Universidade Federal do Rio Grande Do Sul (UFRGS)
Faculdade de Medicina
Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Analaura Centenaro

Contagem de Carboidratos e Diabetes Melito Tipo 1 em um Hospital Terciário no Âmbito do Sistema Único de Saúde

Porto Alegre
2021

Analaura Centenaro

Contagem de Carboidratos e Diabetes Melito Tipo 1 em Um Hospital Terciário no Âmbito do Sistema Único de Saúde

Dissertação de mestrado apresentada como requisito parcial para a obtenção do título de Mestre à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Orientador(a): Profª Dr.ª Ticiana da Costa Rodrigues

Porto Alegre

2021

CIP - Catalogação na Publicação

Centenaro, Analaura
Contagem de Carboidratos e Diabetes Melito Tipo 1 em um Hospital Terciário no Âmbito do Sistema Único de Saúde / Analaura Centenaro. -- 2021.
75 f.
Orientadora: Ticiana da Costa Rodrigues.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2021.

1. Contagem de carboidratos. 2. Diabetes melito tipo 1. 3. Controle glicêmico. 4. Hemoglobina glicada. 5. Peso corporal. I. Rodrigues, Ticiana da Costa, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

ANALAURA CENTENARO

Contagem de Carboidratos e Diabetes Melito Tipo 1 em Um Hospital Terciário no Âmbito do Sistema Único de Saúde

Dissertação de mestrado apresentada como requisito parcial para a obtenção do título de Mestre à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Porto Alegre, 19 de julho de 2021.

A Comissão Examinadora, abaixo assinada, aprova a Dissertação "Contagem de Carboidratos e Diabetes Melito Tipo 1 em Um Hospital Terciário no Âmbito do Sistema Único de Saúde", elaborado por Analaura Centenaro, como requisito parcial para obtenção do grau de Mestre em Endocrinologia.

Comissão Examinadora:

Profª. Drª. Mônica Andrade Lima Gabbay (UNIFESP)

Profª. Drª. Karla Fabiana Santana de Melo Cabral Fagundes (USP)

Profª. Drª. Tatiana Pedroso de Paula (UFRGS)

Profª. Drª. Ticiana da Costa Rodrigues - Orientadora (UFRGS)

AGRADECIMENTOS

Agradeço à minha família pelo apoio e oportunidades oferecidas, essenciais para que eu chegasse até aqui.

À Profª. Drª. Ticiana da Costa Rodrigues por ter me acolhido como aluna em seu grupo de pós-graduação e por todos os ensinamentos ao longo da realização deste estudo.

À Nut. Cigléia do Nascimento pelo carinho e por ter despertado meu interesse pela endocrinologia através de seus conhecimentos e dedicação aos pacientes do ambulatório.

Aos colegas do grupo de pesquisa pela oportunidade de convívio e aprendizado, em especial à Drª. Mileni Vanti Beretta que colaborou para a concretização desta etapa.

Esta dissertação de mestrado segue o formato proposto pelo Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul, sendo constituída de um referencial teórico acerca do tema proposto e um artigo original.

RESUMO

Pacientes com diabetes melito tipo 1 (DM1) estão expostos ao risco de desenvolvimento de complicações, incidência que pode ser reduzida através de um adequado controle glicêmico. Existem evidências de que a contagem de carboidratos (CC) otimiza esse controle, porém nem todos os estudos apontam resultados semelhantes, e poucos dados acerca da população brasileira foram localizados. Diante disso, o objetivo deste trabalho foi verificar o impacto da CC no controle glicêmico de indivíduos com DM1, bem como na variação de peso entre consultas (desfecho primário e secundário, respectivamente) no âmbito de um hospital terciário no Sul do Brasil. Também buscou-se identificar variáveis preditoras do bom controle glicêmico, analisar a aderência à CC e investigar variáveis associadas à adesão. Foi realizado um **e**studo de coorte retrospectiva em que foram incluídos 232 pacientes com DM1 que realizaram acompanhamento nutricional no Hospital de Clínicas de Porto Alegre entre os anos de 2014 – 2018. Foram coletados dados sociodemográficos, clínicos, laboratoriais, antropométricos e de atividade física. Na análise dos desfechos primário e secundário foram incluídos dados de 180 pacientes que utilizaram doses fixas de insulina nesse período e 49 indivíduos que fizeram CC. O impacto da CC no controle glicêmico foi aferido através da média dos valores de hemoglobina glicada (HbA1c) coletadas ao longo das consultas nutricionais realizadas no período de acompanhamento, com análise pelos Modelos Lineares Mistos Generalizados para Medidas Repetidas. Comparado a quem utilizava doses fixas de insulina, o grupo que fez a CC realizou mais consultas nutricionais entre 2014-2018, tinha maior tempo de acompanhamento nutricional no momento basal e durante o tempo de seguimento apresentou maior nível de escolaridade e nº de gestantes, bem como maior proporção de indivíduos brancos, de frequência de automonitorização da glicemia capilar e de uso de análogos de insulina de ação rápida. A diferença de média de Índice de Massa Corporal (IMC) e a proporção de indivíduos suficientemente ou insuficientemente ativos não foi constante entre os grupos ao longo do tempo. No modelo ajustado para o maior nº de possíveis confundidores, com exceção da variável gestação, a média de HbA1c foi melhor em quem realizou CC (8,66 ± 0,4% vs. 9,36 ± 0,39%; p = 0,016) e a variação de peso corporal entre consultas foi menor nesse grupo (0,13±0,28Kg vs. 0,53±0,24Kg; p = 0,024). Foram preditores do bom controle glicêmico a aplicação de menores doses de insulina, a inexistência de outras doenças autoimunes associadas ao DM1 e a ausência de retinopatia diabética; já a direção da associação dos níveis de glicemia de jejum com o desfecho variou durante o tempo de acompanhamento. A aderência à CC foi relatada em 69,2 % das consultas. Foram

significativamente associadas à adesão ao método menores valores de HbA1c e menor nº de faltas entre 2014 - 2018, bem como maiores valores de IMC. Diante dos resultados encontrados concluímos que a CC teve um impacto positivo no controle glicêmico de indivíduos com DM1, mostrando menor efeito sobre a variação de peso corporal quando comparada ao uso de doses fixas de insulina. Logo, a CC parece ser uma estratégia importante na otimização do cuidado do DM1.

Palavras-chave: contagem de carboidratos; diabetes melito tipo 1; controle glicêmico; hemoglobina glicada; peso corporal.

ABSTRACT

Patients with type 1 diabetes mellitus (T1D) are at risk of developing complications, which can be reduced through adequate glycemic control. There is evidence that carbohydrate counting (CC) optimizes control, but the results are not similar among all studies, and few data about the Brazilian population have been found. Thus, the objective of this study was to verify the impact of CC on glycemic control and body weight variation (primary and secondary outcome, respectively) between consultations in patients with T1D followed at a tertiary hospital in southern Brazil. We also sought to identify predictors of good glycemic control and to investigate CC adherence, as well as to identify variables associated with adherence. This retrospective cohort study included 232 patients with T1D who underwent nutritional monitoring at the Hospital de Clínicas de Porto Alegre between 2014 and 2018. Sociodemographic, clinical, laboratory, anthropometric and physical activity data were collected. To assess primary and secondary outcomes, data from 49 patients who underwent CC during this period and from 180 individuals who used fixed doses of insulin were analyzed. The impact of CC on glycemic control was assessed through the mean glycated hemoglobin (HbA1c) level at all consultations during the follow-up period, with analysis by Generalized Linear Mixed Models for Repeated Measures. Compared to those who used fixed doses of insulin, the CC group had more nutritional consultations between 2014-2018, longer nutritional follow-up time at baseline and during the follow-up period had higher education level and number of pregnant women, as well as higher proportion of white individuals, frequency of self-monitoring blood glucose and use of rapid-acting insulin analogs. The difference in mean body mass index (BMI) and the proportion of sufficiently vs. insufficiently active individuals was not constant between groups over time. In the model adjusted for the most confounders (except pregnancy), mean HbA1c was better in the CC group (8.66 ± 0.4% vs. 9.36 ± 0.39%; p = 0.016) and body weight variation was lower (0.13 ± 0.28 kg vs. 0.53 ± 0.24 kg; p = 0.024). Predictors of good glycemic control were lower doses of insulin, no autoimmune diseases associated with T1D and no retinopathy; the direction of association between fasting glucose and the outcome varied during the follow-up period. Adherence to CC was reported in 69,2% of consultations. Higher BMI, lower HbA1c levels and fewer missed consultations between 2014 – 2018 were associated with adherence. Given these results we conclude that CC optimized the glycemic control of individuals with T1D, resulting in less weight variation than the fixed insulin dose group, which indicates that CC is an important care strategy for these patients.

Keywords: carbohydrate counting; type 1 diabetes mellitus; glycemic control; glycated hemoglobin; body weight.

