = 865$) diabetes registries between 2011 and 2012, rates

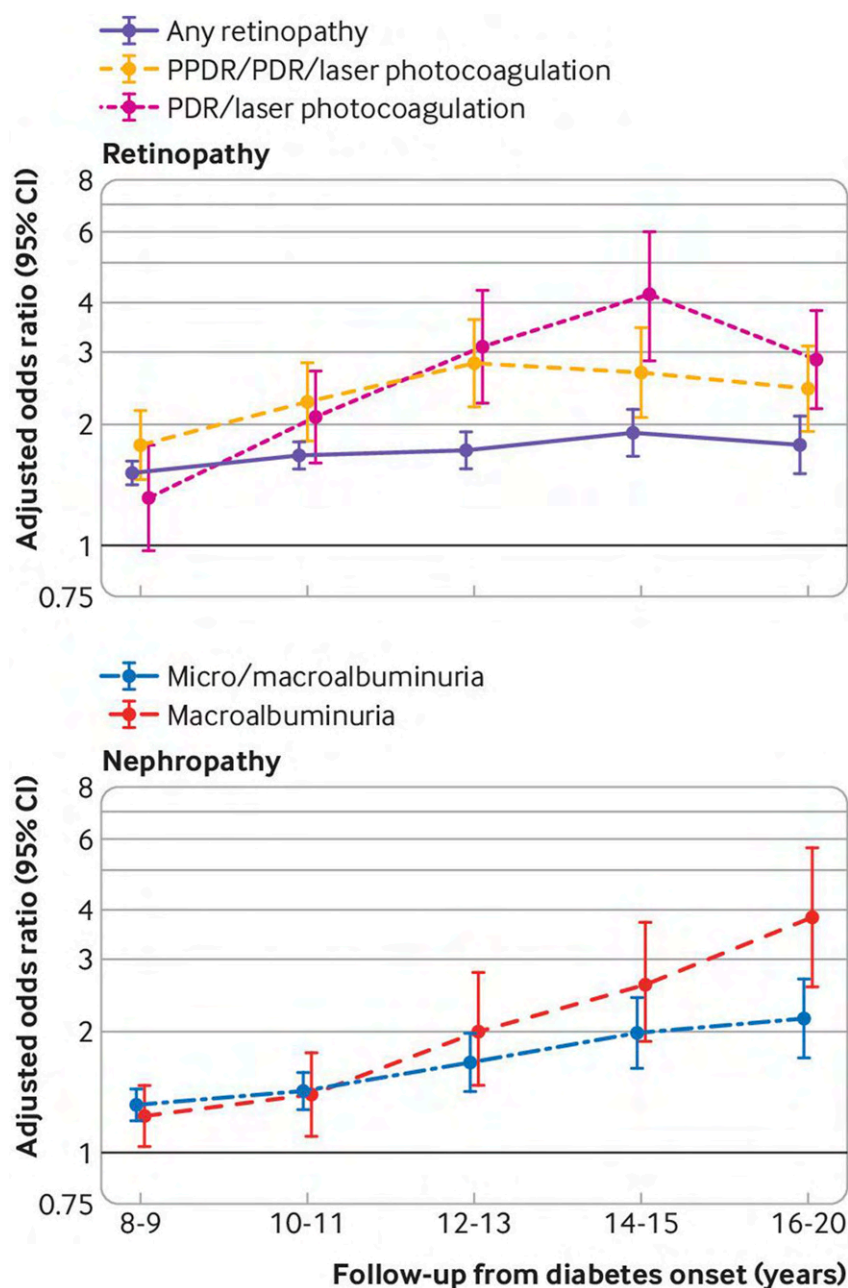


Figure 1—Adjusted odds ratios (95% CI) for retinopathy and nephropathy for 10 mmol/mol increase in A1C area under the curve in the Swedish National Diabetes Registry (19), which collected data between 1 January 1998 and 31 December 2017. Whiskers represent 95% CI. PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy.

of severe hypoglycemia per 100 patient-years were not associated with lower A1C overall or with source registry, treatment regimen, or age-group (32). These results are consistent with a previous analysis of 37,539 participants aged 1 to 20 years old with T1D in the DPV study in Germany and Austria that observed a weakening of the association between lower A1C and severe hypoglycemia (33). A more recently analysis of the DPV and WACDD cohorts confirmed the decreases in A1C

and severe hypoglycemia rate and found similarly low severe hypoglycemia rates in all A1C categories (Fig. 2) (31). Similarly, in a study (34) of 1,770 children (<16 years of age) followed between 2000 and 2011, those with A1C <7% did not have higher rates of hypoglycemia compared with children with A1C 8–9%. A study of 8,806 children <15 years of age ($n = 8,806$) in Nordic countries Denmark, Iceland, Norway, and Sweden between 2008 and 2012 showed that

the risk of severe hypoglycemia was not different between the children with A1C <6.7% and those with higher A1C after adjusting for confounders (35). In the DADD cohort, the risk of severe hypoglycemia associated with a lower A1C decreased between the time periods of 1995–2003 and 2004–2012 (36). A further analysis of data from 17,230 older teenagers (>16 years old) and adults with T1D in the DADD between 2006 and 2012 found that the association between hypoglycemia and A1C was nonlinear, with a much more marked increase for hypoglycemia risk with A1C above 7.6% (60 mmol/mol) than below that level (30).

Newer Treatment Modalities and Hypoglycemic Risk

A plausible explanation for the observed decline in hypoglycemia rates is the increased use of insulin analogs and diabetes technology. The rapid succession of newer and better insulins that started with the approval of the first rapid-acting insulin analog, lispro, in 1996 has been followed by dramatic falls in the rates of hypoglycemia at night and after meals (37).

Advances in technology to administer insulin and monitor glucose have been shown to improve glucose control in T1D. In the study by Cooper et al. (34) with 1,770 children (<16 years of age) followed between 2000 and 2011, children utilizing insulin pumps had lower risk of severe hypoglycemia than children using insulin injections. The study of 8,806 children <15 years of age in the four Nordic countries between 2008 and 2012 showed that pump use was associated with lower risk of severe hypoglycemia (35). In a case-controlled, nonrandomized study, Johnson et al. (38) observed that use of insulin pumps reduced A1C by 0.6% and lowered the risk of severe hypoglycemia by 50%. In the DPV population-based cohort study with over 30,000 pediatric participants with T1D between 2011 and 2015 in Germany, Austria, and Luxembourg, pump therapy was associated with lower A1C and lower rates of severe hypoglycemia and DKA (39).

The recent CGM Intervention in Teens and Young Adults with T1D (CITY) study randomized 153 adolescents and young adults (ages 14–24 years old) with T1D to CGM or blood glucose monitoring (usual care) and demonstrated a significant

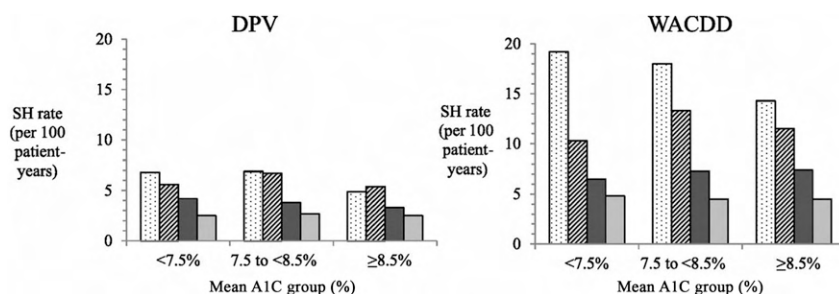


Figure 2—A1C and rates of severe hypoglycemia, adjusted for sex, age at diagnosis, and diabetes duration, observed in the longitudinal, prospective DPV (German-Austrian) and WACDD (Austrian) cohorts since 1991 (31). The rates of severe hypoglycemia (SH) decreased since 1991 and were similar across A1C groups (i.e., <7.5%, 7.5 to <8.5%, and ≥8.5%), particularly in the last time period (2012–2016). Severe hypoglycemia was defined as a hypoglycemic episode resulting in loss of consciousness and/or seizure. White bar with dots represent 1991–2001; striped bar, 2002–2006; dark gray bar, 2007–2011; and light gray bar, 2012–2016.

improvement in glucose control (A1C, time in range) and mean time in hypoglycemia and higher glucose monitoring satisfaction over the 26 weeks of the study (40). This is in contrast with a 2008 study where an early-generation CGM system improved A1C in adult patients (>25 years of age) but not in younger participants, who also had lower device wear times (41). This difference reflects that later-generation devices are better tolerated and have improved in ease of placement and accuracy, leading to greater wear time.

Sensor-augmented insulin pump therapy with the threshold-suspend feature (i.e., predictive low-glucose suspend system) reduced nocturnal hypoglycemia in a randomized trial with 247 participants (42). In a pediatric randomized clinical trial, Ly et al. (43) demonstrated that the predictive low-glucose suspend system significantly reduced time in hypoglycemia although, as expected since the system does not address hyperglycemia, A1C did not decrease.

Closed-loop control systems have been developed to address both hypo- and hyperglycemia. A randomized clinical trial with a total of 168 participants between 14 and 71 years old found 11% significantly higher mean adjusted time in range in participants on the closed-loop system than in those on sensor-augmented pump therapy (control group) (44). A recent study demonstrated that switching to a predictive low-glucose suspend system reduced time in range and increased A1C compared with participants who stayed on a closed-loop system, while time in hypoglycemia did not change (45).

A systematic review and meta-analysis conducted with data up to January 2017

that included 27 comparisons from 24 studies and a total of 585 participants (219 in adult studies, 265 in pediatric studies, and 101 in combined studies) concluded that time in target was 12.59% higher with artificial pancreas systems (95% CI 9.02–16.16; $P = 0.0001$) (46). Similar conclusions were reached by others (47).

Overall, these results support the concept that in the future hypoglycemia rates will continue to decline and time in range will continue to increase. Diabetes technology has consistently demonstrated that it has the potential to improve glucose control in pediatric and adult individuals with T1D. This evidence supports the ADA Standards of Care statement that CGM should be considered for all children and adolescents with T1D (recommendation 7.12, evidence grade B) (5). Studies are needed to translate the interventions proven efficacious in research trials into real-world settings.

A1C and Continuous Glucose Monitoring as Measures of Glycemic Control

Utilization of A1C as an indicator of glycemic control must acknowledge potential nonglycemic confounders. These include factors that lower the measured A1C, e.g., lower erythrocyte life span, and those that increase it, e.g., untreated iron deficiency anemia (48). High or low “glycator” individuals will have, respectively, higher or lower A1C levels than expected based on their glucose levels. In addition, there are significant racial differences in the relationship between glucose levels and A1C, with Black individuals having A1C that is on average 0.4

percentage points (95% CI 0.2–0.6) higher than that in White individuals for a given mean glucose concentration. Of note, this phenomenon was not observed with glycated albumin or fructosamine (49). To overcome the potential risk of error when estimating average glucose from measured A1C, when feasible clinicians can use recent CGM data to document time above and below target range prior to lowering an individual's A1C target. In addition, CGM allows estimation of time in range and, in particular within close-loop systems, minimization of hypoglycemia and hyperglycemic excursions (50). A1C and CGM-derived measures provide complementary assessments of glucose control. Besides widespread accessibility and acceptability of CGM across all population subsets, studies are needed comparing the ability of A1C and CGM-derived measures of glucose control to predict long-term outcomes in individuals with diabetes.

INTERNATIONAL A1C TARGET RECOMMENDATIONS

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines in 2018 (51) recommended a target of <7% for children and youth >5 years old. However, aiming for <7.5% was endorsed for those who cannot articulate symptoms of hypoglycemia or have hypoglycemia unawareness, have a history of severe hypoglycemia, lack access to analogs, are unable to monitor blood glucose regularly, or lack access to advanced insulin delivery technology or CGMs and in high glycators. A target of <6.5% was deemed optimal in situations where this target is attainable without excessive hypoglycemia, poor quality of life, or undue burden of care, and lower targets may be appropriate during the honeymoon period.

The National Institute for Health Care and Excellence (NICE) in the U.K. recommended in 2015 that providers explain to children and young people with T1D and their family members or caregivers (as appropriate) that an A1C target level of 48 mmol/mol (6.5%) or lower is ideal to minimize the risk of long-term complications (52).

The Swedish National Diabetes Register 2018 report revised A1C targets from <57 mmol/mol (<7.4%) to <48 mmol/mol (<6.5%) in May 2017, based on the results from the population-based cohort

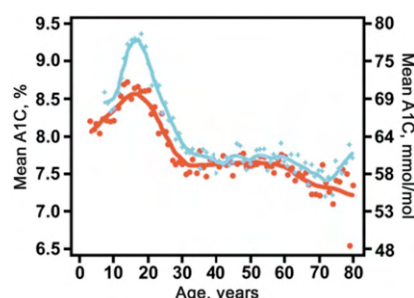


Figure 3—Higher A1C in the 2016–2018 period compared with 2010–2012 across all ages, with particular elevation in adolescents and young adults (56) in the T1D Exchange Clinical Registry, which collected data from multiple clinical centers across the U.S.

analysis between 1998 and 2017 (19). Of note, this decrease in A1C target was followed by a sharp decline in average A1C in children to 54.7 mmol/mol (7.2%).