LISTA DE ABREVIATURAS E SIGLAS – REVISÃO DA LITERATURA

ADA: American Diabetes Association

BA: Bolus de alimentação

BC: Bolus de correção

CC: Contagem de carboidratos

CHO: Carboidrato

DCCT: Diabetes Control and Complication Trial

DCV: Doença cardiovascular

DDTI: Dose diária total de insulina

DM: Diabetes melito

DM1: Diabetes melito tipo 1

DRD: Doença renal do diabetes

DSMP: Diabetes Self-Management Profile

ECR: Ensaio clínico randomizado

EDIC: Epidemiology of Diabetes Interventions and Complications

FS: Fator de sensibilidade

HbA1c: Hemoglobina glicada

IC 95%: Intervalo de confiança de 95%

I/CHO: Razão insulina carboidrato

IDF: International Diabetes Federation

IMC: Índice de massa corporal

ISPAD: International Society for Pediatric and Adolescent Diabetes

MD: Diferença entre médias

MDI: Múltiplas injeções diárias

SBD: Sociedade Brasileira de Diabetes

SCI-R: Self-Care Inventory-Revised

SICI: Sistema de infusão contínuo de insulina

UI: Unidade de insulina

SUMÁRIO

1 REFERENCIAL TEÓRICO

1.1 EPIDEMIOLOGIA E FISIOPATOLOGIA DO DIABETES MELITO TIPO 1

O diabetes melito (DM) compreende um grupo de doenças metabólicas caracterizadas por hiperglicemia, resultante de distúrbios na secreção de insulina e/ou em sua ação. Da totalidade dos casos de DM, 5-10% são de diabetes melito tipo 1 (DM1), o qual resulta da destruição progressiva das células beta pancreáticas produtoras de insulina, usualmente por processo autoimune, embora possa ocorrer também a forma idiopática. O processo de destruição das células beta é mediado tanto por fatores genéticos quanto ambientais, os quais ainda são pouco compreendidos, e a velocidade de progressão é variável, porém comumente rápida em crianças e um pouco mais lenta em adultos. Em decorrência deste quadro manifesta-se a hiperglicemia (1), e o paciente torna-se dependente da administração exógena de insulina para sobrevivência (2). Embora possa desenvolver-se em qualquer idade, essa forma da doença é mais comum em crianças e adolescentes (1). Dados do International Diabetes Federation de 2019 (IDF 2019) apontam que o total estimado de crianças e adolescentes menores de 15 anos com DM1 é de 600.900, sendo 98.200 novos diagnósticos por ano. Com prevalência de 51.500 e incidência anual de 7.300 indivíduos com DM1 nesta faixa etária, o Brasil é o terceiro país do mundo com maior número de casos (3).

A terapia de reposição insulínica é composta por insulina basal e bolus. Enquanto a primeira mantém os níveis glicêmicos estáveis no período entre as refeições e durante a noite (4) para evitar lipólise e a liberação hepática de glicose, a segunda regula o aumento da glicemia que ocorre no momento pós-prandial e/ou corrige a glicemia que não esteja dentro do alvo terapêutico estabelecido para aquele paciente. As principais classes desse hormônio disponíveis atualmente no mercado são a insulina humana de ação intermediária e a de ação rápida e os análogos, que podem ser de ação longa, ultralonga, de ação rápida ou ultrarrápida. Os diferentes tipos variam no tempo para início e pico de ação, bem como na duração do efeito (Figura 1) (5).

Figura 1 - Insulinas humanas e análogos.

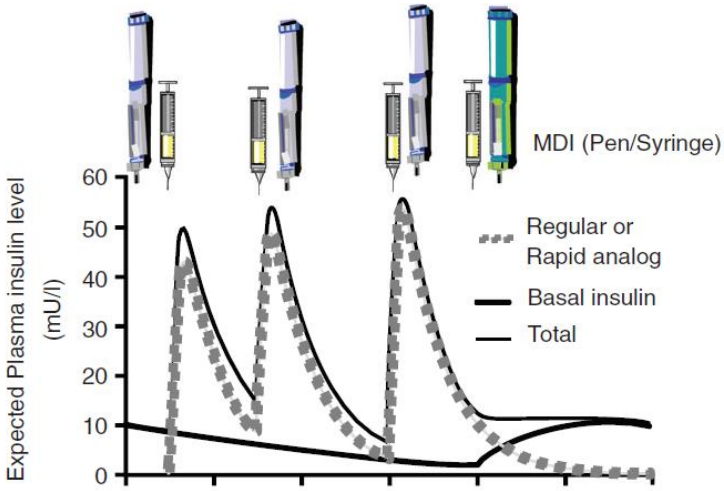
PROPRIEDADES FARMACOCINÉTICAS DAS INSULINAS E ANÁLOGOS			
INSULINA	INÍCIO DE AÇÃO	PICO DE AÇÃO	DURAÇÃO DO EFEITO TERAPÊUTICO
Insulina de Ação Intermediária			
NPH	2-4 h	4-10 h	10-18 h
Insulina de Ação Rápida			
Regular	0,5-1 h	2-3 h	5-8 h
Análogos de Ação Rápida			
Asparte (Novorapid®)	5-15 min	0,5-2 h	3-5 h
Lispro (Humalog®)	5-15 min	0,5-2 h	3-5 h
Glulisina (Apidra®)	5-15 min	0,5-2 h	3-5 h
Análogos de Ação Ultrarrápida			
Faster-aspart (Fiasp®)	0-10 min	0,35-2 h	3-5 h
Inalável tecnosfera (Afrezza®)	12 min	35-55 min	1,5-4,5 h
Análogos de Ação Longa			
Glargina (Lantus®, Basaglar®)	2-4 h	Mínimo	20-24 h
Detemir (Levemir®)	1-3 h	6-8 h	12-20 h
Análogos de Ação Ultralonga			
Glargina U 300 (Toujeo®)	6 h	Ausente	36 h
Degludeca (Tresiba®)	2 h	Ausente	42 h

Fonte: Adaptado Sociedade Brasileira de Diabetes, 2020 (5).

Dentre as estratégias terapêuticas disponíveis, o regime de insulinoterapia do tipo intensivo é o que demonstra melhor equilíbrio entre efetividade e segurança em indivíduos com DM1 (6), mimetizando de forma mais satisfatória a secreção fisiológica de insulina. Esse esquema consiste na utilização de múltiplas injeções diárias (MDI) de insulina basal (insulina de ação intermediária ou análogos de ação longa/ultralonga; 1 – 4 aplicações/dia) e bolus (administração de insulina de ação rápida ou análogos de ação rápida/ultrarrápida nas refeições) (Figura 2A) ou no uso do sistema de infusão contínuo de insulina (SICI) (Figura 2B). Nesse dispositivo, esse hormônio é infundido em uma taxa basal pré-programada complementada por bolus quando o paciente se alimenta (7).

Embora a dose diária total de insulina (DDTI) seja individualizada no tratamento dos pacientes com DM1, dependendo de diversos fatores (8), de forma geral a necessidade varia de 0,4 – 1 unidade de insulina (UI)/Kg de peso/dia (6), sendo que habitualmente a demanda é de 30-50% na forma de insulina basal e o restante em bolus (8).

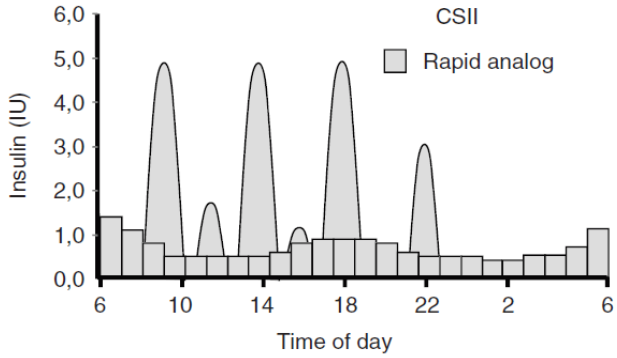
Figura 2A - Insulinoterapia em MDI.



Fonte: Adaptado de Danne et al., 2018 (7).

MDI: Múltiplas injeções diárias.

Figura 2B - Insulinoterapia em SICI.



Fonte: Adaptado de Danne et al., 2018 (7).

CSII: Sistema de infusão contínuo de insulina, do inglês continuous subcutaneous insulin infusion.

1.2 CONTROLE GLICÊMICO E COMPLICAÇÕES DO DIABETES

Embora a sobrevida dos pacientes com diagnóstico de DM1 tenha aumentado consideravelmente ao longo dos anos (9, 10), com a ocorrência dos distúrbios no metabolismo da glicose os indivíduos estão expostos ao risco de desenvolver tanto complicações agudas (hipoglicemia e cetoacidose) (11) quanto crônicas microvasculares - retinopatia, neuropatia e doença renal do diabetes (DRD) - e macrovasculares - doença cardiovascular (DCV) (12-14) - as quais são associadas à consideráveis taxas de morbidade, mortalidade e altos custos em saúde (11, 15). A retinopatia é a causa mais frequente de novos casos de cegueira entre adultos (20 – 74 anos) nos países desenvolvidos, sendo que doenças oculares como glaucoma e catarata, entre outras, ocorrem mais cedo e mais frequentemente em pessoas com DM (16). A DRD ocorre em 20 - 40% dos pacientes com DM, podendo progredir para doença renal em estágio terminal, exigindo assim o tratamento com diálise ou transplante para sobrevivência (17). Já a DCV é a principal causa de morbimortalidade em portadores de DM (18). A literatura ainda mostra que indivíduos com DM1 têm menor expectativa de vida quando comparados à população em geral, sendo que o número de anos de vida perdidos associa-se à idade de diagnóstico, ocorrendo redução mais expressiva (aproximadamente 16 anos) naqueles com desenvolvimento da doença anterior aos 10 anos de idade (13). No entanto, a redução da incidência das complicações crônicas relacionadas ao DM1 pode ser obtida através de um adequado controle glicêmico (19-22).

O estudo Diabetes Control and Complications Trial (DCCT), que randomizou indivíduos com DM1 em dois grupos – o primeiro visando atingir níveis glicêmicos mais estritos através da implementação de terapia insulínica intensiva, e o segundo para o seguimento do tratamento convencional - verificou que ao final de 6,5 anos de intervenção a melhora do controle glicêmico obtida com o tratamento intensivo reduziu o risco de desenvolvimento de retinopatia, albuminúria (≥300 mg/24h) e neuropatia clínica em 76%, 54% e 60%, respectivamente (23).

O estudo observacional que deu seguimento ao anterior, o Epidemiology of Diabetes Interventions and Complications (EDIC), constatou que dentre os fatores de risco modificáveis avaliados o nível de hemoglobina glicada (HbA1c) foi o que teve o maior impacto na ocorrência tanto do primeiro evento cardiovascular quanto dos subsequentes (19).

Outro estudo prospectivo - seguimento médio de quase 10 anos - realizado a partir de registros nacionais de 12.334 indivíduos da população sueca também investigou os fatores associados à incidência de complicações macrovasculares. A amostra foi estratificada em grupos de duração do DM1: 0–19 anos; 20–29 anos; 30–39 anos; 40–49 anos e ≥ 50 anos. Após o ajuste para potenciais fatores de confusão, maiores valores de HbA1c no momento basal foram significativamente associados à incidência de DCV em todos os estratos (24).

Desta forma, torna-se essencial o cuidado contínuo do controle glicêmico dos pacientes, sendo um dos meios de avaliação amplamente utilizados a HbA1c, a qual reflete a glicemia dos 3 meses anteriores ao exame. As seguintes metas são estabelecidas pela American Diabetes Association (ADA) para a maioria dos indivíduos com DM, embora possa haver individualização de valores de acordo com a condição clínica: 1) crianças e adolescentes < 7%; 2) adultos < 7%; 3) idosos < 7 - 7,5%; 4) gestantes < 6% (25-28). Recomenda-se a avaliação pelo menos duas vezes ao ano nos indivíduos com controle estável e que estejam dentro do alvo glicêmico, porém dosagens no mínimo trimestrais são indicadas no caso de alteração do esquema terapêutico ou quando as metas estipuladas não estejam sendo atingidas (25).

1.3 CONTAGEM DE CARBOIDRATOS

1.3.1 Técnicas

Diante de tais evidências, torna-se necessária a utilização de abordagens no tratamento do DM1 que otimizem o controle glicêmico, sendo a contagem de carboidratos (CC) uma estratégia nutricional recomendada pelas diretrizes em diabetes (29).

Esta abordagem tem como foco a quantidade de carboidrato (CHO) ingerida (30), baseando-se no fato de que esse nutriente é o maior determinante da resposta glicêmica pós-prandial - e consequentemente da necessidade insulínica – sendo a totalidade do que é ingerido convertida em glicose em um período de 15 minutos a 2 horas, enquanto 35 – 60% das proteínas e apenas 10% das gorduras passam por essa conversão, a qual ocorre em um período mais tardio (3 – 4 e 3 – 5 horas, respectivamente) (8).

Como técnicas de contagem existe o método em gramas de CHO e a CC pela lista de equivalentes (ou substitutos) de CHO (8). Nesse último, mais simples, para cada refeição realizada são estabelecidas metas de equivalentes de CHO, os quais correspondem a porções de alimentos que contêm aproximadamente 15 gramas deste nutriente. Além das metas, são oferecidas ao paciente possibilidades de troca entre esses equivalentes, estimulando-se que elas ocorram dentro do mesmo grupo alimentar (31).

Já a CC em gramas busca estabelecer a dose de insulina bolus a ser aplicada nas refeições através do equilíbrio entre o nível glicêmico pré-prandial e a quantidade de CHO ingerida (6, 8). Para a realização desse cálculo é necessário definir previamente dois parâmetros, a razão insulina carboidrato (I/CHO) e o fator de sensibilidade (FS), já que os mesmos variam entre os indivíduos. O primeiro indica as gramas de CHO metabolizadas por uma UI, enquanto o segundo informa o quanto a glicemia (mg/dl) reduz para cada UI aplicada (32). A I/CHO pode ser estimada por uma regra geral, em que 1 UI metaboliza 20-30g de CHO para crianças, 10-15g para adolescentes e 15g para adultos, bem como - nesse último grupo – determinada pelo peso corporal (Figura 3) (5).

Figura 3 - I/CHO em adultos de acordo com o peso.

Peso (kg)	RIC (1U/g)
45-49	1:16
49,5-58	1:15
58,5-62,5	1:14
63-67	1:13
67,5-76	1:12
76,5-80,5	1:11
81-85	1:10
85,5-89,5	1:9
90-98,5	1:8
99-107,5	1:7
≥ 108	1:6

Fonte: Sociedade Brasileira de Diabetes, 2020 (5).

RIC: razão insulina carboidrato; 1U: uma unidade de insulina; g: gramas de CHO metabolizadas por uma unidade de insulina.

Uma forma bastante utilizada para obter a I/CHO, bem como o FS, é aquela em que se divide uma constante pela DDTI aplicada pelo paciente (5). A constante utilizada não é uma unanimidade entre as diferentes sociedades e autores. A seguir são descritos os valores preconizados pela Sociedade Brasileira de Diabetes (SBD) e pela International Society for Pediatric and Adolescent Diabetes (ISPAD). Para I/CHO: 400, porém se uso de SICI 500 para crianças e 450 para adultos - diretriz da SBD (8); 400 a 500, porém em < 5 anos 300 ou 350 – posicionamento da SBD sobre Conduta Terapêutica no DM1 (5); 500 para a faixa etária pediátrica – guideline da ISPAD (7). Já para o FS as recomendações são as seguintes: 1500 para insulina de ação rápida ou 2000 (1700, 1800, 2100) se utilização de análogos de ação rápida, entretanto se uso de SICI 1700 a 1800 para adultos e 1800 a 2000 para crianças - diretriz da SBD (8); 1800, porém 2000 para crianças e naqueles < 5 anos usar 2.500 a 3.500 – posicionamento da SBD sobre Conduta Terapêutica no DM1 (5); 1500 para insulina de ação rápida ou 1800 se utilização de análogos para crianças e adolescentes – guideline da ISPAD (7).

Através desses parâmetros, da quantificação das gramas de CHO ingeridas na refeição e da mensuração da glicemia pré-prandial, bem como do conhecimento da meta glicêmica, o paciente - capacitado por um profissional - calcula o bolus de insulina a ser aplicado (32), conforme a seguinte fórmula (8):

Insulina bolus total = Bolus de alimentação (BA) + Bolus de correção (BC)**,** sendo,
BA= gramas de carboidrato da refeição/(I/CHO)
BC = (glicemia pré-prandial – meta glicêmica)/FS

O BA corresponde a quantidade de insulina necessária para metabolizar os CHO da refeição a ser ingerida, enquanto o BC é a insulina requerida para corrigir a glicemia caso essa não se encontre na meta pré-prandial estipulada (8).

A seguir é mostrado um exemplo de aplicação da CC em gramas: paciente com DM1, 30 anos, o qual aplica em média 36 UI ao dia (análogo de ação longa + análogo de ação rápida) através de MDI e tem como meta de glicemia pré-prandial o intervalo de 70 – 100 mg/dl. A partir dessas informações podem ser determinados a I/CHO e o FS:

I/CHO = 500/DDTI I/CHO = 500/36 I/CHO=13,8 – (arredondamento para 14)
FS = 1800/DDTI FS = 1800/36 FS = 50

Supondo-se que esse indivíduo consuma um almoço com um total de 54 gramas de CHO e esteja com uma glicemia pré-prandial de 155 mg/dl, a dose de insulina bolus a ser aplicada nesta refeição pode ser calculada da seguinte forma:

Bolus total = BA + BC, sendo,
BA = 54/14 BA = 3,8 UI
BC = (155 – 100) / 50 BC = 1,1 UI
Bolus Total = 4,9 UI (arredondamento para 5 UI)

Nas consultas de seguimento avalia-se a necessidade de ajustes na I/CHO e FS, através dos valores glicêmicos registrados pelos pacientes. Considera-se que a CC está adequada quando a glicemia 2 horas pós-prandial está dentro da meta estabelecida para esse horário e quando não difere por mais do que 20 a 30 mg/dl da glicemia pré-prandial (8, 33, 34).