COMMON BARRIERS TO ACHIEVING A1C TARGETS IN T1D IN YOUTH AND STRATEGIES TO ADDRESS THEM

Although near-normalization of A1C in children is associated with better diabetes outcomes during childhood and beyond, there are numerous barriers to achieving this goal. A major one is the fear of hypoglycemia on the part of persons with diabetes, their caregivers, and their clinical care providers (53). However, as detailed in the previous sections, the previously reported correlation between hypoglycemia and A1C is not observed with contemporary therapies and technology. The use of insulin analogs and diabetes technologies has increased the feasibility of achieving near-normal glycemia and demonstrably lowered the risk of severe hypoglycemia for children with T1D. It is expected that ongoing studies on the impact of the newest devices and systems on hypoglycemia and other diabetes-relevant outcomes including or focusing on pediatric participants (e.g., NCT04084171 in preschoolers, NCT02129868 in children and adolescents, NCT02302963, NCT02844517, and others; ClinicalTrials.gov) will demonstrate further risk reductions. Weight gain is another potential concern with intensive control, as the DCCT reports showed greater weight gain in persons in the intensive group (54). However, a subsequent pediatric study of children in four cohorts (1999, 2002, 2006, and 2009) found that, although use of intensive therapy increased, prevalence of overweight or obesity remained stable

over time (55). In addition, in this study there was no relationship between A1C and BMI z-score after adjusting for potential confounders. Working with children and their parents to prevent weight gain is crucial in this population.

There are multiple levels where barriers to optimal glucose control may exist: biological (e.g., lack of residual β -cell function), behavioral (e.g., burnout), familial (e.g., burden of care), societal (e.g., lack of health insurance), as well as at the health care provider level (e.g., therapeutic inertia). An interplay of influences may result in marked worsening in glucose control, such as during adolescence, when puberty and growth hormones that promote gluconeogenesis and insulin resistance compound with the normal psychological process of striving for independence. Therefore, overcoming hurdles to optimal glucose control will require combinations of strategies. While diabetes technology has been demonstrated to lower A1C, the recent rise in A1C in the pediatric cohort of the T1D Exchange (56) (Fig. 3), despite increased technology adoption, emphasizes the need for multilayer approaches, including strategies that preserve β -cell function after T1D onset (57), improve quality of life, promote adherence to evidence-based recommendations and ongoing treatment plans, provide education to caregivers, advocate for policy changes, and combat therapeutic inertia, among others. The long-term tracking of glucose control from the time of onset (25,26) supports efforts to optimize modifiable factors as close to diagnosis as possible.

Wide disparities exist in A1C and other health outcomes among youth with T1D. Socioeconomically disadvantaged children and those from racial/ethnic minority backgrounds have worse glycemic control, more frequent comorbidities (58–60), more frequent diabetes complications (61), and higher diabetes-associated costs (62). Strategies are needed that address the potentially modifiable factors that underlie disparities at multiple levels, including less access to care and technology, lower health education, and higher frequency of comorbidities (e.g., obesity, hypertension, dyslipidemia) (63). Racial and ethnic disparities in health outcomes are apparent from stage 3 diabetes onset, when African Americans are more likely to present in DKA and less likely to experience a partial remission period, and continue during the first years after diagnosis, with higher A1Cs and

more frequent severe hypoglycemia and cardiovascular risk factors (64). Therefore, intervention approaches that are delivered early in the disease course among socioeconomically disadvantaged youth are needed to promote optimal T1D management and prevent costly complications.

Unfortunately, not every child worldwide has access to modern insulins, diabetes supplies, and even food. Similarly, diabetes technologies are not equally accessible to everyone. Studies demonstrate disparities in their use based on factors related to socioeconomic, health insurance type, age, access to care, race/ethnicity, education, and geography, among others (59). Trials to translate efficacious interventions into real-world settings, cost analyses, and advocacy are needed to help close the gaps in access to diabetes technology.

Mean A1C is higher in the U.S. than in some European countries. A comparison of eight high-income countries for glucose control in youth with T1D, with adjustment for sex, age, diabetes duration, and racial/ethnic minority status, found the lowest A1C in Sweden, where variation within centers was also lowest (65) (Fig. 4). Although all registries in this study reported International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-aligned values, differences in methodology across the different laboratories could have contributed to the variation observed. However, supporting international differences in A1C, a decline in A1C levels was observed in Sweden after lowering the target, unlike in the U.S., where a 2014 decrease in A1C target did not modify the upward temporal trend of A1C in youth with T1D. Participation in a quality improvement collaborative was a significantly differential factor between centers that experienced a decrease in A1C and others that did not between 2010 and 2014 in Sweden (66). In the U.S., the T1D Exchange Quality Improvement Collaborative (T1DX-QI) was established in 2016, initially with 10 U.S. participating diabetes clinics, and has since expanded with the goal to share data and best practices to improve care delivery in T1D (67).

CONCLUSIONS AND FUTURE DIRECTIONS

The 2020 Standards of Care recommends adopting an A1C goal of , 7% (53 mmol/

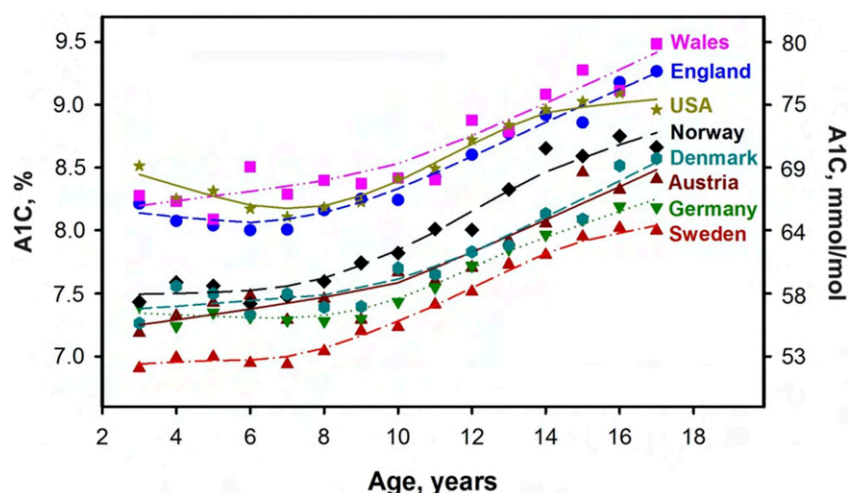


Figure 4—Comparison of mean A1C by age across eight high-income countries (69) in the Pediatric Diabetes Quality Registry, which collected data from Austria, Denmark, England, Germany, Norway, Sweden, the U.S., and Wales between 2013 and 2014.

mol) for many children with T1D, with an emphasis on individualized targets based on the individual risk-benefit ratio (recommendation 13.21, evidence grade B). This recommendation is driven by the overwhelming evidence of the deleterious influences of both chronic and acute hypoglycemia and hyperglycemia (e.g., brain structure changes, neurocognitive defects, long-lasting effects on the risk of microvascular and macrovascular complications), the decrease in overall incidence of severe hypoglycemia, the waning association between lower A1C target and hypoglycemia, and newer insulins and technological advances that have increased the feasibility of minimizing out-of-range glucose levels. The recent adaptation of a lower target for children by the ADA reflects similar guidance from other societies worldwide. Specifically, ISPAD proposed 7% in 2018 (51), NICE in the U.K., 6.5% in 2015 (52), and the Swedish National Diabetes Register 6.5% in 2018 (68).

Current gaps in knowledge include the risk factors for poor diabetes outcomes and hypoglycemia that allow identification of high-risk individuals for targeted interventions. Additionally, it will be important to understand the pathophysiology of the deleterious consequences of hypo- and hyperglycemia (e.g., effects on the brain, relative contribution of the degree and duration of hyperglycemia) that can be leveraged for prevention and treatment. A key gap area is socioeconomic and racial/ethnic disparities in diabetes outcomes and inequality in access to diabetes

care and technology; this recognized need is fueling multiple initiatives at the research level, including trials to translate efficacious interventions to real-world settings, advocacy, and public policy. Furthermore, the implementation of strategies proven effective to optimize diabetes outcomes will be facilitated by ongoing behavioral research to address lack of adherence to treatment plans, concerns about quality of life, undue burden of care, and therapeutic inertia. International data indicate that lower A1C can be achieved safely in pediatrics, and there are ongoing efforts to utilize quality improvement methodology to implement proven efficacious strategies to optimize A1C in the U.S.

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Systematic Review

The Role of Protein and Fat Intake on Insulin Therapy in Glycaemic Control of Paediatric Type 1 Diabetes: A Systematic Review and Research Gaps

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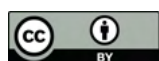
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Abstract: Carbohydrate counting (CHC) is the established form of calculating bolus insulin for meals in children with type 1 diabetes (T1DM). With the widespread use of continuous glucose monitoring (CGM) observation time has become gapless. Recently, the impact of fat, protein and not only carbohydrates on prolonged postprandial hyperglycaemia have become more evident to patients and health-care professionals alike. However, there is no unified recommendation on how to calculate and best administer additional bolus insulin for these two macronutrients. The aim of this review is to investigate: the scientific evidence of how dietary fat and protein influence postprandial glucose levels; current recommendations on the adjustment of bolus insulin; and algorithms for insulin application in children with T1DM. A PubMed search for all articles addressing the role of fat and protein in paediatric (sub-)populations (<18 years old) and a mixed age population (paediatric and adult) with T1DM published in the last 10 years was performed. Conclusion: Only a small number of studies with a very low number of participants and high degree of heterogeneity was identified. While all studies concluded that additional bolus insulin for (high) fat and (high) protein is necessary, no consensus on when dietary fat and/or protein should be taken into calculation and no unified algorithm for insulin therapy in this context exists. A prolonged postprandial observation time is necessary to improve individual metabolic control. Further studies focusing on a stratified paediatric population to create a safe and effective algorithm, taking fat and protein into account, are necessary.

Keywords: diabetes; type 1 diabetes mellitus; children; fat; protein; nutrition; high fat; high protein; mixed meal; paediatric; insulin

1. Introduction

Worldwide the prevalence of children with Type 1 Diabetes mellitus (T1DM) is increasing [1]. The current cornerstones of T1DM therapy include lifetime management of exogenous insulin delivery, dietary and exercise management [2]. Insulin pump therapy and continuous glucose monitoring (CGM) represent the current technical state of the art of insulin management and have been shown to be associated with a reduction of cardiovascular comorbidities (CVC) [3]. Given the availability of 24/7 glucose monitoring, health care professionals have become more aware of the effects of all macronutrients on prolonged postprandial glucose levels. In fact, optimal postprandial glucose levels depend

on matching insulin to the macronutrient meal composition. However, although there is evidence that fat and protein influence insulin requirement of children with T1DM, current recommendations are still solely based on meal-based carbohydrate content [4]. The aim of this review is to summarize the current evidence of the effects of dietary fat and protein in children with T1DM on prandial insulin requirements.

2. Background

2.1. Epidemiology

T1DM is the main type of diabetes in children and adolescents with a rise in prevalence and incidence [4,5]. It is currently estimated that each year 96,000 children under the age of 15 develop T1DM worldwide [6]. T1DM incidences show a great variability between different countries as well as between ethnic populations [7]. In addition, the prevalence rates for overweight/obesity in children with T1DM at least parallels the worldwide increase in the general paediatric population [8,9], which highlights the particular importance of healthy nutrition including the role of macronutrients in this subgroup.

2.2. Treatment of T1DM

The current therapy of T1DM in children is based on three cornerstones: insulin replacement, physical activity, and nutrition.

2.2.1. Insulin and Monitoring

Insulin replacement should mimic physiological patterns including baseline as well as bolus insulin for meals and in hyperglycaemia. It can be conducted either by multiple daily injections (MDI) or as a continuous subcutaneous insulin infusion (CSII). Mealtime bolus insulin is commonly calculated by counting carbohydrates (CHC). CHC is defined as how much insulin is given per 10 g of carbohydrates [4]. The International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines state that fat and protein should be considered for determining the insulin bolus dose and delivery (e.g., dual bolus), yet do not provide any detailed recommendations [4].

Methods that not solely take carbohydrates into consideration for calculating bolus insulin are the Food Insulin Index (FII) [10] and the Pankowska Index/equation (additional 1 U of insulin for every 100 kcal of fat or protein) [11]. While the FII is based on the total calorific sum of a meal given by a reference list, the Pankowska equation converts the kcal of fat and protein into carbohydrate units [11]. However, these are not routinely used in everyday life.

Home self-monitoring of glucose levels is possible by finger stick or tissue glucose monitoring, which is also known as continuous glucose monitoring (CGM). CGM is nowadays commonly paired with CSII. The invention and establishment of CGM has resulted in improved levels of HbA1c [12,13]. The usage of CGM allows for continuous measurements instead of single point measurements. The definition of area under the curve (AUC) for glucose levels allows calculation of euglycemic time in target range (also called time in range (TIR)) [14]. This AUC/TIR via CGM is already complementing and will probably supersede HbA1c in the future in patients with CGM, as HbA1c only reflects glycemia over the previous 4 to 12 weeks and is unable to provide information on daily and postprandial glucose levels [15]. Since its introduction in everyday use, CGM has put a focus on the composition of meals and how macronutrients (protein, fat and carbohydrates) influence and shape glycaemic curves [16].

2.2.2. Nutrition

A healthy and balanced diet is recommended for the entire paediatric T1DM population. Nutritional education should consider the patient's cognitive and psychosocial behaviour and should be appropriate for culture, ethnic background, and family tradition. Daily calorific intake and the distribution of macronutrients should focus on maintaining ideal body weight, optimize growth and development. According to ISPAD guidelines,

carbohydrates should cover 45–55%, fat 30–35% and protein 15–20% of the daily energy intake [4]. A high total intake of fat is linked to an increased risk of being overweight and obesity [17]. A protein intake of 15% to 20% of total daily energy dose is equal to 2 g/kg/d in early infancy, 1 g/kg/d for a 10-year-old and 0.8–0.9 g/kg/d in later adolescence [18]. However, these goals are irregularly met, especially with a surplus of consumed fat [19,20]. In line with the focus of this review on fat and protein, these two macronutrients and their respective roles will be addressed in detail.

2.3. Physiology of Dietary Fat and Protein on Blood Glucose Levels

Dietary fat and protein have been recognized to significantly elevate postprandial blood glucose levels [21]. The mechanisms by which dietary fat influences blood glucose levels include direct effects (free fatty acids (FFAs) stimulate pancreatic beta cells and insulin secretion), effects on other hormones (release of glucagon, glucagon-like-protein 1 (GLP-1), gastric inhibitor polypeptide (GIP) and ghrelin), gastric emptying (additional fat as part of a meal delays gastric emptying) and gluconeogenesis [22,23]. Dietary protein elevates blood glucose levels by alteration of the hormones affecting glucose homeostasis (high protein meals induce elevated plasma glucagon levels, cortisol, growth hormone, insulin-like-growth-factor 1 (IGF-1) and ghrelin) and gluconeogenesis [22]. Dietary fat, added to carbohydrates results in an initially reduced glycaemic postprandial response (first 1–3 h (h)), due to delayed gastric emptying. This extends and increases the glycaemic response over multiple hours [22].

In non-diabetic individuals, dietary protein does not elevate postprandial blood glucose levels [24]. In contrast, the addition of protein to carbohydrates in diabetic patients leads to elevated blood glucose levels and insulin requirements. Several studies investigated the influence of protein on postprandial glycaemic response. Paterson et al. showed that adding ≥ 28 g protein to a mixed meal or consuming ≥ 75 g of protein by itself leads to significant and prolonged postprandial hyperglycaemia in children and young adults aged 7 to 40 years [25]. Hyperglycaemia was demonstrated to start 2–3 h postprandially and last at least 5 h [25,26]. The effect of dietary fat and protein influences blood glucose levels individually but is also accumulative. This reflects the composition of our diet that usually combines all three macronutrients [21,22].

3. Methods

We performed a literature search using the electronic database Pubmed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology.

The search parameters included original articles or reviews about patients (any sex, age, race, or comorbidity were included). The search was limited to articles published between 1 January 2011 and 1 May 2021. The first search without filters was performed relating to “type 1 diabetes” and “protein” and “fat” and “insulin”. This resulted in a total of 496 articles. Non-English publications were excluded. For the purpose of this review, the paediatric population was defined as being under the age of 18 years old. This search resulted in a total of 213 articles ($496 - 283 = 213$). In an additional search the parameters “ISPAD” and “guideline” and “nutrition” were searched for, resulting in four additional original articles, reviews, and guidelines (see Figure 1). This left 217 articles.

Two of the authors (TP, DF) reviewed the titles and abstracts for articles with a paediatric population with type 1 diabetes that focused on high-fat and/or high-protein meals, postprandial glucose levels and insulin and excluded articles deemed irrelevant or with a study population exclusively 18 years and older.

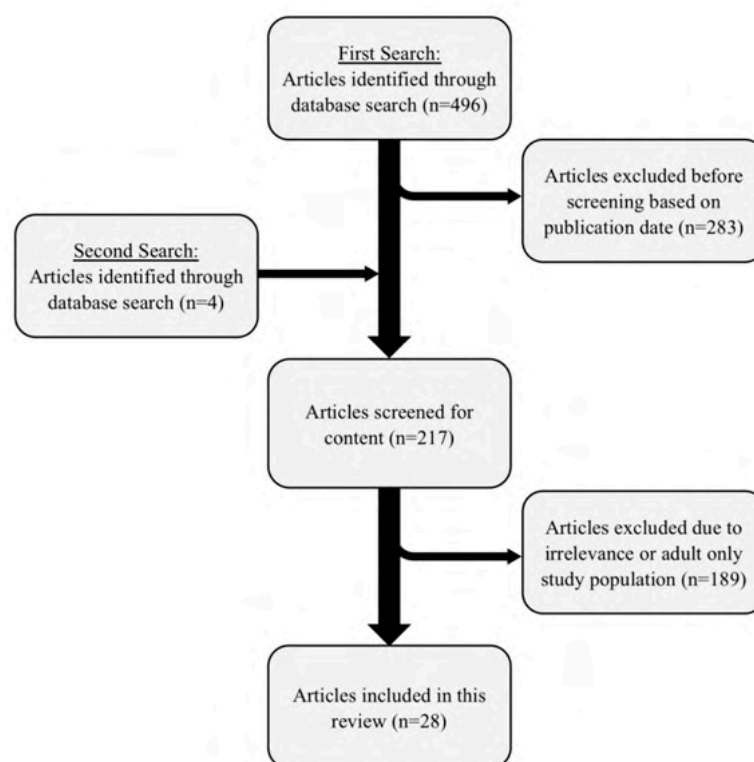


Figure 1. Graphic display of literature search using the electronic database PubMed in accordance with the Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA) methodology.

Two of the authors (TP, DF) reviewed the titles and abstracts for articles published in 1989, a population with type 1 diabetes that focused on high-fat and/or high-protein meals, postprandial glucose levels and insulin and excluded articles deemed irrelevant or with a study population exclusively 18 years and older.

Table 1. Characteristics of reviewed articles. After exclusion of entirely adult study populations and non-relevant publications protein for prandial insulin (equivalent to 22 available type 1 diabetes and the ISPAD guidelines [4] remained for analysis (see Tables 1 and 2).

Authors and Year	Sample Size	Average Age ± SD in Years (Range of Age)	BMI z-Score	HbA1c (% or mmol/mol)	Meal Type (HF/HP/ Mixed Meal)	Composition of the Test Meals (Carbohydrates/Fat /Protein in g)	Measurement Methods/ Duration of Observation	Insulin Regimen (Absolute/%)	Algorithm for Calculating Bolus Insulin
Paediatric Study Population Only									
Seckold R et al., 2019 [19]	22	4.9 ± 1.3 (2.5 to 6.6)	z-Score 0.8 ± 0.9	6.4% ± 0.9% 47 ± 10 mmol/mol	retrospective 3-day meal observation via questionnaire			CSII 41%, MDI 59%	CHC
Katz ML et al., 2014 [20]	252	13.2 ± 2.8 (8 to 18)	z-Score 0.7 ± 0.8	8.51% ± 1.3%	retrospective 3-day meal observation via questionnaire			CSII 69%, MDI 31%	no data on specific algorithms
Smart CE et al., 2013 [21]	33	12.2 ± 2.5 (8 to 17)	z-Score 0.6 ± 0.8	7.2% ± 0.8%	LFLP//LFHP/ /HFHP/ P	LFLP 30.3 g/4 g/5.3 g//LFHP 30 g/3.9/40 g//HFHP 30.3 g/35 g/5.3 g//HFHP 29.8 g/35.2 g/40 g	CGM/5 h	CSII n = 27, MDI n = 6	CHC

Table 1. Characteristics of reviewed original articles between 1 January 2011 and 1 May 2021 with effect of dietary fat and protein for prandial insulin requirements in children with Type 1 Diabetes.

Authors and Year	Sample Size	Average Age $\pm$ SD in Years (Range of Age)	BMI z-Score	HbA1c (% or mmol/mol)	Meal Type (HF/HP/Mixed Meal)	Composition of the Test Meals (Carbohydrates/Fat/Protein in g)	Measurement Methods/Duration of Observation	Insulin Regimen (Absolute/%)	Algorithm for Calculating Bolus Insulin
Paediatric Study Population Only									
Seckold R et al., 2019 [19]	22	4.9 $\pm$ 1.3 (2.5 to 6.6)	z-Score 0.8 $\pm$ 0.9	6.4% $\pm$ 0.9% 47 $\pm$ 10 mmol/mol	retrospective 3-day meal observation via questionnaire			CSII 41%, MDI 59%	CHC
Katz ML et al., 2014 [20]	252	13.2 $\pm$ 2.8 (8 to 18)	z-Score 0.7 $\pm$ 0.8	8.51% $\pm$ 1.3%	retrospective 3-day meal observation via questionnaire			CSII 69%, MDI 31%	no data on specific algorithms
Smart CE et al., 2013 [21]	33	12.2 $\pm$ 2.5 (8 to 17)	z-Score 0.6 $\pm$ 0.8	7.2% $\pm$ 0.8%	LFLP//LFHP//HFLP//HFHP	LFLP 30.3 g/4 g/5.3 g//LFHP 30 g/3.9/40 g//HFLP 30.3 g/35 g/5.3 g//HFHP 29.8 g/35.2 g/40 g	CGM/5 h	CSII n = 27, MDI n = 6	CHC
van der Hoogt M et al., 2017 [27]	22	10.4 $\pm$ 4 (4 to 17)	z-Score −1–+3	8.23% $\pm$ 0.82%	LFLP//HFHP	individually calculated total daily energy requirement using age/weight/gender: LFLP 60%/25%/15%/HFHP 40%/35%/25% LFLP 40.2 g fat ($\pm$ 9.08)/7.72 ($\pm$ 2.25)/10.6 ($\pm$ 3.37) 10.6//HFHP 40.2 ($\pm$ 9.08)/15.3 ($\pm$ 4.03)/26.6 ($\pm$ 6.72)	CGM + cap/10 h	CSII	CHC
Abdou M et al., 2021 [28]	51	11.24 $\pm$ 2.41 (6 to 18)	no data	8.35% $\pm$ 0.99%	mixed meal//HP//HF	25% daily caloric intake//HP (+125 kcal Protein)//HF (+125 kcal Protein)	cap/5 h	MDI	CHC
Kaya N et al., 2020 [29]	30	16 (16 to 18)	z-Score −0.2	7.6% (6–11.2%)	mixed meal//HP//HFHPa//HFHPb(mit Pankowska)	meals were age adjusted: 25% of the total daily energy requirement—mixed meal 70 g/17 g/26 g//HP 70 g/26 g/36 g//HFHPa 70 g/30 g/36 g//HFHPb 70 g/30 g/36 g	cap/4 h	MDI	CHC and Pankowska Equation
Piechowiak K et al., 2017 [30]	58	14.7 $\pm$ 2.2 (10.5 to 18.0)	z-Score 0.3 $\pm$ 1.1 (BMI 21.5 $\pm$ 3.6)	8.3% $\pm$ 11% 67.2 $\pm$ 12 mmol/mol	LFHP	30 g/5 g/36 g	CGM + cap/3 h	CSII	CHC and Pankowska Equation
Lopez PE et al., 2018 [10]	33	12.3 $\pm$ 3.6 (7 to 17)	z-Score 0.2 $\pm$ 1.0	7.3% $\pm$ 0.7%	HF//HP	47 g/27 g/16 g//48 g/13 g/34 g	CGM/5 h	CSII	CHC and Pankowska Equation and Food Index
Pankowska E et al., 2012 [31]	24	12.7 to 17.9	z-Score 0.7 (−1.1–0.98)	7.5% $\pm$ 1.3% (5.1–9.9%)	mixed meal (Pizza)	46.8 g/33.1 g/25.4 g	cap/6 h	CSII	CHC and Pankowska Equation

BMI: Body Mass Index (in kg/m²), SD: standard deviation, HbA1c: glycosylated haemoglobin concentration (in % or mmol/mol), HF: high fat, HP: high protein, LF: low fat, LP: low protein, LFLP: low fat low protein, HFLP: high fat low protein, HFHP: high fat high protein, LFHP: low fat high protein, Measurement methods: cap: capillary blood sample, CGM: continuous glucose monitoring, CSII: continuous subcutaneous insulin infusion, MDI: multiple daily injection, CHC: carbohydrate counting.

Table 2. Reviews for mixed study population between 1 January 2011 and 1 May 2021.