Embora o CHO tenha impacto predominante sobre a glicemia pós-prandial, em situações em que ocorre consumo excessivo de proteína e gordura pode haver necessidade de ajustes na dose de insulina a fim de compensar a hiperglicemia decorrente, já que o efeito destes nutrientes é menor e mais tardio, porém não nulo. Embora já tenham sido propostos diversos algoritmos para compensação insulínica em tais situações (35), até o momento não está estabelecido um que possa ser utilizado de forma generalizada com segurança e efetividade, de forma que recomenda-se individualização para cada paciente, estabelecendo metas realistas e incentivando a monitorização glicêmica (8).

1.3.2 Efeito sobre o controle glicêmico e peso corporal

Estudos prévios avaliaram a CC como estratégia nutricional de otimização do controle glicêmico, porém nem todos encontraram resultados semelhantes. Enquanto alguns ensaios

clínicos randomizados (ECR) resultaram em efeito nulo da CC em comparação a um grupo controle sobre a HbA1c (36-39), outros mostraram melhor controle glicêmico com a intervenção (40-43), sendo a maior diferença encontrada no estudo DAFNE: diferença entre médias (MD) de HbA1c; Intervalo de Confiança de 95 % (IC 95%) = -1; -1,4 a -0,5% (40).

Buscando determinar o impacto desta ferramenta na redução da HbA1c, uma revisão sistemática e metanálise de ECR (incluindo os acima citados) ou quasi-randomizados publicada em 2016 comparou indivíduos com DM1 em CC com aqueles que recebiam dieta para DM ou educação alimentar em diabetes, encontrando valores menores de HbA1c nos pacientes que realizavam contagem (MD; IC 95% = -0,35; -0,65 a -0,05%; p=0,023). Porém a qualidade da evidência produzida foi avaliada como moderada, havendo risco de viés e expressiva heterogeneidade entre os estudos. Na análise de subgrupos foi mantida a significância a favor da CC nos estudos que a comparavam com educação alimentar, mas não em relação a outras dietas para DM, e naqueles estudos realizados em adultos, mas não na população pediátrica (44).

Outro estudo recente, que randomizou crianças e adolescentes em dois grupos (CC vs. controle), também resultou em melhora do controle glicêmico em quem que recebeu a intervenção aos 3 meses de acompanhamento (HbA1c = 7,53 ± 0,61% vs 7,88 ± 0,56%; p = 0,009), porém houve perda do benefício aos 6, 9 e 12 meses. No entanto, ao considerar-se a média geral, durante 1 ano de intervenção, a HbA1c foi menor em quem recebeu o tratamento (7,63 ± 0,43% vs 7,85 ± 0,47%, p < 0,05) (45). De maneira semelhante, outro ECR publicado em 2021 mostrou efeitos positivos da CC na HbA1c à curto prazo (3 meses de intervenção), porém houve ausência de diferença significativa ao término dos 12 meses de tratamento (46).

A literatura oriunda da população brasileira sobre o efeito da CC no controle glicêmico em DM1 é limitada, e o grau da evidência produzida é mais frágil. Em um estudo transversal realizado com 120 crianças e adolescentes tratados em um serviço público de referência no Rio de Janeiro, o uso da CC foi associado a menores níveis de HbA1c (47). Ainda há dados provenientes de um ensaio clínico, o qual foi incluído na metanálise anteriormente citada (44), que avaliou 28 adolescentes de um hospital de Goiás alocados em 2 grupos, sendo que ambos receberam orientação nutricional porém somente o intervenção foi tratado com CC. Ao fim do acompanhamento de 4 meses houve aumento e redução

significativos de HbA1c no grupo controle e intervenção, respectivamente, com diferença também significativa entre grupos (48).

O efeito da CC em outras variáveis também tem sido investigado. Enquanto para indivíduos em uso de doses fixas de insulina o planejamento alimentar enfatiza um padrão de consumo de CHO relativamente fixo tanto em quantidade quanto nos horários do dia (29), a CC, por possibilitar ajustes na dose do bolus de acordo com o consumo do nutriente, proporciona maior flexibilização na alimentação do paciente com DM (40, 49, 50). Essa flexibilização em si poderia resultar em aumento do peso, bem como associar-se à aplicação de maiores de insulina. Dessa forma, alguns autores buscaram avaliar o impacto desta técnica no peso corporal, no entanto a maioria dos estudos não mostraram associação entre esta estratégia nutricional e mudança de peso (36, 40, 42) ou índice de massa corporal (IMC) (42, 43, 45), sendo que em um estudo ocorreu redução de IMC no grupo que realizava CC quando comparado ao controle (49).

1.4 ADERÊNCIA AO TRATAMENTO E PREDITORES DO CONTROLE GLICÊMICO

Apesar dos avanços no conhecimento sobre os benefícios da intensificação do controle da glicemia, um percentual expressivo de pacientes com DM1 permanece com metas de HbA1c subótimas (51), sendo o grau de adesão às orientações da equipe assistencial um dos fatores que podem afetar a efetividade do tratamento clínico (52). Um estudo transversal que avaliou indivíduos com DM1 do SEARCH for Diabetes in Youth Study que haviam sido ensinados a realizar CC, investigou através de um questionário se o controle glicêmico diferia entre os pacientes que autorrelatavam o uso da CC "frequentemente", "às vezes" ou "nunca". Para aqueles com baixo peso e os eutróficos, aplicar a CC "frequentemente" foi associado a menores valores HbA1c do que utilizar "às vezes / nunca". No entanto, nos indivíduos com sobrepeso/obesidade essa associação não foi significativa (53).

Como já citado anteriormente, a CC é uma importante estratégia nutricional no cuidado do DM1 (29), desta forma é importante avaliar a adesão ao tratamento dos pacientes que seguem essa abordagem terapêutica. No entanto, a literatura que investiga a aderência especificamente à esta técnica ainda carece de uniformidade e de método padrão-ouro.

Em um ECR os autores analisaram a aderência verificando se a CC, quando comparada ao controle (uso de doses fixas de insulina com correção para a glicemia pré-prandial), resultava em maior ajuste na dose de insulina por dia. Para tanto calcularam um coeficiente de variação da dose de insulina aplicada por refeição e o compararam entre os grupos. O valor encontrado – coeficiente geral e por refeição (café da manhã, almoço e janta) – foi maior em quem realizou a CC, o que indica que o grupo intervenção realmente fez mais ajustes de dose, como seria esperado (36).

Outros autores avaliam apenas a acurácia dos pacientes em contabilizar as gramas de CHO dos alimentos (54, 55). Um estudo realizado em adultos verificou que as gramas de CHO contabilizadas foram subestimadas em 62,7% das refeições, com MD de 15,4±7,8 gramas por refeição (55). Outros dados provenientes de crianças, adolescentes e seus cuidadores mostram que do total de refeições e lanches analisados, 43% das estimativas realizadas estavam dentro de 5–7 g do conteúdo real de CHO e 73% dentro de 10–15g (54).

Também há instrumentos como o PedCarbQuizz, o qual não possui validação para a população brasileira, que acessa o conhecimento que o paciente possui acerca dos carboidratos e dosagem de insulina. O questionário é dividido em domínios: reconhecimento de alimentos fonte de CHO e das gramas desse nutriente em porções de alimentos e refeições, leitura de rótulos, uso de escalas de correção da dose de insulina com base no nível glicêmico, utilização da I/CHO para cálculo do bolus e determinação da dose total de insulina a ser aplicada na refeição (56).

A literatura também investiga possíveis barreiras que podem impactar negativamente a adesão ao tratamento. Um estudo transversal realizado com 83 indivíduos com DM1 sugeriu que a falta de confiança do paciente na habilidade em realizar a CC (ou seja, o quão fácil eles achavam que era cometer erros contando CHO em uma refeição) foi uma barreira significativamente associada com os níveis de HbA1c, a qual foi utilizada como uma medida indireta de aderência (57). De forma semelhante, outro estudo que não avaliou a CC em si, mas sim a dieta, sugere que a falta de conhecimento ou falhas no entendimento sobre o manejo alimentar do DM1 poderiam ser fatores de risco para a baixa adesão à dieta prescrita (58). Em um dos ECR anteriormente citados também foi aferida a percepção de complexidade da CC, sendo essa intervenção vista pelos pacientes como uma abordagem mais complexa do

que o uso de doses fixas de insulina (36), o que poderia potencialmente ser uma barreira para sua implementação. No entanto, os autores relataram aderência dos indivíduos à técnica (36).

Ainda existem dados que analisam a aderência à dieta, não especificamente à CC, sendo um dos métodos utilizados a aplicação de inquéritos alimentares, com posterior comparação do consumo alimentar com as recomendações existentes (59), e outros autores que avaliam a adesão ao tratamento do DM1 de forma geral, através de diferentes metodologias. Dentre as técnicas empregadas estão a avaliação da frequência de monitoramento da glicemia capilar, relato de profissionais da saúde (60) e ferramentas como o Diabetes Self-Management Profile (DSMP) (61, 62) e o Self-Care Inventory-Revised (SCI-R) (63).

A literatura investiga também fatores associados à aderência ao tratamento do DM1. Embora não tenham sido encontrados estudos que façam essa análise especificamente em relação à CC, há dados brasileiros que sugerem que a etnia caucasiana, o maior nº de consultas médicas e a prática da CC ou outras dietas recomendadas pelas sociedades de DM são associadas à maior aderência à dieta em indivíduos com DM1. Já a idade (adolescência), maiores valores de IMC e o tabagismo foram associados à pior aderência (64).

Além da CC diversos outros fatores têm sido investigados como possíveis preditores do controle glicêmico no DM1. Dentre eles, os estudos têm sido mais consistentes em demonstrar que indivíduos que monitoram a glicemia têm menores valores de HbA1c do que aqueles que não realizam ou fazem poucas medições diárias (65-68). Também há dados que mostram associação entre a aderência ao tratamento e o melhor controle glicêmico, associação não linear entre idade e HbA1c (maiores valores na puberdade) (69) e pior controle metabólico na presença de doenças psiquiátricas como a depressão e ansiedade (69, 70).

JUSTIFICATIVA

Indivíduos com DM1 estão expostos ao maior risco de desenvolver desfechos desfavoráveis (12-14), porém essa incidência pode ser reduzida através de um adequado controle glicêmico (19-22), sendo necessária a adoção de tratamentos que otimizem esse controle**.** Existem evidências de que a CC pode ser uma dessas estratégias, porém nem todos os estudos encontraram efeitos similares no controle metabólico (44). Além disso, foram

localizados poucos estudos e com curta duração na população brasileira, sendo que nenhum desses foi realizado na região Sul do país (47, 48). Desta forma, desejamos avaliar o impacto da CC na HbA1c, seu efeito na variação de peso corporal bem como a aderência à técnica e possíveis variáveis associadas à adesão e ao bom controle glicêmico, através de uma coorte de pacientes com DM1 acompanhados em hospital escola de referência ao atendimento em diabetes no sul do Brasil.

REFERÊNCIAS

1. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S15-S33. doi: 10.2337/dc21-S002.

2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014 Jan 4;383(9911):69-82. doi: 10.1016/S0140-6736(13)60591-7.

3. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 9th ed. Brussels, Belgium; 2019 [cited 2021 Feb 4]. Available from: diabetesatlas.org/em/resources/.

4. Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocr Rev. 2020 Oct 1;41(5):733-755. doi: 10.1210/endrev/bnaa015.

5. Sociedade Brasileira de Diabetes. Posicionamento Oficial SBD nº 01/2020. Conduta Terapêutica no Diabetes Tipo 1: Algoritmo SBD 2020 [Internet]. 2020 [cited 2021 Feb 4]. Available from: https://www.diabetes.org.br/publico/images/Posicionamento_Oficial_Sbd_N012020v6_brLC.PDF?fbclid=IwAR0SsEnS6znmOt7bb5UvjSdSZkc9EFSVMPXUV8vRIjKFI5kkxi4cB-m3XcU.

6. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S111-S24. doi: 10.2337/dc21-S009.

7. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:115-35. doi: 10.1111/pedi.12718.

8. Sociedade Brasileira de Diabetes. Diretrizes Sociedade Brasileira de Diabetes 2019-2020 [Internet]. São Paulo: Clannad; 2019. p. 97 – 129, 179 – 188 and 206 – 219. [cited 2021 Feb 4]. Available from: https://www.diabetes.org.br/profissionais/images/DIRETRIZES-COMPLETA-2019-2020.pdf

9. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. Diabetes. 2012 Nov;61(11):2987-92. doi:10.2337/db11-1625.

10. Rawshani A, Gudbjörnsdottir S. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med. 2017 Jul 20;377(3):300-1. doi: 10.1056/NEJMc1706292.

11. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016 Apr;12(4):222-32. doi: 10.1038/nrendo.2016.15.

12. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993 Jun 10;328(23):1676-85. doi: 10.1056/NEJM199306103282306.

13. Rawshani A, Sattar N, Franzén S, Hattersley AT, Svensson AM, Eliasson B, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug 11;392(10146):477-86. doi: 10.1016/S0140-6736(18)31506-X.

14. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. 2014 Sep 23;130(13):1110-30. doi: 10.1161/CIR.0000000000000034.

15. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018 May;41(5):917-28. doi: 10.2337/dci18-0007.

16. Solomon SD, Chew E, Duh EJ, Sobrin L, Sun JK, VanderBeek BL, et al. Diabetic Retinopathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017 Mar;40(3):412-8. doi: 10.2337/dc16-2641.

17. American Diabetes Association. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S151-S67. doi: 10.2337/dc21-S011.

18. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S125-S50. doi: 10.2337/dc21-S010.

19. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care. 2020 Apr;43(4):867-74. doi: 10.2337/dc19-2292.

20. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):31-8. doi: 10.2337/dc13-2114.

21. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):24-30. doi: 10.2337/dc13-2113.

22. Aiello LP; DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):17-23. doi: 10.2337/dc13-2251.

23. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86. doi: 10.1056/NEJM199309303291401.

24. Adamsson Eryd S, Svensson AM, Franzén S, Eliasson B, Nilsson PM, Gudbjörnsdottir S. Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up. Diabet Med. 2017 Mar;34(3):411-8. doi: 10.1111/dme.13266. Epub 2016 Oct 19.

25. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S73-S84. doi: 10.2337/dc21-S006.

26. American Diabetes Association. Older Adults: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S168-S79. doi: 10.2337/dc21-S012.

27. American Diabetes Association. Children and Adolescents: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S180-S99. doi: 10.2337/dc21-S013.

28. American Diabetes Association. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S200-S10. doi: 10.2337/dc21-S014.

29. American Diabetes Association. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S53-S72. doi: 10.2337/dc21-S005.

30. Anderson EJ, Richardson M, Castle G, Cercone S, Delahanty L, Lyon R, et al. Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial. The DCCT Research Group. J Am Diet Assoc. 1993 Jul;93(7):768-72. doi: 10.1016/0002-8223(93)91750-k.

31. Sociedade Brasileira de Diabetes. Manual Oficial de Contagem de Carboidratos para as Pessoas com Diabetes [Internet]. Rio de Janeiro; 2009 [cited 2021 Feb 4]. p. 21 -23. Available from: https://www.diabetes.org.br/publico/images/pdf/a-manual-carboidratos.pdf

32. Tascini G, Berioli MG, Cerquiglini L, Santi E, Mancini G, Rogari F, et al. Carbohydrate Counting in Children and Adolescents with Type 1 Diabetes. Nutrients. 2018 Jan 22;10(1). doi: 10.3390/nu10010109.

33. Zagury RL, Rodacki M, Mello de Oliveira L, Saunders C, de Carvalho Padilha P, Zajdenverg L. Carbohydrate Counting during Pregnancy in Women with Type 1 Diabetes:

Are There Predictable Changes That We Should Know? Ann Nutr Metab. 2017;70(2):140-6. doi: 10.1159/000471859.

34. Hegab AM. Prospective evaluation of insulin-to-carbohydrate ratio in children and adolescents with type 1 diabetes using multiple daily injection therapy. Pediatr Diabetes. 2019 Dec; 20(8):1087-93. doi: 10.1111/pedi.12911.

35. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. 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. Diabetes Care. 2015 Jun;38(6):1008-15. doi: 10.2337/dc15-0100.

36. Kalergis M, Pacaud D, Strychar I, Meltzer S, Jones PJ, Yale JF. Optimizing insulin delivery: assessment of three strategies in intensive diabetes management. Diabetes Obes Metab. 2000 Oct;2(5):299-305. doi: 10.1046/j.1463-1326.2000.00107.x.

37. Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, et al. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care. 2012 May;35(5):984-90. doi: 10.2337/dc11-2044.

38. Gilbertson HR, Brand-Miller JC, Thorburn AW, Evans S, Chondros P, Werther GA. The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes. Diabetes Care. 2001 Jul;24(7):1137-43. doi: 10.2337/diacare.24.7.1137.

39. Enander R, Gundevall C, Strömgren A, Chaplin J, Hanas R. Carbohydrate counting with a bolus calculator improves post-prandial blood glucose levels in children and adolescents with type 1 diabetes using insulin pumps. Pediatr Diabetes. 2012 Nov;13(7):545-51. doi: 10.1111/j.1399-5448.2012.00883.x.

40. Dafne Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ. 2002 Oct 5;325(7367):746. doi: 10.1136/bmj.325.7367.746.

41. Scavone G, Manto A, Pitocco D, Gagliardi L, Caputo S, Mancini L, et al. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in Type 1 diabetic subjects: a pilot study. Diabet Med. 2010 Apr;27(4):477-9. doi: 10.1111/j.1464-5491.2010.02963.x.

42. Trento M, Trinetta A, Kucich C, Grassi G, Passera P, Gennari S, et al. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes managed by Group Care. J Endocrinol Invest. 2011 Feb;34(2):101-5. doi: 10.1007/BF03347038.

43. Gökşen D, Atik Altınok Y, Ozen S, Demir G, Darcan S. Effects of carbohydrate counting method on metabolic control in children with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol. 2014;6(2):74-8. doi: 10.4274/Jcrpe.1191.

44. Fu S, Li L, Deng S, Zan L, Liu Z. Effectiveness of advanced carbohydrate counting in type 1 diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2016 Nov 14; 6:37067. doi: 10.1038/srep37067.