Authors and Year	Sample Size	Average Age ± SD in Years (Range of Age)	BMI z-Score	HbA1c (% or mmol/mol)	Meal Type (HF/HP/Mixed Meal)	Composition of the Test Meals (Carbohydrates/Fat/Protein in g)	Measurement Meth- ods/Duration of Observation	Insulin Regimen (Absolute/%)	Algorithm for Calculating Bolus Insulin
Mixed Study Population (Children And Adults)									
Neu A et al., 2015 [32]	15	16.8 ± 2.9	BMI 21.1 ± 2.19	6.9% ± 0.8	mixed meal//HFHP	70 g/19 g/28 g//70 g/52 g/110 g	CGM/12 h	CSII 6, MDI 9	CHC
Evans M et al., 2019 [33]	11	16.5 ± 2.7 (12 to 21)	z-Score 0.4 ± 0.6	6.9% ± 0.8 52 ± 8.7 mmol/mol	HP//LP	31 g/8 g/60 g//31 g/8 g/5 g	Insulin clamp variation, cap/5 h	Intravenous Insulin infusion to maintain euglycaemia	Pankowska Equation
Lopez PE et al., 2017 [34]	19	12.9 ± 6.7 (6.2 to 19.6)	z- Score 0.4 ± 0.7	6.9% ± 0.6	HFHP	30 g/35 g/40 g	CGM/5 h	CSII	CHC
Kordonouri O et al., 2012 [35]	42	12.3 ± 3.6 (6 to 21)	no data	no data	mixed meal (Pizza)	Pizza—50% carbohydrate, 34% fat, 16% protein—corresponding to 33%of age-adjusted daily energy requirement	cap/6 h	CSII, normal and dual-wave bolus	CHC and Pankowska Equation
Paterson MA et al., 2016 [25]	27	21.7 ± 11.7 (7 to 40)	BMI 21 ± 3.1	6.9% ± 0.8 52 ± 9.1 mmol/mol	2× carbohydrates only//LP to HP	10 g/0 g/0 g//20 g/0 g/0 g//0 g/0 g/ 0 g/0 g//0 g/0 g/12.5 g//0 g/0 g/25 g//0 g/0 g/50 g//0 g/0 g/75 g// 0 g/0 g/100 g	CGM/5 h	CSII 14, MDI 12	CHC
Schweizer R et al., 2020 [36]	16	18.2 ± 2.8 (15.2 to 24)	no data	7.15% (6.2–8.3%)	mixed meal//HFHP	70 g/19 g/28 g//57 g/39 g/92 g	CGM/12 h	CSII 10, MDI 6	CHC +20% and +40% extra insulin for fat and protein
Smith TA et al., 2021 [37]	24	19 ± 9 (9 to 35)	BMI 20.9 (children) BMI 24.6 (adults)	6.7% ± 0.7 49 ± 8 mmol/mol	HFHP	30 g/40 g/50 g	CGM/5 h	MDI	CHC
Paterson M et al., 2020 [38]	26	21.7 ± 8.14 (8 to 40)	BMI 22 ± 3.6	6.9% ± 0.6 52 ± 9.1 mmol/mol	LFHP	30 g/<1 g/50 g	CGM/4 h	CSII	CHCand Pankowska Equation
Smith TA et al., 2021 [39]	27	15 ± 4 (10 to 23)	BMI 21.3 (children) BMI 24.6 (adults)	7.0% ± 0.7 53 ± 7 mmol/mol	HFHP	30 g/40 g/50 g	CGM/5 h	CSII	CHC
Paterson MA et al., 2017 [40]	27	20.7+/-10.3 (10 to 40)	BMI 22 ± 3.6	7.1% ± 0.95 54 ± 3.1 mmol/mol	LFLP//LFHP	30 g/0.4 g/0–12.5–25–50–75 g	CGM/4 h	CSII 16, MDI 11	CHC
De Palma A. et al., 2011 [41]	38	6 to 19	BMI 21.9 ± 4.3	7.66% ± 0.81	mixed meal (Pizza)	carbohydrate 60%, fat 23%, protein 16%; 35% of total daily caloric intake	cap/6 h	CSII	CHC

BMI: Body Mass Index (in kg/m²), SD: standard deviation, HbA1c: glycosylated haemoglobin concentration (in % or mmol/mol), HF: high fat, HP: high protein, LF: low fat, LP: low protein, LFLP: low fat low protein, HFLP: high fat low protein, HFHP: high fat high protein, LFHP: low fat high protein, Measurement methods: cap: capillary blood sample, CGM: continuous glucose monitoring, CSII: continuous subcutaneous insulin infusion, MDI: multiple daily injection, CHC: carbohydrate counting.

Out of the 20 original articles, nine publications [10,19–21,27–31] investigated a paediatric population (<18 years old) only with a total number of 525 participants. Two of these articles (total number of 274 children) feature a questionnaire about dietary habits of diabetic children only and had no focus on blood sugar or bolus insulin following high fat and/or high protein meals [19,20]. This leaves 251 children in paediatric population only in therapeutic studies. Study group characteristics are given in Table 1.

Two studies that were defined as paediatric population by the original authors included patients up to the age of 19; we included these in the mixed population study group [34,41]. The youngest participant in an original therapeutic (meal based) study was 4 years old [27], while the youngest participant in a questionnaire-based study was 2.5 years old [19].

We found 11 original articles with a mixed (paediatric and adult) study population [25,32–41]. The youngest participant was 6 years old [41], the oldest was 40 years old [38]. The mixed study population included a total of 272 persons.

Tables 1 and 2 give the age, duration of illness, BMI, HbA1c, method and duration of glucose monitoring, insulin regimes (MDI vs. CSII) and the number of participants as listed. All original articles included male and female participants with a primarily balanced gender distribution, except for Neu et al. [32] which included 13 males and two females. The results between both genders did not differ significantly. Duration of illness was reported to be at least one year in all original articles. In the paediatric population the maximum duration was 16 years [29], in the mixed population 23 years [39]. HbA1c in the paediatric population only was between 5.0% ($6.4 \pm 0.9\%$, mean $\pm$ SD) [19] and 11.2% (mean 7.6%) [29]. In the mixed population HbA1c was between 6.0% (mean $\pm$ SD $6.7 \pm 0.7\%$) [37] and $7.66 \pm 0.81\%$ (mean $\pm$ SD) [41]. No original article reported a mean HbA1c of $\geq 8.5\%$.

Body composition as represented through body-mass-index (BMI) was not comparable as it was listed as a mixture of total values [25,32,38–41], depending on z-score [10,19–21,27,29,30,33] or according to percentile [31,34]. The widest range for the z-score in the paediatric population only was between -1 and $+3$ [27]. This study included 16 participants with normal weight, five children with a risk of becoming overweight and one overweight [27]. All Studies included children with obesity, but the mean BMI according to z-score was always around 1.0 (normal weight). In the mixed population, reporting of BMI was according to percentile [34], z-score [33] or a total number [25,32,37–41] or no data [35,36] was given.

4. Results

4.1. Effect of Macronutrients Fat and Protein on Glycaemic Control and Therapy

4.1.1. Protein as Dominant Macronutrient

Glycaemic Response

Neu et al. showed peak blood glucose level after 2–3 h postprandially to their protein based standard meal (see Table 2) and a significantly increased AUC after 12 h [32]. Bell et al. reported that postprandial blood glucose is not just affected by the amount of protein but the composition of the meal's other macronutrients as well [42]. The effect of protein varies on its combination with carbohydrates. Paterson et al. concluded that ≥ 75 g of protein alone significantly increases the blood glucose level between minutes 150 to 300 postprandially, while Smart et al. wrote that 30 g of protein in combination also leads to elevated glucose levels [21,40].

Amount of Protein Studied

ISPAD reports protein requirements of 2 g/kg/d in infancy, decreasing to 0.9 g/kg/d in later adolescence but does not give absolute numbers per meal [4]. Protein content in test-meals ranged from 5 g [21] to 100 g. In the article with 100 g of protein, a test-drink was given without age-adjustment to a population between seven and 40 years old [25]. No meal was without protein and while no definition of low protein was given, the authors'

definition of high protein was non comparable. Evans et al. defined high protein as 60 g total, while Paterson et al. defined high protein as 50 g and Smart et al. defined 40 g of protein as high [21,33,38]. Abdou et al. used a stratification according to age that defined high protein as 53 g (age 6–10 years), 61.9 g (10–14 years), 71.5 g (14–19 years) [28].

Insulin Therapy

Evans et al. (60 g protein) report that about 50% more insulin is necessary to maintain euglycemia after a high protein meal, with a high interindividual variability (90% to 600% total bolus insulin) [33]. Piechowiak et al. (36 g protein) used a dual wave bolus with additional insulin to improve postprandial glucose levels after a high protein meal, using CFP-based bolus insulin calculation [30].

4.1.2. Fat as Predominant Macronutrient

Glycaemic Response

Glycaemic responses to high fat meals (and low protein) have been described as initially reducing glucose levels within the first 1–2 h, followed by elevated levels of up to 5 h [21,25]. This is explained by delayed gastric emptying, inducing gluconeogenesis, direct effect of free fatty acids and the influence of fat on hormones [28]. The two high fat (and low protein) articles contradict these findings. Abdou et al. reported glucose peak levels at 2 h postprandially with a normalization towards 5 h (insulin was based on CHC) [28]. Lopez et al. documented the peak glucose excursion between 120 and 180 min after a high fat meal depending on the bolus insulin calculation algorithm (CHC, FII, Pankowska) but without significant difference between the blood glucose levels [10].

Amount of Fat Studied

ISPAD recommends a fat intake of 30–35% of the total daily energy intake [4]. While this represents the daily distribution, it does not reflect the individual meal level. Fat content in test meals ranged from 0 g [25] to 52 g [32]. All authors focusing on fat as the predominant macronutrient except Van der Hoogt [27] defined their non age-adjusted meal as high fat with a fat content of 30 g or higher, but not exceeding 52 g [21,27–29,32,34,36,37,39]. Van der Hoogt et al. used a HFHP meal in a paediatric population (4–17 years old) and an age-adjusted meal with a meal fat content of 15.3 ± 4.03 g (mean $\pm$ SD) [27]. There were two studies that included a high fat meal only as part of the dietary regimen [10,28]. In the other articles fat was administered in a combination meal with varying carbohydrate and protein content. No study with low fat or high fat only (i.e., without any protein) was found (see Tables 1 and 2).

Insulin Therapy

Lopez et al. reported 17% additional bolus insulin for a high fat meal, based on Pankowska equation, than based on CHC, resulting in a better glycaemic profile but with a higher rate of hypoglycaemia [10]. Wolpert et al. noted that fifty grams of fat can double the insulin requirements but interindividual differences in the glycaemic response were noted [43].

4.1.3. Combination of High Fat and High Protein in Meals

Glycaemic Response

High fat and high protein meals resulted in an additive effect with a delayed postprandial glycaemic elevation. Smart et al. found hyperglycaemia from 3 to 5 h after the meal [21]. Van der Hoogt et al. observed hyperglycaemia up to 8.5 h (total observation time was 10 h) [27]. Neu et al. even observed 12 h of hyperglycaemia [32].

Amount of High Fat and High Protein Studied

Please see Tables 1 and 2.

Insulin Therapy

Additional insulin for a HFHP combination was necessary and dosage increased with the duration of illness [27]. Lopez concluded that combination bolus 70%/30% compared to a standard bolus resulted in significantly lowered AUC [34]. Smith et al. recommended 40% additional bolus insulin in CSII. In a different study Smith et al. recommended 125% of CHC-calculated bolus insulin in MDI [37,39]. Neu et al. point out that a diurnal variation in insulin sensitivity may influence bolus insulin requirements [32]. Authors concluded that calculation based solely on CHC was insufficient for maintaining postprandial euglycaemia. Taking high fat and high protein into account for calculating bolus insulin was a common recommendation [21,27,29,32,34,37,39] echoing the ISPAD clinical guidelines [4]. Schweitzer et al. suggested that the introduction of a protein unit (50 g protein) equalling 1 carbohydrate unit (10 g carbohydrates) was necessary. They do not recommend taking high fat into account, quoting articles by Peters and Nordt [36,44,45]. Van der Hoogt found that high fat (15 g in a test meal), high protein content (26 g in a test meal) required an average of eight times more postprandial correction insulin than in low fat (7 g in a test meal), low protein meals (10.6 g in a test meal) [27].

4.1.4. Meal Adjustment According to Age and/or Weight

Meal composition between studies was non comparable. In the articles with a paediatric population four publications adjusted the test meals according to age and/or weight [21,27–29]. Three publications were not including test meals [4,19,46] and 6 articles [10,20,30,32–34] did not adjust the test meals according the age and/or weight.

In the 11 articles with a mixed (paediatric and adult) study population (see Table 2) there were two publications that adjusted the test meals according to age and/or weight. These articles featured a study population of up to 19 [41] and 21 years [35]. Six articles of the mixed population did not specify a test meal [22,42,47–50] and 6 did not adjust the test meals [25,36–40]. Tables 1 and 2 list the meal compositions used in the articles mentioned.

4.2. Insulin Therapy

4.2.1. Counting of Macronutrients: CHC vs. CFP (Carbohydrate-Fat-Protein)

Eleven papers based the calculation of bolus insulin for meals on the individualized, standardized CHC, regardless of the meal composition (four paediatric only [19,21,27,28], seven mixed population [25,32,34,37,39–41]). Eight articles focused on calculating bolus insulin dose depending on fat and/or protein in addition to CHC (four paediatric only [10,29–31], four mixed population [33,35,36,38]).

The methods used for calculating additional protein and fat were the Pankowska Index/equation [10,29–31,33,35,38] as well as the Food Insulin Index (FII) [10]. Lopez et al. found that FII was not better than CHC to manage postprandial glycaemic excursions [10]. Piechowiak et al. used the term fat-protein exchange (1 fat-protein exchange 100 kcal for protein and fat equaling 40 kcal of carbohydrates) mimicking the Pankowska equation [30]. In the original articles by Pankowska, no hypoglycaemia was mentioned [11,51]. In contrast, in four other articles, use of the Pankowska equation resulted in an improved postprandial glycaemic profile, but resulted in significantly more hypoglycaemic events [10,30,35,38]. Kordonouri et al. found significantly more hypoglycaemic events (35.7% vs. 9.5%) when using the Pankowska equation compared to CHC in a 6 h observation period [35]. Lopez et al. argue that a longer observation time (6 h) compared to Pankowska's (2 h) [51] led to the discovery of more hypoglycaemic events [10]. Further, Schweitzer et al. used an individual calculational approach, suggesting that beside carbohydrates only protein and not fat should be taken into calculation ("protein unit") with 50 g of protein equalling 10 g of carbohydrates for extra insulin [36].

4.2.2. Amount of Bolus Insulin for Covering Fat and/or Protein

Only one study was performed using a modified intravenous insulin clamp technique in 11 patients, aged 12 to 21 years (16.5 ± 2.7 , mean $\pm$ SD) and focused on dietary protein

only. The investigators found that high protein meals require about 50% more insulin to maintain euglycemia than a low protein meal that contains the same amount of carbohydrates. The majority (60%) of bolus insulin was required within the first two hours. Large interindividual differences (−1.3 to 9.4 units) of bolus insulin were described [33]. There were no clamp studies focusing on high fat or the combination of high fat and high protein.