45. Donzeau A, Bonnemaison E, Vautier V, Menut V, Houdon L, Bendelac N, et al. Effects of advanced carbohydrate counting on glucose control and quality of life in children with type 1 diabetes. Pediatr Diabetes. 2020 Nov;21(7):1240-1248. doi: 10.1111/pedi.13076.

46. Sterner Isaksson S, Bensow Bacos M, Eliasson B, Thors Adolfsson E, Rawshani A, Lindblad U, et al. Effects of nutrition education using a food-based approach, carbohydrate counting or routine care in type 1 diabetes: 12 months prospective randomized trial. BMJ Open Diabetes Res Care. 2021 Mar;9(1). doi: 10.1136/bmjdrc-2020-001971.

47. Fortins RF, Lacerda EMA, Silverio RNC, do Carmo CN, Ferreira AA, Felizardo C, et al. Predictor factors of glycemic control in children and adolescents with type 1 diabetes mellitus treated at a referral service in Rio de Janeiro, Brazil. Diabetes Res Clin Pract. 2019 Aug; 154:138-45. doi: 10.1016/j.diabres.2019.05.027.

48. de Albuquerque IZ, Stringhini MLF, Marques RMB, Mundim CA, Rodrigues MLD, Campos MRH. Contagem de carboidratos, estado nutricional e perfil metabólico em adolescentes com diabetes *mellitus* tipo 1. Scientia Medica. 2014;24(4):343-52. Brazilian. doi:10.15448/1980-6108.2014.4.18381

49. Laurenzi A, Bolla AM, Panigoni G, Doria V, Uccellatore A, Peretti E, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). Diabetes Care. 2011 Apr;34(4):823-7. doi: 10.2337/dc10-1490.

50. Elise R, Lisa GC, Charles S, Elysabeth BS, Frédérique G, Antoine T, et al. Variation of carbohydrate intake in diabetic children on carbohydrate counting. Diabetes Res Clin Pract. 2019 Apr;150:227-35. doi: 10.1016/j.diabres.2019.03.010.

51. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019 Feb;21(2):66-72. doi: 10.1089/dia.2018.0384.

52. Hood KK, Peterson CM, Rohan JM, Drotar D. Association between adherence and glycemic control in pediatric type 1 diabetes: a meta-analysis. Pediatrics. 2009 Dec;124(6):e1171-9. doi: 10.1542/peds.2009-0207.

53. The NS, Crandell JL, Thomas J, Couch SC, Shah AS, Maahs DM, et al. Correlates of medical nutrition therapy and cardiovascular outcomes in youth with type 1 diabetes. J Nutr Educ Behav. 2013;45(6):661-8. doi: 10.1016/j.jneb.2013.06.003.

54. Smart CE, Ross K, Edge JA, King BR, McElduff P, Collins CE. Can children with Type 1 diabetes and their caregivers estimate the carbohydrate content of meals and snacks? Diabet Med. 2010 Mar;27(3):348-53. doi: 10.1111/j.1464-5491.2010.02945.x.

55. Brazeau AS, Mircescu H, Desjardins K, Leroux C, Strychar I, Ekoé JM, et al. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Res Clin Pract. 2013 Jan;99(1):19-23. doi: 10.1016/j.diabres.2012.10.024.

56. Koontz MB, Cuttler L, Palmert MR, O'Riordan M, Borawski EA, McConnell J, et al. Development and validation of a questionnaire to assess carbohydrate and insulin-dosing knowledge in youth with type 1 diabetes. Diabetes Care. 2010 Mar;33(3):457-62. doi: 10.2337/dc09-0390.

57. Lancaster BM, Pfeffer B, McElligott M, Ferguson AT, Miller M, Wallace D, et al. Assessing treatment barriers in young adults with type 1 diabetes. Diabetes Res Clin Pract. 2010;90(3):243-9. doi: 10.1016/j.diabres.2010.07.003.

58. Patton SR. Adherence to diet in youth with type 1 diabetes. J Am Diet Assoc. 2011 Apr;111(4):550-5. doi: 10.1016/j.jada.2011.01.016.

59. Patton SR, Dolan LM, Powers SW. Dietary adherence and associated glycemic control in families of young children with type 1 diabetes. J Am Diet Assoc. 2007 Jan;107(1):46-52. doi: 10.1016/j.jada.2006.10.012.

60. Gandhi K, Vu BK, Eshtehardi SS, Wasserman RM, Hilliard ME. Adherence in adolescents with Type 1 diabetes: strategies and considerations for assessment in research and practice. Diabetes Manag (Lond). 2015 Nov;5(6):485-98. doi: 10.2217/dmt.15.41.

61. Wysocki T, Buckloh LM, Antal H, Lochrie A, Taylor A. Validation of a self-report version of the diabetes self-management profile. Pediatr Diabetes. 2012 Aug;13(5):438-43. doi: 10.1111/j.1399-5448.2011.00823.x.

62. Harris MA, Wysocki T, Sadler M, Wilkinson K, Harvey LM, Buckloh LM, et al. Validation of a structured interview for the assessment of diabetes self-management. Diabetes Care. 2000 Sep;23(9):1301-4. doi: 10.2337/diacare.23.9.1301.

63. Weinger K, Butler HA, Welch GW, La Greca AM. Measuring diabetes self-care: a psychometric analysis of the Self-Care Inventory-Revised with adults. Diabetes Care. 2005 Jun;28(6):1346-52. doi: 10.2337/diacare.28.6.1346.

64. Davison KA, Negrato CA, Cobas R, Matheus A, Tannus L, Palma CS, et al. Relationship between adherence to diet, glycemic control and cardiovascular risk factors in

patients with type 1 diabetes: a nationwide survey in Brazil. Nutr J. 2014 Mar;13:19. doi: 10.1186/1475-2891-13-19.

65. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care. 2013 Jul;36(7):2009-14. doi: 10.2337/dc12-1770.

66. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R, et al. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2011 Feb;12(1):11-7. doi: 10.1111/j.1399-5448.2010.00650.x.

67. Schwandt A, Best F, Biester T, Grünerbel A, Kopp F, Krakow D, et al. Both the frequency of HbA testing and the frequency of self-monitoring of blood glucose predict metabolic control: A multicentre analysis of 15199 adult type 1 diabetes patients from Germany and Austria. Diabetes Metab Res Rev. 2017 Oct;33(7). doi: 10.1002/dmrr.2908.

68. Moström P, Ahlén E, Imberg H, Hansson PO, Lind M. Adherence of self-monitoring of blood glucose in persons with type 1 diabetes in Sweden. BMJ Open Diabetes Res Care. 2017 Apr 6;5(1):e000342. doi: 10.1136/bmjdrc-2016-000342.

69. Gloaguen E, Bendelac N, Nicolino M, Julier C, Mathieu F. A systematic review of non-genetic predictors and genetic factors of glycated haemoglobin in type 1 diabetes one year after diagnosis. Diabetes Metab Res Rev. 2018 Nov;34(8):e3051. doi: 10.1002/dmrr.3051.

70. Sildorf SM, Breinegaard N, Lindkvist EB, Tolstrup JS, Boisen KA, Teilmann GK, et al. Poor Metabolic Control in Children and Adolescents With Type 1 Diabetes and Psychiatric Comorbidity. Diabetes Care. 2018 Nov;41(11):2289-96. doi: 10.2337/dc18-0609.

2 ARTIGO ORIGINAL

Carbohydrate counting as a strategy to optimize glycemic control in type 1 diabetes mellitus

Revista de escolha:

Clinical Nutrition

Carbohydrate counting as a strategy to optimize glycemic control in type 1 diabetes mellitus

Analaura Centenaro, RD,[a] Cigléa do Nascimento, RD,[c] Mileni Vanti Beretta, PhD,[a] Ticiana C. Rodrigues, MD, PhD [a,b,c]

a Post Graduate Program in Medical Sciences: Endocrinology, School of Medicine, Federal University of Rio Grande do Sul (UFRGS), Ramiro Barcelos Street, 2350, 90035-903, Porto Alegre, Rio Grande do Sul, Brazil

b Department of Internal Medicine, School of Medicine, Federal University of Rio Grande do Sul (UFRGS), Ramiro Barcelos Street, 2400, 90035-903, Porto Alegre, Rio Grande do Sul, Brazil.

c Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos Street, 2350, 90035-903, Porto Alegre, Rio Grande do Sul, Brazil

E-mail address for each author:

Centenaro, A: analauracentenaro@yahoo.com.br

Nascimento, C: cnascimento@hcpa.edu.br

Beretta, MV: mileni.nutri@gmail.com

Rodrigues, TC: ticianacr@yahoo.com.br

Corresponding author: Ticiana C. Rodrigues, MD, PhD

Division of Endocrinology, Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos Strett, 2350, 90035-903, Porto Alegre, RS, Brazil,

Phone: +55 51 3359 8127

Abstract

Background & aims: Patients with type 1 diabetes mellitus (T1D) are at risk of developing complications, which can be reduced through adequate glycemic control. There is evidence that carbohydrate counting (CC) optimizes control, but the results are not similar among all studies. Thus, the objective of this study was to verify the impact of CC on glycemic control and body weight variation (primary and secondary outcome, respectively) between consultations in patients with T1D followed at a tertiary hospital in southern Brazil in a public health system environment. We also sought to identify predictors of good glycemic control and to investigate CC adherence, as well as to identify variables associated with adherence. **Methods:** This retrospective cohort study included 232 patients with T1D who underwent nutritional monitoring at the Hospital de Clínicas de Porto Alegre between 2014 and 2018. To assess primary and secondary outcomes, data from 49 patients who underwent CC during this period and from 180 individuals who used fixed doses of insulin were analyzed. The impact of CC on glycemic control was assessed through the mean glycated hemoglobin (HbA1c) level at all consultations during the follow-up period. **Results:** In the model adjusted for the most confounders (except pregnancy), mean HbA1c was better in the CC group (8.66 ± 0.4% vs. 9.36 ± 0.39%; p = 0.016), and body weight variation was lower (0.13 ± 0.28 kg vs. 0.53 ± 0.24 kg; p = 0.024). Predictors of good glycemic control were lower doses of insulin, no autoimmune diseases associated with T1D, and no retinopathy; the direction of association between fasting glucose and the outcome varied during the follow-up period. Adherence to CC was reported in 69,2% of consultations. Higher body mass index, lower HbA1c levels, and fewer missed consultations were associated with adherence. **Conclusion:** CC optimized

the glycemic control of individuals with T1D, resulting in less weight variation than the fixed insulin dose group, which indicates that CC is an important care strategy for these patients.

Keywords: Carbohydrate Counting. Type 1 Diabetes Mellitus. Glycemic Control. Glycated Hemoglobin. Body Weight.

Abbreviations

ADA: American Diabetes Association

BMI: Body mass index

CB: Correction bolus

CC: Carbohydrate counting

cHDL: high-density-lipoprotein cholesterol

CHO: Carbohydrate

95% CI: 95% confidence interval

cLDL: Low-density-lipoprotein cholesterol

CVD: Cardiovascular disease

DKD: Diabetic kidney disease

DM: Diabetes mellitus

GFR: Glomerular filtration rate

HbA1c: Glycated hemoglobin

HCPA: Hospital de Clínicas de Porto Alegre

ICR: Insulin to carbohydrate ratio

ISF: Insulin sensitivity factor

MB: Meal bolus

MD: Mean difference

OR: Odds ratio

RCT: Randomized control trial

SD: Standard deviation

SE: Standard error

SMBG: Self-monitoring of capillary blood glucose

TC: Total cholesterol

TDID: Total daily insulin dose

T1D: Type 1 diabetes mellitus

TG: Triglycerides

UI: Unit of insulin

Introduction

Treating type 1 diabetes mellitus (T1D) is a challenge for patients, their families, and the multidisciplinary care team due to the disease's characteristics, the use of insulin and the constant monitoring of blood glucose levels. Hyperglycemia exposes individuals to the risk of developing chronic complications (1-3), which are associated with considerable rates of morbidity, mortality and high health cost (4, 5). However, long-term observational follow-up studies and clinical trials have demonstrated a lower incidence of microvascular and macrovascular disease through adequate glycemic control (6-9). Given that, different treatment approaches that optimize glycemic control should be explored, including carbohydrate counting (CC) (10). This technique focuses on the amount of carbohydrates (CHO) consumed (11), since this nutrient is the major determinant of postprandial glycemic response (12).

Divergent results have been found in previous studies on CC as a strategy for optimizing glycemic control in individuals with T1D. While some studies have reported that CC has no effect on glycated hemoglobin (HbA1c) compared to a control group (13-16), others have found better control through the intervention (17-20). The greatest difference was found in the DAFNE study: approximately 1% difference in HbA1c reduction (18). Some short-term Brazilian studies have also found that CC optimizes glycemic control, although none were conducted in the southern region of the country (21, 22).

Because CC provides dietary flexibility in the diet by allowing bolus dose adjustments according to CHO consumption, which could additionally result in higher doses of insulin (18, 23, 24), it is also important to investigate the effect of this technique on body weight, since obesity is associated with a less favorable cardiometabolic profile (25). However, most

studies have not associated CC with weight (16-18) or body mass index (BMI) (17, 20, 26), with some data indicating that CC leads to reduced BMI (23).

In view of such evidence, the aim of the present study was to evaluate the effects of CC on glycemic control, as well as on variation in body weight between consultations, in T1D patients treated at a tertiary hospital in southern Brazil in a real-life public health care model. We also sought to identify predictor variables of good glycemic control and assess CC adherence, as well as investigate variables associated with adherence.

Materials & Methods

This retrospective cohort study included all patients (children, adolescents, adults, older adults, and pregnant women) diagnosed with T1D who had consultations with the dietitian at the outpatient endocrinology clinic of the Hospital de Clínicas de Porto Alegre (HCPA), Rio Grande do Sul, Brazil, between January 2014 and December 2018. A total of 326 potentially eligible patients were identified through the hospital's electronic records of consultations during the period. We excluded a total of 94 patients who, during the study period: had only one nutritional consultation (n=80), received less than 3 months of nutritional follow-up (n = 13), or performed CC for less than 3 months (n = 1). Thus, the final sample consisted of 232 patients. To assess glycemic control and body weight change between consultations (primary and secondary outcome, respectively), the patients were divided into two groups, a group that only underwent conventional nutritional monitoring but not CC (n=180) and used fixed doses of insulin, and a group that performed CC between 2014 and 2018 (n=52). Patients in the second group could have begun CC before or during the study period or interrupted it between 2014-2018. Thus, since some CC group patients were

using fixed doses of insulin at the time of one or more consultations, only data from the period in which the patients were actually performing CC were included in the primary and secondary outcome analysis, then only these consultations were considered as follow-up time in the analysis. As a result, 3 additional individuals were excluded for this assessment, since only one nutritional consultation could be analyzed; hence, the CC group included a total of 49 individuals. However, to determine predictors of good glycemic control, data from all nutritional consultations between 2014-2018 for all 232 patients were included, although to determine adherence to CC and variables associated with adherence, the only consultations considered were those in which CC was performed.

Patients who underwent CC were trained by the outpatient dietitian (27). The dose of insulin bolus to be applied at the meal was calculated using the following formula (12, 28):

Total bolus = meal bolus (MB) + correction bolus (CB), being,

MB = grams of carbohydrate in the meal/insulin-to-carbohydrate ratio (ICR)

CB = (preprandial glucose - glycemic target)/insulin sensitivity factor (ISF)

The ICR indicates the grams of carbohydrates metabolized by one unit of insulin (UI), while the ISF reports the blood glucose reduction (mg/dl) for each administered UI (12, 29). Initially, the ICR was estimated as 500 divided by the total daily insulin dose (TDID), while the ISF was calculated as 1500 or 1800 (for short-acting insulin or rapid-acting insulin analogs, respectively) divided by the TDID (12, 30, 31). Necessary adjustments to the ICR and the ISF were made at follow-up consultations based on patient-recorded glycemic controls and insulin doses (12). Changes in basal insulin doses were made by an endocrinologist at the diabetes clinic.

Patients who underwent nutritional monitoring but not CC received individual nutritional guidance at each consultation and administered fixed doses of bolus insulin

adjusted only to the preprandial blood glucose value; these doses were also prescribed by an endocrinologist.

The data were extracted entirely from the electronic records of each patient. The following sociodemographic data were collected: sex, ethnicity, and maximum education level reported during the follow-up period (classified as ignored, none, elementary/high school/ higher education or graduate school - complete or incomplete). The following clinical data were also collected: date of T1D diagnosis and date of initial nutritional monitoring and CC.

The following repeated measures variables were collected at each nutritional consultation between January 2014 and December 2018: CC (yes vs. no), self-monitoring of capillary blood glucose (SMBG) as recommended (yes vs. no), pregnancy (yes vs. no - adult and adolescent women), medications used, types of insulin administered (basal: intermediate-acting or long-acting analogues; bolus: short-acting or rapid-acting analogs) and daily dose per kg of body weight. The following laboratory tests performed for routine consultations were verified: plasma levels of fasting glucose, HbA1c, total cholesterol (TC), high density lipoprotein cholesterol (cHDL), triglycerides (TG), and albuminuria from urine sample. The low density lipoprotein cholesterol (cLDL) concentration was calculated using the Friedewald formula: cLDL = TC – (cHDL + TG/5) when TG levels < 400 mg/dl (32). Kidney function was determined by calculating the glomerular filtration rate (GFR) using the CKD-EPI formula for adults and Schwartz' method for children and adolescents (33). For anthropometric evaluation, weight and height were collected to calculate BMI using the formula weight/height^2, and nutritional status was evaluated using the cutoff points recommended for adults (34), elderly (35) and pregnant women (36). For children and adolescents the WHO Anthro and WHO AnthroPlus software were used to calculate BMI-for-

age z-scores (37, 38). Patients were divided in two categories: underweight/eutrophic vs. excess weight (overweight or obesity). The variation in body weight in relation to that of the previous nutritional consultation was also calculated. To assess the patients' physical activity level, the total time of activity (minutes) per week was determined, and the individuals were then classified as either sufficiently active (≥ 60 minutes/day for children and adolescents and ≥ 150 min/week for adults) or insufficiently active (10).