Three articles in a paediatric-only population administered insulin based on CHC only with meals that included a varying amount of fat and protein. No additional insulin was added based on calculation (e.g., +20% of additional insulin) or fat and protein content. Elevated and prolonged blood glucose levels were observed, and it was concluded that additional insulin for fat and protein is necessary as well as longer postprandial observation time [21,27,28]. Similar studies exist for a mixed age population with equal results [32,40,41].

Four articles investigated increased insulin doses. Based on CHC, participants' individual insulin: carbohydrate ratios were used to calculate insulin (100%) and then adding insulin (e.g., +20%, +40%). No study administered more than 160% based on CHC [36–39].

Paterson et al. argued that 60% additional insulin was the upper limit, as the Pankowska equation would lead to comparable additional insulin. The authors concluded that 30% additional insulin, delivered via combination bolus, results in improved postprandial blood glucose without an increased risk of hypoglycaemia [38].

Schweitzer et al. used CHC for various meals (carbohydrate only, high-fat-high-protein (HFHP), standard meal) and added different amounts of additional insulin (+20%, +40%) to cover fat and protein. This article concludes that the AUC for glucose in the observed time for fat- and protein-rich meals without additional insulin was significantly higher (1968 ± 581 mg/dL/12 h) than with additional insulin (+20% 1603 ± 561 mg/dL/12 h; +40% 1527 ± 461 mg/dL/12 h). The authors suggest that only protein and not fat should be taken into calculation with 50 g of protein equalling 10 g of carbohydrates [36]. Smith et al. compared single- vs. split-bolus, insulins (aspart vs. regular) and insulin dose (100% vs. 125%) in an MDI regimen. They concluded that 25% additional aspart-insulin for a HFHP breakfast significantly improved postprandial glycemia without hypoglycaemia [37].

In a different study Smith et al. increased the insulin dose from 100% to 140% and 160% for a HFHP breakfast and found that 140% of calculated insulin based on CHC, administered as a combination bolus via CSII, improved the postprandial AUC without increasing hypoglycaemia, which was at higher risk at 160% [39]. These results are in accordance with previous results that state, that using the Pankowska equation (equalling around 160% insulin compared to CHC) leads an increased risk of hypoglycaemia [10,30,35,38].

4.2.3. Ways of Administering Insulin (MDI vs. CSII)

Tables 1 and 2 display the ways in which insulin was administered (MDI vs. CSII).

4.2.4. Choice of Bolus Type in CSII and MDI

Piechowiak et al. compared different bolus algorithms for CSII (normal-dual vs. dual-normal bolus). Bolus insulin was calculated by CHC and adding additional insulin for protein (one fat-protein exchange 100 kcal for protein and fat equaling 40 kcal of carbohydrates) in 58 children aged 10.5–18 years (14.7 ± 2.2 years). This study contained high protein, low fat meals only. A dual wave bolus for high protein and additional insulin for protein gave the best results (finger prick blood glucose) in the 3 h observation time. Mean blood glucose level after 180 min postprandially was 123 ± 43.18 mg/dL with a standard bolus and no additional insulin as compared to a dual-wave bolus 87.15 ± 38.74 mg/dL [30].

Paterson et al. investigated various amounts of insulin, using a combination bolus (65% of the standard dose given up front) for a study comparing the blood glucose elevation after a breakfast drink (50 g protein, 30 g carbohydrate, 0.3 g fat). The study included 26 patients, age 8–40 years (21.7 ± 8.14 , mean $\pm$ SD). Observation time was 4 h, using CGM and CHC. The authors concluded that an additional 30% of insulin resulted in the best result and almost return to baseline after 4 h without increased risk of hypoglycaemia (higher

risk at 145% and 160% bolus insulin), based on CHC calculation. Authors recommend adding 30% of insulin for a high protein (≥ 50 g) meal [38].

Lopez et al. investigated five different combination boli in patients with CSII in comparison to their individual standard bolus. They concluded that for a high fat and high protein meal additional insulin of up to 70% of the insulin:carbohydrate ratio in the extended bolus is needed to maintain euglycemia. A standard bolus based on CHC was only able to provide blood sugar control within the first 120 min, resulting in progressive elevation of blood glucose levels afterwards until the end of observation at 300 min. A combination bolus of $\geq 60\%$ of the insulin:carbohydrate ratio was required in order to control postprandial blood glucose elevation [34].

Kordonouri et al. performed a study on 42 patients aged 6–21 years (12.3 ± 3.6 , mean $\pm$ SD), using sensor-augmented-pumps. Glucose profiles over a period of 6 h postprandially to a standardized pizza meal were obtained. CHC only resulted in a significantly higher AUC (926 ± 285 mg/dL $\times$ 6 h) and average glucose level (160.5 ± 51.9 mg/dL) as compared to taking supplementary fat and protein into account (AUC: 805 ± 261 mg/dL $\times$ 6 h, average glucose 137.8 ± 46.2 nmg/dL). The type of bolus setting (normal vs. dual-wave bolus) made no difference. At the end of the observation period, pre-prandial glucose levels were not reached, with the standard bolus and CHC resulting in the longest time of hyperglycaemia [35].

De Palma et al. investigated a simple bolus versus a double wave bolus (30/70) extended over a 6 h period administered given either immediately or 15 min before a pizza meal. The study population included 38 patients, aged 6–19. Observation period was 6 h via finger prick glucose measurements. The study was based on CHC and found that a simple bolus given 15 min before the meal led to best results (simple bolus 15 min before meal: AUC 6.9 ± 14.9 mg/dL/min $\times 10^3$; simple bolus immediately before meal: AUC 4.2 ± 25.9 mg/dL/min $\times 10^3$; double-wave bolus given 15 min before the meal AUC 1.9 ± 21.3 mg/dL/min $\times 10^3$; double-wave bolus given immediately before the meal AUC 13.3 ± 15.6 mg/dL/min $\times 10^3$) [41].

Smith et al. investigated standard vs. split bolus based on CHC and MDI in a population of 24 patients, aged 9–35 years (19 ± 9 , mean $\pm$ SD) after a high fat, high protein meal (40 g fat, 50 g protein, 30 g carbohydrates). Observation time was 5 h and glucose levels were monitored using CGM. Baseline glucose levels were achieved with 125% of a standard bolus, resulting in a significantly better AUC (341 ± 169.512 mmol/L $\times$ min) compared to 100% insulin (AUC 620 ± 451.788 mmol/L $\times$ min; p -value 0.016). A split bolus resulted in no glycaemic benefit [37].

4.2.5. Interindividual Variation of Insulin Therapy

Four papers highlighted interindividual variations of results and advocated the need for an individualized insulin therapy. Authors stated that a unified recommendation was difficult because of individual glycaemic response to protein intake, individual insulin resistance and duration of illness [10,28,30,33].

5. Discussion

Type 1 Diabetes mellitus is a disease that affects around 1.1 million children and adolescents <20 years worldwide. These numbers are on the increase [6]. The number of studies in the last 10 years ($n = 28$) is limited as is the maximum size of the study populations ($n = 58$ for paediatric only [30] vs. $n = 42$ in a mixed population [35]) after excluding retrospective questionnaire-based articles. Study populations were heterogenous concerning age, treatment, and study parameters.

5.1. Effect of Fat and Protein on Glucose Response

ISPAD recommends taking fat and protein into account when calculating bolus insulin but gives neither a threshold for these macronutrients nor a specific insulin dosage algorithm but refers to a number of reviewed articles [4,21,31,43,52,53].

5.1.1. Fat

In the course of research, the definition of high fat was a dietary recommendation concerning daily intake at 30–35% but no definition per single meal [4]. All author focused on fat as a predominant nutrient, but Van der Hoogt et al. [27] used 30 g and more as a definition of high fat, with a maximum of 52 g [21,27–29,32,34,36,37,39]. Van der Hoogt et al. defined $15.3 \text{ g} \pm 4.03 \text{ g}$ (mean $\pm$ SD) in their age adjusted meal as high fat [27]. Except for two high fat only studies, all fat was part of a mixed meal [10,28]. Authors do not declare the type of fat (e.g., triacylglycerols).

Glycaemic responses to nutritional fat were reported in the results section with partly contradictive results (see above). What remains is a prolonged hyperglycaemia after ingestion of nutritional fat that requires a prolonged monitoring (e.g., CGM) and prolonged dispense of insulin. As noted in the results section fifty grams of fat can double the insulin requirements but interindividual differences in the glycaemic response were noted [43]. The role of fat as a single macronutrient remains controversial as Peters and Davidson stated that fat does not increase the postprandial glucose response. They argue that in non-study settings high fat meals are often conjugated with high carbohydrate contents hence resulting in postprandial hyperglycaemia [44]. In one article by Abdou et al., authors found that added fat led to an early rise of blood glucose (0–3 h postprandially), that regressed after 3 h. The comparative test meal (high protein meal) caused a gradual rise of blood glucose levels in the first 3 h that peaked at 4.5 to 5 and were higher than the high fat meal [28]. This result contradicted the traditional perception that high content fat delays gastric emptying rise of blood glucose levels. Glycaemic responses to high fat meals (and low protein) have been described as initially reducing glucose levels within the first 1–2 h, followed by elevated levels of up to 5 h. These controversial findings advocate the need for further investigation into the role of fat depending on the type (e.g., triacylglycerol), amount and combination with other macronutrients.

5.1.2. Protein

ISPAD gives clear recommendations for daily intake based on age (see results section) but no intake per meal [4]. No unified definition for high protein exists in literature. Definitions of high protein ranged between 40 g of protein and 60 g total [21,33,38]. In high protein only test meals Paterson et al. used 75 g in one study population and found significantly increased blood glucose levels between minutes 150 to 300 postprandially [25,40]. This suggests even longer monitoring for high protein meals [32].

With the popularity of alternative resources of protein (plant based vs. meat based) further research on protein thresholds and sources will be necessary. While low carb diets are not recommended, especially for patients with diabetes, they contain a higher percentage of protein and are becoming ever more popular. Glycaemic response to protein was reported in the results section (see above).

Bell et al. wrote that $\geq 230 \text{ g}$ of a lean steak with salad may require a different insulin dosing strategy than for protein and carbohydrate meals [42]. Evans et al. found that 50% more insulin is necessary to maintain euglycaemia after a high protein meal (as defined as 60 g protein) [33].

While these statements are reasonable, the question remains which diabetic toddler/infant consumes these investigated absolute (and non-age-adjusted) amounts of fat and protein in a single serving. The use of non-adjusted meals in a high number of reviewed studies advocates the need for further paediatric studies with stratification depending on age and/or body weight. These studies may help to define age-adjusted thresholds for when macronutrients start becoming relevant when calculating bolus insulin. The existence of thresholds could further influence patient education. Not only based on levels of patient expertise, (as already proposed) [46] but also through age-stratification for insulin-algorithm and considering macronutrients as well as meal preferences.

5.1.3. Mixed Meals (Fat and Protein Combined)

No unified definition could be found when researching HFHP in single meals. As presented in Tables 1 and 2 various combinations were used to define HFHP. A relevant number of meals consumed in western societies are based on fast food and pre-prepared convenient food containing high amounts of fat and carbohydrates but also protein.

The effect of fat and protein on postprandial hyperglycaemia is additive [21]. In HFHP meals found prolonged hyperglycaemia from 3 h to 12 h depending on the observation time but with different return to baseline glucose levels results [21,32]. This reflects the fact that the more complex a meal, the longer the observation period should be.

In the literature research we identified three authors, who decided to use pizza (composition between studies and macronutrients of pizzas were non comparable) as a meal. All three studies used CSII [31,35,41]. When using CHC prolonged hyperglycaemia up to 6 h was observed [35]. When taking fat and protein into calculation, returning to baseline glucose levels was achieved but resulted in four hypoglycaemic events in 12 patients (significant at 240 min of observation time) [31]. No studies on standardized fast food with a stable macronutrient composition (e.g., BigMac®) were found during research.

5.2. Special Issues: Insulin Resistance—The Role of Puberty and Duration of Illness

While duration of illness (at least 1 year) was regularly stated, pubertal stage was not given. Study populations were almost equally distributed by gender except for one article [32]. BMI and HbA1c (see Tables 1 and 2) reflect adherence to therapy. Short duration of illness and prepubertal stages result in a lower insulin resistance. Van der Hoogt et al. stated that the amount of insulin increased with the duration illness [27]. This is understandable as a longer duration of illness usually results in an increased insulin resistance as well as a beta cell exhaustion and therefore more significantly insulinopenia. These factors lead to higher insulin doses.

Insulin resistance is at a peak during time of puberty as well as in patients with poor diabetes management. The role of insulin resistance is insufficiently discussed in the articles. This leaves the question if results from paediatric populations are comparable to those of adult patients and what this means for mixed age study populations. The role of insulin resistance on calculating bolus insulin should be taken into account as part of the inter-individual therapy. Further studies on this point will be necessary [27].

5.3. The Role of Diets, Daytime of Consumption and Order of Nutrients

In the studies we read, the increased interest of children and adolescents in specialised diets (e.g., low carb diets, vegan) was discussed but not investigated. The same is true for the influence of the time of day the meal is consumed and the order in which macronutrients (e.g., desert before main course) are consumed. This is even more important for children who can be picky eaters and results in switching meals. The Grill study by Neu et al. put an emphasis on the diurnal variation in insulin sensitivity. The authors stated that consuming the same meal on various times of the day may result in different amounts of needed bolus insulin [32]. Various authors showed that consuming carbohydrates at the beginning of a meal leads to lower levels of ghrelin, shortened period of satiety and increased risk for obesity. On the other hand, consuming fat before carbohydrates leads to a delay in gastric emptying resulting in postponed elevation of glucose levels rising [1–3,47,54].

5.4. Technical Aspects—Role of MDI, CSII & CGM

While both CSII and MDI were used to administer bolus insulin, a clear preference for CSII in combination with CGM was observable (see Tables 1 and 2) in the articles.

CSII combined with CGM is considered state of the art [55]. As it is readily available in most richer nations the tendency of study protocols to lean towards this technology leaves the question of how patients and countries unable/unwilling to use CSII and or CGM will benefit from new algorithms. In the studies investigating CSII the dual wave bolus was considered the superior method for maintaining postprandial euglycemia after

HFHP meals. There is no unified recommendation on the amount of bolus insulin or the details of the dual wave bolus (split-percentage and duration) [49].

In conventional MDI therapy with finger prick single point measurements the dynamic of prolonged elevation of glucose levels may be missed. Therefore, CGM can help identify prolonged postprandial hyperglycaemia better. This aids individual needs for adaptation of bolus insulin, both in dosage and algorithm for MDI and CSII. It should further lead the user (i.e., patient) to self-reflect on the impact of macronutrients and modify his therapy thereafter. If a CGM is not available/not wanted, blood glucose after a HFHP meal should be measured for a longer period of time. Further studies need to focus on how to best apply (duration and frequency) single point measurements after a HFHP meal. In all original articles with HFHP additional insulin for a HFHP combination was necessary.

5.5. Current Approaches to Estimate Bolus Insulin

While all reviewed articles (see Tables 1 and 2) agree that additional bolus insulin is necessary for covering protein and/or fat in meals, they do not agree on a threshold to take these macronutrients into account.

Results for additional insulin compared to CHC varied widely. Smith et al. recommended 40% additional bolus for CSII insulin and 25% additional bolus insulin in MDI [37,39].

In all studies for MDI we found no more than 160% of CHC-calculated bolus insulin. Smith et al. justified this percentage by arguing that 160% is what Pankowska equation would result in [39]. As previously stated Pankowska equation was linked to increased hypoglycaemia by some authors [10,30,35,38].

This leads to the question if modifying Pankowska equation in further studies should be attempted. For this, three points need to be considered. First, which macronutrients need to be taken into consideration? All reviewed authors (see Tables 1 and 2) conclude that carbohydrates and protein are relevant for bolus insulin. Some authors like Schweitzer et al. argue that fat can be left out [36]. In the studies on high fat meals the last statement is clearly contradicted. The second point is if all fat and protein need to be considered or if thresholds for a single macronutrient or the combination exist. Suggestions for protein rich only meals exist as stated in the results section. No such thresholds were given for high fat and HFHP meals. Third, a correction of the amount of insulin administered seems reasonable as increased rates of hypoglycaemia were reported [10,30,35,38]. Additional bolus insulin between 25% and 40% for HFHP meals was reported, which is well below the additional 60% when using Pankowska equation [39]. This contradicts findings by Lopez et al. who found that the insulin dose was about 17% higher for high fat (HF) meals and 24% higher for high protein (HP) meals compared to CHC when using Pankowska equation but they used no more than 40% [29]. This resulted in better glycaemic control and a better safety profile. Simply adding insulin to a CHC based insulin dose may be simple but is not representative of reality. In everyday use and patient education taking fat and protein into consideration may be more sophisticated. Pankowska et al. are correct in using fat and protein units to calculate insulin. The equation is elegant and usable. Stated risks of hypoglycaemia cannot be denied but may be improved. In the future, studies with a bigger study population may lead to modifications of the equation or a completely new one. The risk of hypoglycaemia could further be reduced when used closed loop systems that suspend insulin before hypoglycaemia.

6. Gaps of Research & Outlook

During the review process of the articles the following gaps of research and future needs became apparent.

6.1. Study Design

6.1.1. Gaps

Currently there are only a small number of studies with very low numbers of paediatric participants. These studies are heterogeneous and the majority of these studies consist of a mixed-study population (adults and paediatric population). Parameters for study meals, glucose monitoring, duration and outcome differ vastly.

There is no unified complex test meal adapted to age/body weight for studies.

6.1.2. Future Needs

Studies with a large number population (paediatric only).

Expansion of observation time of 12 h and even longer seems reasonable based on the current results. CGM should be routinely used as a time in range reflects the glucose levels better than single-point measurements [13]. Studies should further use a stratified approach (e.g., age, gender, pubertal stage, duration of diabetes, BMI, HbA1c and kind of treatment (CSII vs. MDI)).

Further research on the amount, quality and intake-order of macronutrients and the role of daytime of a meal on postprandial glucose levels. Further studies regarding the influence of duration of illness and insulin resistance. No insulin clamp study for fat currently exists.

6.2. Nutritional Key Points

6.2.1. Gaps

Unified definitions what high fat and/or high protein in a meal means.

A clear threshold of when fat and/or protein must be taken into calculation for bolus insulin.

6.2.2. Future Needs

Recommendation of food composition for a diabetic's single meal, as only a daily recommendation of macronutrient content exists.

6.3. Monitoring of Glucose Levels

In studies: Use of CGM to provide glucose -AUC/TIR for at least 12 h postprandially

In everyday life: providing patients with CGM if possible/desired by patient. In everyday life: If single-prick measurement is the existing monitoring a clear recommendation on postprandial measurements (frequency and duration) has to be given.

6.4. Administering of Bolus Insulin

Development of a safe and easy to use algorithm for bolus insulin. This should reflect carbohydrates, fat, and protein as well as inter-individual needs. Needs to be usable by CSII and MDI patients alike, independent of CGM-use. This could include a modification of the Pankowska equation to reduce the risk of hypoglycaemia.

6.5. Special Issues

Improved patient education models that include fat and protein are essential in the improvement of glycaemic control. Only if the patient understands the effects of nutritional (high) fat and (high) protein an optimal and individualized therapy can be conducted.

7. Conclusions

The search of current literature resulted in a limited number of publications ($n = 28$) investigating the role of nutritional (high) fat and/or (high) protein in children with T1DM. These studies proved to be highly heterogeneous and contained only a limited number of paediatric participants. The research showed that there is no unified definition of HF/HP.

The role of protein and fat as macronutrients in children with diabetes has been recognized, yet CHC (not taking fat and protein into account) is still the dominant form of

calculating insulin boli. This however leads to prolonged hyperglycaemia and unsatisfying results when it comes to AUC/TIR. Improving AUC/TIR leads to reducing long term complications of T1DM.

Although methods for calculating additional insulin for HF/HP meals have been developed (e.g., Pankowska equation and Food Insulin Index), they are impractical in daily use or offer a higher risk of hypoglycaemia. Therefore, an easy to use, inter-individual algorithm for bolus insulin covering HF/HP is necessary (e.g., modifying Pankowska equation or creating a new one). This emphasizes the future need for tailored therapy regimen, improved patient education on macronutrients and if possible, usage of CGM. Improved therapy and education that are implemented early in a patient remain for the rest of life.

Concerning further studies: a clear definition of HF/HP is inevitable for comparison.

Further studies are necessary due to a rising prevalence of T1DM in children and the technical advantages of CGM and AUC/TIR as the “new” HbA1c. These studies should include a greater number of participants and focus of stratification (age, gender etc.), unified definition of HF/HP and even consider developing a standardized mixed meal test to facilitate individual therapy.

A one fits all therapy-approach for children with T1DM is outdated and the future clearly lies in tailored therapy emphasizing the role of macronutrients and the role of nutrition itself. Due to the incomparability of studies and the low number of study participants, study findings were inconsistent regarding the role of dietary fat and protein for prandial insulin requirements in children with type 1 diabetes. The conclusion remains that high fat and/or high protein meals require more bolus insulin than low fat/low protein meals with the identical amount of carbohydrates [42].

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Adjunct Therapies in Treatment of Type 1 Diabetes

Running title: Adjunct therapies in type 1 diabetes

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Abstract

In spite of developments with novel insulin preparations, novel modes of insulin delivery with insulin infusion pumps, and the facility of continuous glucose monitoring, only 20% of patients with type 1 diabetes are under adequate control. The need for innovation is clear and, therefore, the use of adjunct therapies with other pharmacological agents, currently in use for type 2 diabetes, has been tried. Currently, pramlintide is the only agent licensed for use in this condition in addition to insulin. Global trials have been conducted with liraglutide, a GLP-1 receptor agonist (GLP-1RA), dapagliflozin, an SGLT2 inhibitor, and sotagliflozin, an inhibitor of both SGLT1 and SGLT2 transporters. While dapagliflozin and sotagliflozin have now been licensed for clinical use in this condition in Europe and Japan, they have hitherto not been licensed in the US due to a small increase in the risk of diabetic ketoacidosis. However, these agents reduce HbA1c by 0.4%, reduce glycemic oscillations and do not increase the risk of hypoglycemia. Liraglutide, on the other hand, induced a smaller reduction in HbA1c and thus, was not considered for a license. However, further trials are currently being conducted with a combination of semaglutide, the most potent GLP-1RA and dapagliflozin to determine whether this approach would yield better outcomes.

Keywords: Type 1 diabetes, pramlintide, GLP-1 receptor agonists, SGLT inhibitors

Highlights: GLP-1 receptor agonists and SGLT inhibitors have been tried globally with some benefit in type 1 diabetes. Dapagliflozin and sotagliflozin have been licensed for use in type 1 diabetes, as the first two oral agents, in Europe and Japan.

Introduction

Type 1 diabetes (T1D) is an autoimmune disorder due to the loss of the pancreatic β -cell function which is either total or near-total such that endogenous insulin secretion is either totally or nearly lost. There is also concomitant α -cell dysfunction, with excess glucagon in both fasting and postprandial states worsening the hyperglycemia^[1]. Insulin has been the mainstay of the treatment of this condition since its discovery nearly 100 years ago. Despite the evolution of insulin preparations, various modes of insulin delivery through pens and pumps, and the use of continuous glucose monitoring (CGM) devices, only 20% of such patients are under adequate control^[2, 3]. This is associated with both acute and chronic complications; diabetic ketoacidosis (DKA) and hypoglycemia, and microangiopathic and macroangiopathic complications^[4, 5]. The Diabetes Control and Complications Trial (DCCT) data showed a 35–76% reduction in microvascular disease in the intensive treatment group (median HbA_{1c} 7%), compared with the conventional treatment group (median HbA_{1c} 9%) over an average of 6.5 years^[6]. Tight glycemic control with insulin intensification reduces the risk of development and progression of microvascular and macrovascular complications as evident from the DCCT and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study^[7]. Tight glycemic control has

long term positive effects on the development and progression of hypertension, cardiovascular disease (CVD), and atherosclerosis as well^[8].

An ideal treatment for T1D should enable patients to maintain glycated hemoglobin (HbA1c) < 7.0% without weight gain or an increased risk of hypoglycemia/DKA, and also reduce the risk of CVD. Insulin being the crucial treatment for T1D comes with many limitations. Intensive insulin therapy to achieve the glycemic goal is associated with an increased risk of hypoglycemia^[6, 7, 9]. Hypoglycemia is a major deterrent in achieving glycemic targets and affects the quality of life^[10, 11]. Despite advancements in insulin delivery devices and the availability of CGM, patients with T1D still suffer from unpredictable blood glucose profiles and increased frequency of hypoglycemia. The 12-month risk of severe hypoglycemia associated with seizure or loss of consciousness was recently reported at 11.6% in adults and 9.9% in youth, rising to 18.6% in T1D with >40 years of insulin therapy^[5, 12]. Frequent hypoglycemia causes fear among patients leading to insulin injections being missed/dose reductions, subsequently producing hyperglycemia. Insulin therapy poses a challenge in patients with altered gastric emptying, often resulting in a mismatch between glucose absorption and insulin peak, causing significant postprandial blood glucose excursions. About 30% of patients with T1D in the U.S. are obese and nearly 50% of patients have metabolic syndrome^[13, 14]. Overweight and obesity are important cardiovascular risk factors^[15], and increased weight gain associated with intensive insulin therapy further adversely affects the cardiovascular risk profile and negates the benefits of improved glycemic control^[16-18].

We clearly, therefore, need new therapeutic strategies for the treatment of T1D to achieve glycemic goals as well as address the limitations encountered with insulin therapy. As a result, the field of adjunct therapies in T1D has developed. The drugs used in these strategies should exert effects that reduce blood glucose concentrations independently of insulin and provide additive actions that help to control diabetes

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better. These strategies involve the suppression of appetite, slowing of gastric emptying, the suppression of postprandial increase of glucagon, the stimulation of residual insulin secretion when possible, reduction in glycemic oscillations, and the excretion of glucose by the kidney tubules by inhibition of its reabsorption. Additionally, weight reducing properties of such drugs would be of immense use and cardiovascular benefit would be an added advantage. Various drugs like pramlintide, incretin-based drugs; glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-1 and 2 (SGLT1/SGLT2) inhibitors and metformin, that utilize these mechanisms have now been investigated as add-on therapies to insulin for the treatment of T1D and have given us hope. Here, we discuss the mechanism of action, efficacy, and adverse effects of these drugs as adjunctive therapies in the treatment of T1D. In future, one or more of these agents in combination with insulin might be used to achieve treatment goals in patients with T1D.

Pramlintide

Amylin, a glucoregulatory hormone, is co-secreted with insulin from pancreatic β -cells and complements insulin action in controlling postprandial glucose excursions^[19]. It slows gastric emptying^[20, 21], suppresses postprandial glucagon secretion^[22, 23], and also stimulates the satiety centers, reducing appetite^[24, 25]. Pramlintide, a derivative of amylin, is the first noninsulin treatment and the only approved drug by the Food and Drug Administration (FDA) as adjunctive therapy to insulin for the treatment of T1D. The usual dose of pramlintide is 30-60 μ g, with a starting dose of 15 μ g, given as a subcutaneous injection before meals. Three large multicenter, randomized, placebo-controlled clinical trials^[26-28] have shown that

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pramlintide is an effective agent that can be used as an adjunct to mealtime insulin in patients with T1D, resulting in an overall reduction of HbA1c (placebo-corrected HbA1c reduction of 0.3-0.5%), decreasing TDD of insulin (6-12% reductions) and a small reduction in bodyweight. The most common adverse effect with pramlintide is gastrointestinal in nature, nausea being the most common. It is usually mild-moderate in intensity, improves over time, and with gradual dose escalation, tolerability is better. In clinical practice, insulin dose has to be reduced when using this drug to reduce the risk of hypoglycemia.

Glucagon-like peptide-1 receptor agonists (GLP-1RA)

GLP1-RA enhance residual endogenous insulin secretion from pancreatic β -cells and suppress postprandial glucagon release^[29, 30]. These agents induce the release of insulin in a glucose-dependent manner and insulin secretion stops when the patient is euglycemic. Postprandial glucagon levels get suppressed but this is not observed when the patient is experiencing hypoglycemia^[29, 31]. Additionally, they delay gastric emptying and cause appetite suppression resulting in weight loss^[32]. GLP1-RA are commonly used in patients with type 2 diabetes and they have known cardioprotective and nephroprotective benefits^[33-36]. Based on these actions, GLP1-RA have a promising role in the treatment of T1D. The earliest studies evaluating GLP1-RA for treatment of T1D were either retrospective^[37, 38] or prospective, open-label design with treatment duration varying from 4-56 weeks^[39-42]. The effect of adding GLP1RA to insulin on glycemic control has been conflicting in these studies. Some studies reported a reduction in HbA1c by 0.4-0.9% in the GLP1RA plus insulin treatment group compared to insulin alone^[37-39]. However, other studies demonstrated a similar effect on glycemic control between the two treatment regimens^[40-42]. The first three randomized, double-blinded, placebo-controlled studies, using liraglutide as an add-on to insulin, also show conflicting data.^[43-45] The clinical trials performed by Frandsen et al.^[43] and Dejgaard et al.^[44] showed no difference in the HbA1c reduction between the

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liraglutide and placebo groups. By contrast, the third trial^[45] showed significant reduction in HbA1c in the 1.2 mg liraglutide dose (-0.8%) but not for liraglutide 1.8 mg (-0.4%) and 0.6 mg (-0.2%) compared to placebo (-0.3%) at the end of 12 weeks.

In regards to total daily dose (TDD) of insulin and weight loss, the data has been consistent in all these clinical trials. In all studies^[37-41, 43-45], except one^[42], there was a robust weight loss ranging from 2.2-6.6% (1.8-5.8 kg reduction in bodyweight) in the liraglutide group compared to weight gain (0.2-1.1 kg) in the placebo arm. The TDD of insulin decreased significantly in almost all studies. The basal insulin dose was reduced between 0-49% and bolus insulin dose between 11-46%. The reductions in insulin dose were more pronounced in the C-peptide positive (residual β -cell reserve) T1D patients receiving liraglutide compared to c-peptide negative. In the 4-week open-label study by Kielgast et al.^[40] using 1.2 mg liraglutide, there was a 29% reduction in basal and 46% reduction in bolus insulin in C-peptide positive T1D patients compared to a reduction of 6% in basal and 28% in bolus insulin in C-peptide negative T1D patients. This is consistent with what we have seen in our clinical practice. Some of our c-peptide positive T1D patients were able to eliminate the prandial insulin after the addition of a GLP1RA. Elimination of prandial insulin not only improves glycemic control but also reduces the occurrence of hypoglycemia and improves the quality of life.

Recently there have been 2 large, multicenter phase 3a trials evaluating the long-term effects of liraglutide as an adjunct therapy in T1D. ADJUNCT ONE was a 52-week, multicenter, randomized, double-blinded, placebo-controlled, treat-to-target trial that enrolled 1389 subjects with uncontrolled T1D to receive once-daily subcutaneous liraglutide (0.6, 1.2 or 1.8 mg) or placebo in addition to insulin^[46]. Because this was a treat-to-target trial, all the groups had HbA1c reduction from a mean baseline of 8.2% during the study period. However, the drop was largest in the liraglutide treated subjects. The maximum drop was seen

around 16-20 weeks (HbA1c reduction of 0.8% in liraglutide 1.8 mg group), but partially lost by week 52 (-0.54%, -0.49%, -0.43% for liraglutide 1.8, 1.2, and 0.6 mg, respectively, and -0.34% for placebo, $P<0.05$ for liraglutide 1.8, 1.2 mg only). Nearly twice the number of subjects in liraglutide 1.8 and 1.2 mg groups were able to reach the ADA target of HbA1c $< 7.0\%$ compared to placebo. The TDD of insulin decreased by 5% and 2% in the liraglutide 1.8 mg and 1.2 mg groups, respectively, but increased in the placebo arm. There was a significant dose-dependent weight reduction in the liraglutide arm (-4.0 kg for liraglutide 1.8 mg group) compared to a weight gain of 0.9 kg in the placebo arm ($P<0.0001$). The most common adverse effects were those of gastrointestinal (mostly nausea), reported more frequently in the liraglutide arm and increased dose-dependently. The rate of symptomatic hypoglycemia increased in all liraglutide groups and hyperglycemia with ketosis increased significantly for liraglutide 1.8 mg dose only.

ADJUNCT TWO trial was a 26-week, randomized, double-blinded, placebo-controlled trial which enrolled 835 subjects with uncontrolled T1D to receive once-daily subcutaneous liraglutide (0.6, 1.2 or 1.8 mg) or placebo to an individually capped TDD of insulin^[47]. Adjustments in insulin doses within the limits of insulin cap were allowed following standard medical care. There was a statistically significant reduction in mean HbA1c (8.1%) in liraglutide groups versus placebo (placebo-corrected reduction - 0.35%, -0.23%, -0.24% for doses 1.8, 1.2, 0.6 mg, respectively, $P<0.01$ for all) at week 26. There was a significant dose-dependent decrease in TDD of insulin across all liraglutide groups compared to placebo at 26 weeks and this was mainly achieved through prandial dose reductions. Liraglutide significantly reduced mean bodyweight in a dose-dependent manner (-5.1, -4.0, and -2.5 kg for doses 1.8, 1.2, and 0.6 mg, respectively) versus placebo (-0.2 kg). Significantly more subjects in the liraglutide 1.8 mg group achieved ADA target of $<7.0\%$ compared to placebo (18.8 vs. 10.0%, respectively, odds ratio 2.12, $P<0.05$). Nausea was the most common GI side effect in the liraglutide arm but tended to occur in the first

few weeks of therapy and subsiding after. For all liraglutide doses, there was no difference in severe (BG < 55) or nocturnal hypoglycemic episodes compared to placebo. There were higher rates of hyperglycemia with ketosis in the liraglutide 1.8 mg group. Within the subgroup analyses, subjects with positive C-peptide fared better than the subjects without measurable C-peptide with improved treatment effect on HbA1c across all liraglutide doses.

ADJUNCT ONE and ADJUNCT TWO trials are the first two large-scale multicenter clinical trials to investigate the efficacy and safety of adding liraglutide to insulin for the treatment of T1D. When added to insulin therapy, liraglutide resulted in modest HbA1c reduction (~0.5%), reduction in total insulin dose, and bodyweight (upto 5.1 kg) reduction. What is interesting to note is a significantly greater reduction in HbA1c (-0.8%) in C-peptide positive patients compared to C-peptide negative patients, also seen in our clinical practice. Most of the insulin dose reduction in the liraglutide treatment group was due to reductions in prandial insulin. Our previous work has shown that there is a reduction in carbohydrate intake, appetite suppression, and reduction in postprandial glucagon with liraglutide treatment in subjects with T1D, and therefore, by these mechanisms, there could be reduced exogenous insulin requirement^[45]. Weight loss is another benefit of treatment with GLP1RA, making it an ideal adjunctive therapy, as weight gain associated with insulin therapy increases the risk of insulin resistance, metabolic syndrome, and cardiovascular disease. The most common adverse effect associated with GLP1RA use is nausea, however, it is transient in nature and can be mitigated with gradual dose titration. The increased rates of symptomatic hypoglycemia seen with liraglutide in ADJUNCT trials might relate to difficulties in adjusting bolus insulin, nausea, satiety, or miscalculated food intake. Since GLP1RA do not affect the glucagon counter-regulatory response to hypoglycemia, severe hypoglycemia rates were not increased in the liraglutide groups compared to placebo. Higher rates of hyperglycemia with ketosis observed in the

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liraglutide arm in ADJUNCT trials may partly be due to nausea leading to more ketone reporting by the patients, and partly due to reduction in TDD of insulin leading to peripheral lipolysis and subsequent ketogenesis. Overall, GLP1RA have a great potential as adjunctive therapy in the treatment of T1D, improving glycemic control, reducing glycemic oscillations, decreasing insulin requirements, and causing weight loss leading to more favorable cardiovascular risk profile.

Sodium-glucose cotransporter-1 and 2 (SGLT1 and SGLT2) inhibitors

SGLT2 is present in human renal proximal tubular cells that are responsible for renal reabsorption of 95% of filtered glucose (160–180 g/day)^[48, 49]. SGLT2 inhibitors work by inhibiting renal glucose reabsorption and thereby, reducing the plasma glucose in an insulin-independent manner^[50-52]. SGLT1, on the other hand, is primarily of importance in the small intestine, an organ that does not express SGLT2, while in the kidney they are expressed in the late renal proximal tubules, where it reabsorbs the glucose escaped from the upstream SGLT2^[53]. Blockade of SGLT1 in small intestine decreases glucose absorption which leads to increased glucose delivery to the distal small intestine, stimulating the release of GLP1 and other GI peptides (such as polypeptide tyrosine)^[54, 55], and thereby, blunting postprandial glucose peaks^[56] and assisting in appetite control as well^[57]. Sotagliflozin is a novel, dual inhibitor of SGLT1 and SGLT2, with 20-fold more sensitivity for SGLT2 than for SGLT1, and designed to reduce glucose absorption in the gastrointestinal tract via SGLT1 inhibition and renal glucose reabsorption via SGLT2 inhibition^[58]. While the SGLT2 inhibitors have been approved by FDA for the management of T2DM^[59] and their safety, efficacy, and cardiovascular and renal outcomes in T2DM are well demonstrated in several studies^[60-64]; they have not yet been FDA approved for use in patients with T1D. The potential role of SGLT inhibitors in T1D has been studied in various short-term human studies^[65-68] and long-term randomized clinical trials.

DEPICT-1 was the first long-term, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial, enrolling a total of 833 patients with uncontrolled T1D, who were randomly assigned (1:1:1) to receive dapagliflozin 5 mg or 10 mg once daily or matched placebo^[69]. The study consisted of a 24-week short-term period and a 28-week extension period. Mean baseline HbA1c was 8.5% and at week 52, the placebo-corrected reduction in HbA1c from baseline was -0.33% (95% CI -0.49%, -0.17) for dapagliflozin 5 mg and -0.36% (CI -0.53, -0.20) for dapagliflozin 10 mg. The TDD of insulin decreased drastically at week 2 for both groups of dapagliflozin and remained lower over 52 weeks of the study period compared to placebo. There was a significant reduction in bodyweight observed in dapagliflozin 5 mg and 10 mg groups (difference vs. placebo -2.95% [CI -3.83, -2.06] and -4.54% [CI -5.40, -3.66], respectively) at week 52, with maximum weight loss difference of 5.5 kg in dapagliflozin 10 mg dose. Almost twice the number of subjects in dapagliflozin 5 mg and 10 mg groups compared to placebo achieved an HbA1c reduction >0.5% without an episode of severe hypoglycemia. Among the adverse events, genital infections occurred almost 5 times more in the dapagliflozin groups compared to placebo. The event rates for hypoglycemia were balanced across the treatment groups but more patients in the dapagliflozin groups had DKA episodes (almost twice) versus placebo.

DEPICT-2 was the second of two, randomized, double-blinded, placebo-controlled, 52-week phase 3, multicenter clinical trial providing further supportive evidence for the use of dapagliflozin as an adjunct therapy in T1D^[70]. Study design being similar to DEPICT-1, participants were from different geographical regions, DEPICT-1 trial having majority subjects of European descent but DEPICT-2 trial having ~20% from the Asia-Pacific region. At 52 weeks, dapagliflozin 5 and 10 mg were associated with a significant reduction in HbA1c (placebo-corrected reduction of -0.20% [CI -0.34, -0.06] and -0.25% [CI -0.38, -0.11], respectively) from a mean baseline HbA1c of 8.4%. Similar outcomes were observed for

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reductions in TDD of insulin in DEPICT-2 as were seen in DEPICT-1 trial. Reductions in bodyweight seen at 24-week were sustained over 52 week treatment period for both dapagliflozin treatment groups (difference [95% CI] vs. placebo, dapagliflozin 5 mg -4.42% [-5.19, -3.64]; and dapagliflozin 10 mg -4.86% [-5.63, -4.08]). The proportion of hypoglycemic events was similar across groups, and as in DEPICT-1, more participants in the dapagliflozin 5 and 10 mg groups had DKA events versus placebo (4.1%, 3.7%, and 0.4%, respectively).

EASE-2 and 3 trials were phase 3, randomized, double-blind, placebo-controlled trials to evaluate the efficacy and safety of empagliflozin in the treatment of T1D, conducted over 52 weeks (EASE-2) and 26 weeks (EASE-3)^[71]. Empagliflozin 10 and 25 mg doses were studied in both trials but a unique lower dose of 2.5 mg was included in EASE-3 trial to characterize an effective and safer dose. A total of 730 subjects were assigned treatment in EASE-2 and 977 subjects in EASE-3. There was a significant reduction of HbA1c in all empagliflozin groups across both the trials. The placebo-corrected change in HbA1c from baseline was upto -0.54% at week 26 and upto -0.45% at week 52 in empagliflozin groups in the EASE-2 trial, and upto -0.52% at week 26 in the EASE-3 trial. Empagliflozin 2.5 mg also significantly reduced HbA1c (placebo-corrected change -0.28%; $P < 0.0001$) at week 26. The largest placebo-corrected HbA1c reduction occurred in patients with baseline HbA1c $> 8\%$ (upto -0.70% in empagliflozin 10 mg dose). Empagliflozin 2.5/10/25 mg doses, respectively, reduced mean weight by -1.8/-3.0/-3.4 kg (placebo-corrected weight, all $P < 0.0001$), and there was a reduction in total insulin doses compared to placebo (-6.4 to -13.3%) in all empagliflozin groups after 26 weeks of treatment. Empagliflozin significantly increased CGM-derived glucose time-in-range (70-180 mg/dL) and decreased glycemic variability. The event rates for both symptomatic and nocturnal hypoglycemia were significantly reduced with empagliflozin groups compared to placebo ($p < 0.05$). Genital infections

occurred more frequently with empagliflozin. Diabetic ketoacidosis occurred more with empagliflozin 10 mg (4.3%) and 25 mg (3.3%) but was comparable between empagliflozin 2.5 mg (0.8%) and placebo (1.2%).

The role of dual SGLT-1/2 inhibitor sotagliflozin as an adjunct therapy in T1D was first investigated in a randomized, double-blind, placebo-controlled trial including 33 subjects over 29 days^[72]. This study primarily demonstrated reduction in total daily bolus insulin (-32.0% vs -6.4%), lower mean blood glucose as measured by CGM (148 vs 170 mg/dL), more time spent in target range (68.2% vs. 54.0%), less postprandial glycemic excursions, and a reduction in A1c (-0.55% vs +0.06%) and bodyweight (-1.7 kg vs +0.5 kg) in the treatment group compared to placebo after 29 days. GI disorders were the most frequently reported adverse events with sotagliflozin. A larger study, inTandem3, was a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial of 24 weeks duration, enrolling 1402 patients with T1D to receive sotagliflozin (400 mg daily) or placebo in addition to insulin therapy^[73]. Almost twice the number of patients in the sotagliflozin group than the placebo achieved the primary endpoint of HbA1c <7.0% at week 24 with no severe hypoglycemia or DKA (28.6% vs 15.2%, $P<0.001$). The reduction in HbA1c (placebo-corrected change from baseline -0.46%, $P<0.001$) and reduction in bodyweight (difference vs. placebo -2.98 kg, $P<0.001$) were significantly greater for sotagliflozin than for placebo at week 24. There were also significant reductions in total daily insulin (difference vs placebo -9.7%) and systolic blood pressure (difference vs placebo -3.5 mm) in the sotagliflozin group. Event rates for hypoglycemia (BG < 70) were similar between the two groups but rates for severe hypoglycemia (BG < 55) were significantly lower in the sotagliflozin group compared to placebo. Gastrointestinal events (consistent with SGLT1 inhibition, nearly 2 fold) and genital mycotic infections (consistent with SGLT2 inhibition, nearly 3-fold) were more common in the sotagliflozin

group than in the placebo group. The rate of DKA was higher in the sotagliflozin group than in the placebo group (3.0% and 0.6%, respectively).

These clinical trials demonstrate a remarkable potential of SGLT inhibitors as add-on therapy to insulin in the treatment of T1D. HbA1c reduction has been to the degree of 0.3-0.7% without the added risk of hypoglycemia, in fact, the rates for severe (BG < 55 mg/dL) and nocturnal hypoglycemia were even lower in the SGLT-1/SGLT-2 inhibitors treatment groups^[71, 73]. HbA1c reduction was observed despite the reduction in TDD of insulin, up to ~13%, and more significant reductions seen in the bolus insulin doses (up to ~30%) than basal. Marked reduction in bolus insulin is probably the reason for lower rates of hypoglycemia observed with SGLT-1/SGLT-2 inhibitors. Additionally, these agents reduce the magnitude of postprandial glucose excursions and increase glucose time-in-range (BG 70-180 mg/dL) as supported by the CGM data^[69-71, 74]. Improved glycemic control is accompanied by a meaningful (3-5% of bodyweight from baseline) and sustained weight loss with these agents, which is due to fat reduction related to caloric loss from increased glycosuria. The beneficial effect of SGLT-1/SGLT-2 inhibitors on weight may help to rectify the negative effect of weight gain associated with intensive insulin treatment on cardiovascular risk profile. The significant reductions seen in systolic blood pressure with these agents further confers benefit and provides protection against adverse cardiovascular events. Improved glycemic control, reduced risk of hypoglycemia, reduction in insulin dosages, and significant reduction in bodyweight with SGLT inhibitors provide compelling evidence of their benefit in the treatment of T1D patients, targeting major problems around metabolic control in these patients. Based on the DEPICT-1/2 trials, dapagliflozin is now licensed for treatment in T1D in Europe and Japan and so is sotagliflozin but FDA in the US has not approved of these yet.

The major adverse effect associated with all the SGLT-1/SGLT-2 inhibitors is DKA which was present with more frequency (about 2-3 times) than the placebo and led to discontinuation from the trials. Most of the cases were mild and were managed by standard of care for DKA. An interesting finding from the EASE-3 trial was the significant, although small in magnitude but clinically relevant, reductions in HbA1c, insulin doses, and bodyweight with the lower dose (2.5 mg) of empagliflozin but notably lower DKA risk (comparable to placebo). A possible explanation for the increased occurrence of DKA with SGLT inhibitor therapy may be due to SGLT inhibitor-associated increase in glucagon^[75], drastic reduction in TDD of insulin (such as pump failure or insulin doses < 0.5U/kg) leading to peripheral lipolysis and subsequent ketogenesis, excess alcohol intake or concurrent illness, inadequate carbohydrate intake as well as lower glucose value that delays detection (euglycemic DKA). The frequency of DKA is more in patients using insulin pumps due to the risk of pump failure or other operational failures whereas once-daily injection of basal insulin in subcutaneous regimens might reduce the risk of DKA. With the on-going risk of DKA with these agents, it is important to provide repeated education and appropriate support to patients and healthcare providers on signs and symptoms of DKA, risk factors of DKA, the importance of ketone monitoring (especially in stressful situations) and appropriate reductions in insulin doses before initiation and during treatment with SGLT-1/SGLT-2 inhibitors to mitigate DKA risk. In case of an acute infection, illness, or major stress, SGLT inhibitors should be withheld temporarily and if DKA is suspected or diagnosed, treatment should be stopped immediately.

Triple therapy (Insulin + GLP1RA + SGLT inh)

With GLP1RA and SGLT inhibitors, both individually showing efficacy in improving glycemic control as adjunctive therapies in T1D, one might wonder the role of combination therapy with GLP1RA and

SGLT inhibitors in the treatment of T1D. Kuhadiya et al. conducted a small (26 patients) but landmark RCT of 12 weeks duration, the first and only study that included addition of both Dapagliflozin (an SGLT2 inhibitor) and Liraglutide (a GLP1RA) as adjunctive therapy to insulin in patients with T1D (Triple therapy)^[75]. The objective of the study was to investigate whether the addition of dapagliflozin to an already established regimen of insulin and liraglutide (6 months before the start of study) results in a significant reduction in glycemia and bodyweight. HbA1c in triple therapy group fell by 0.66% whereas there was no significant change in the placebo group ($P<0.01$). The incidence of hypoglycemia remained unchanged between the two groups and so did the mean total insulin dose. Bodyweight fell by 1.9 kg ($P<0.05$ vs placebo) in the triple therapy group, whereas it remained unchanged in the placebo group.

The addition of dapagliflozin to insulin and liraglutide was associated with DKA in two patients leading to discontinuation of the drug. This study looked into the pathogenesis behind the increased incidence of DKA with SGLT-2 inhibitors and demonstrated that fasting concentrations of glucagon, hormone-sensitive lipase (HSL), free fatty acids (FFAs), glycerol, acetoacetate, and β -hydroxybutyrate were increased significantly after the administration of dapagliflozin. This supports the hypothesis that SGLT-2 inhibitors induce hyperglucagonemia and an increase in lipolysis and ketogenesis. In our previous work, we have shown the acute suppression of ketogenesis by liraglutide^[76], but it would appear that the ketogenic effect of dapagliflozin overwhelms the suppressive action of liraglutide in this process. Because of the possibility of dose-dependent effect of SGLT-2 inhibitor on ketogenesis^[71], a lower dose can potentially be used with a GLP1RA to balance clinical benefit against an increased risk of ketogenesis. The combined beneficial effects of SGLT inhibitors and GLP1RA on glycemic control, bodyweight, and total insulin doses should result in overall cardiovascular risk reduction and needs to be explored further in larger prospective trials to establish this combination in the treatment of T1D. Currently, 2 ongoing

larger clinical trials are looking into the efficacy of the combination of exenatide and dapagliflozin, and combination of semaglutide and dapagliflozin (52-week multicenter study, JDRF funded) as adjunct therapies to insulin in T1D and results should be expected soon.

Metformin and Dipeptidyl peptidase IV (DPP-4) inhibitors

Metformin (MTF) suppresses hepatic glucose production (gluconeogenesis), causes weight loss, and has a long-term positive effect on mortality^[77]. Although often prescribed in real-life practice as off-label use, especially in overweight/obese patients, the role of MTF in the treatment of T1D remains ill-defined. A meta-analysis by Vella et al.^[78] looking into the efficacy of MTF in T1D summarized 5 randomized, double-blind trials, including the study by Lund et al. which was the largest study with 100 subjects^[79]. A significant reduction in insulin dose and bodyweight were noted in some trials, but no consistent evidence for HbA1c reduction was found in this systematic review. In the Type 1 Diabetes Exchange study enrolling 140 overweight and obese adolescent subjects with uncontrolled T1D to metformin versus placebo^[80], HbA1c was reduced by 0.3% at 3 months but not sustained at the end of 6-month trial. The REMOVAL study which was primarily aimed to investigate the lack of cardiovascular data with metformin use in T1D patients^[81], also showed transient improvement in HbA1c (-0.24%) but not sustained thereafter. There was a sustained reduction in weight with metformin (by 1.2 kg), as well as modest reductions in insulin dose requirements. These data suggest that there is no evidence to support the use of MTF in improving glycemic control in T1D patients.

DPP-4 inhibitors increase endogenous GLP-1 and glucose-dependent insulintropic polypeptide (GIP) levels^[82, 83] by inhibiting their degradation through the dipeptidyl peptidase-4 enzyme and thus, causing glucose-dependent insulin release and glucagon inhibition^[84, 85]. However, unlike GLP1RA, they have no effect on gastric emptying, appetite suppression, and bodyweight^[85, 86]. One of the first clinical trials

looking into the efficacy and safety of DPP-4 inhibitors in T1D was a multicenter, randomized, double-blind, placebo-controlled trial enrolling 125 patients to receive either sitagliptin (100 mg/day) or placebo for 16 weeks in addition to insulin therapy^[87]. The reductions in HbA1c at week 16 from baseline did not differ significantly in either treatment group and the magnitude of the change in A1c did not differ by the treatment group. There were no significant changes in daily insulin dose or bodyweight. Although the glucagon levels were significantly lower at 30 minutes post-meal after 16 weeks of treatment with sitagliptin, the 4-hour AUC for glucagon was not different in the 2 groups at any visit during the meal challenge tests. In a meta-analysis conducted by Guo et al.^[88], six randomized controlled trials were included for the final analysis of which 4 were double-blinded in Caucasians^[87, 89-91] and 2 were open-label in Asians^[42, 92], and showed no significant improvement in HbA1c from baseline in individuals treated with DPP-4 inhibitors compared to placebo. Overall, the use of DPP-4 inhibitors in T1D has no beneficial effect on glycemic control and any off-label use of such medications should be avoided in clinical practice.

Conclusion

Most patients with T1D do not achieve the ADA recommended HbA1c targets and meet several barriers along the way such as weight gain and hypoglycemia with intensive insulin therapy. Frequent hypoglycemia in T1D patients could be very detrimental and is an extremely important barrier in achieving goal HbA1c. Fear of hypoglycemia affects the behavior of the patients, making them less compliant to their insulin regimen, and psychologically, makes them feel less empowered of their health which can have unfavorable consequences. Therefore, a non-insulin antihyperglycemic pharmacological therapy that not only improves glycemic control, reduces insulin requirements, and minimizes the risk of hypoglycemia but also targets the bodyweight to improve insulin resistance and cardiovascular risk

profile, is the need of the hour. The trial data on GLP1RA, SGLT-2 inhibitors, and the dual SGLT1/SGLT2 inhibitor sotagliflozin, and the combination of GLP1RA and SGLT inhibitors as add-on therapy to insulin in T1D looks promising. Indeed, dapagliflozin and sotagliflozin have been approved for use in type 1 diabetes in Europe and Japan. Not only do they improve glycemic control (HbA1c), they decrease glycemic variability and time spent in hyperglycemia, reduced postprandial glucose excursions, and induce remarkable (up to 5%) weight loss. These drugs have the most hopeful prospects in the future given their long-term cardiovascular benefits.

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