At each nutritional consultation, patients in the CC group were asked about performing the technique according to the instructions received. Until deemed necessary (usually until assimilation of the method), the dietitian requested records of the food and quantities ingested, the calculation of corresponding CHO grams, the MB and CB. Adherence to CC was assessed by the report in the dietitian's records, and patients were classified as adherent (when the dietitian reported correct CC performance according to her prescription) vs. not-/partially adherent (if the professional reported not performing/partially performing the provided orientation).

Based on the information collected, age, diabetes mellitus (DM) duration, nutritional follow-up time, and time of CC were calculated for each nutritional consultation. The total number of nutritional consultations and absences between 2014 and 2018 was also calculated.

Data were also collected on comorbidities and chronic complications of DM (developed before or during the follow-up period). Complications included medical diagnosis of retinopathy, neuropathy, diabetic kidney disease (DKD) or cardiovascular events (death from cardiovascular disease (CVD), acute myocardial infarction, stroke, and peripheral or coronary artery disease requiring revascularization or angioplasty). DKD was considered confirmed when the patient had at least two values indicating albuminuria ≥14 mg/l or a GFR < 60 ml/min/1.73m² at least 6 months before diagnosis of DKD (12). Comorbidities included

hypertension, psychiatric diseases (depression, bulimia, panic syndrome, anxiety disorder, bipolarity, attention deficit, and hyperactivity), functional thyroid diseases (hypothyroidism or hyperthyroidism), other autoimmune diseases in addition to T1D (celiac disease, Hashimoto's thyroiditis, rheumatoid arthritis, Graves' disease, Sjogren's syndrome and vitiligo), and eye diseases other than diabetic retinopathy (amaurosis, cataracts and glaucoma).

Due to the complexity of estimating the TDID per patient, data imputations were made in some situations of missing or confusing values, ie, the mean of the previous and subsequent consultation or, when referring to the last and first consultations, repeating the value immediately before or after, respectively. For the other variables, missing data were considered missing. The primary outcome was the effect of CC on glycemic control through HbA1c values. As a secondary outcome, the impact of CC on body weight variation between appointments was considered. Possible predictors of good glycemic control were also analyzed. For this analysis, the HbA1c values collected at each visit were classified. Values that attained the HbA1c target - determined according to the following American Diabetes Association (ADA) cutoff points - were generally designated as good glycemic control: 1) children and adolescents < 7%; 2) adults < 7%; 3) elderly <7.5%; 4) pregnant women < 6% (39-42). In individual cases of severe complications, such as CVD or advanced DKD, individual goals were discussed with the medical team. We also calculated the proportion of CC consultations in which patients were considered adherent, subsequently determining variables associated with adherence.

This study was approved by the Research Ethics Committee of the HCPA Graduate Studies Group (protocol 2019-0079). All researchers involved in the study signed the Data Use Agreement.

Statistical Analysis

Variables were analyzed as either single measure (a single value during the follow-up period or referring to baseline, ie, the first consultation evaluated between 2014 and 2018) or as repeated measures over the follow-up period (measured at each nutritional consultation).

For the primary and secondary outcomes, single-measure variables are presented as mean ± standard deviation (SD), median (interquartile range P25 – P75) or number of cases (%). The distribution of continuous variables was evaluated using the Shapiro-Wilk test. The *t*-test, the Mann-Whitney test, and the chi-square test were used to compare parametric, nonparametric, and categorical variables, respectively, between the CC group and the group that used fixed doses of insulin. A linear mixed model for repeated measures, a generalized linear mixed model for repeated measures and a generalized linear mixed model for dichotomous response were used to compare parametric, nonparametric and categorical variables, respectively, measured at each nutritional consultation. In addition to the main effect of the variable (p-value), its interaction with time (p for interaction) was also analyzed. Continuous variables will be presented as means ± standard error (SE) and 95% confidence interval (95% CI), and dichotomous variables as estimated proportion (%) ± SE and 95% CI. Variables whose effect was not constant during the follow-up period (p for interaction < 0.05) will only have this effect cited in the text, since the values are not the same in the different periods and the follow-up time was treated as a continuous variable in this analysis (number of weeks elapsed between each nutritional consultation during the follow-up period and the baseline consultation), therefore, it varies among patients, with considerable extension and variability of values.

For the CC adherence analysis, we calculated the frequency (%) of consultations (among those in which CC was performed) in which patients were classified as compliant.

Variables associated with good glycemic control and CC adherence were analyzed using generalized linear models (generalized estimating equations), showing odds ratio (OR) and 95% CI. For a categorical response model to have good convergence, it is necessary to have an adequate frequency of data at all times. Thus, in this analysis, the data were filtered for a maximum of 10 follow-up time points (here, time was treated as a categorical variable, with each point corresponding to a consultation between 2014 and 2018), since few patients had more consultations. The variables that obtained the necessary convergence for the analysis are listed below. Single-measure predictors of good glycemic control included retinopathy, neuropathy, positive albuminuria, other autoimmune diseases associated with T1D, hypertension, sex, education, age at DM diagnosis, and number of consultation absences between 2014-2018. Repeated-measure predictors included physical activity level, performance or not of CC, age, duration of nutritional follow-up, duration of illness, TDID, fasting glucose, BMI, nutritional status and type of basal insulin applied. Single measure predictors of CC adherence included retinopathy, thyroid disease, sex, education, age at DM diagnosis, and number of consultation absences between 2014-2018. Repeated measure predictors included physical activity level, age, duration of nutritional follow-up, duration of illness, TDID, fasting glucose, HbA1c and BMI.

Although education was included in the between-group analyses (CC vs. fixed insulin doses) in all categories (ignored, none, elementary school/high school/ higher education or graduate school - complete or incomplete), it will be presented as ignored/≤ completed elementary school, high school, or ≥ incomplete higher education. Due to the impossibility of data convergence in the model identifying variables associated with good glycemic control

and CC adherence, this variable was grouped into the three aforementioned categories still in the analyses.

All repeated measures analyses were adjusted for the duration of the patients' nutritional follow-up at baseline, as well as for the time (continuous or categorical variable, depending on the model). Multivariate models were developed based on univariate results and clinical judgment. As the number of pregnant women was different between groups (CC vs. fixed doses of insulin), this variable was included in the multivariate analysis, however, the number of individuals in this model was significantly reduced (only adult and adolescent women), therefore an analysis with the total sample, but excluding consultations during pregnancy, was also carried out. In the CC adherence analysis, data convergence was impossible when all significant variables from the univariate model were added. Thus, only HbA1c, BMI, and the number of absences during the follow-up period were selected for the multivariate model.

P-values < 0.05 were considered statistically significant. The analyses were performed in SPSS, version 22.0 (IBM Corp, Armonk, NY), except for the OR when there was a significant interaction between variable and time (p for interaction < 0.05) in the multivariate model, which was calculated using SAS version 9.4 (SAS Institute, Cary, NC).

Results

The median follow-up time was 105 (43 – 198) weeks. Table 1 compares the single measure variables between the groups (CC vs. not CC), including sociodemographic and clinical characteristics, the number of pregnant women, and the number of consultations. Regarding ethnicity, there was higher percentage of whites in the CC group than the group

using fixed doses of insulin [49 (100%) vs. 161 (89.4%); p = 0.045]. The CC group also had a higher education level (ie, more patients with at least incomplete higher education and fewer with ignored education degree or with no more than primary education p = 0.001). In addition, the CC group had more pregnant women [5 (10.2%) vs. 1 (0.55%); p = 0.003] and longer nutritional follow-up at baseline [97 (5.5-129.5) vs. 43.5 (0-126.75) months]. The total number of nutritional consultations carried out between 2014 and 2018 was also higher in the CC group [10 (6-14) vs. 5 (3-9); p = 0.000]. There were no significant differences between the groups for the other variables.

Table 2 shows the comparisons regarding repeated measures clinical, laboratory and anthropometric variables. SMBG was performed more frequently in the CC group (92.2 ± 2.4 vs. 84.4 ±1.8; p value = 0.005), as well as the use of rapid-acting insulin analogs (100 ± 0 vs. 77.9 ± 3.1; p value = 0.000). There were significant differences in BMI and the proportion of patients classified as sufficiently vs. insufficiently active between the two groups, although these values were not constant throughout follow-up (p for interaction = 0.008 and 0.005, respectively).

HbA1c values collected in both groups at each nutritional consultation analyzed during follow-up are shown in Figure 1. Table 3 shows the association between CC and glycemic control during the follow-up period. After adjusting for most confounding variables (model 1), mean HbA1c was significantly lower in the CC group than in the fixed doses of insulin group (8.66 ± 0.4% vs. 9.36 ± 0.39%, p value = 0.016) and this difference was constant over time (p for interaction = 0.841). When performing an additional adjustment for pregnancy (model 2), although there was a lower mean HbA1c in the CC group (8.26 ± 0.58% vs. 8.82 ± 0.55%), it was not significant (p value = 0.107 and p for interaction = 0,999).

The mean weight variation between nutritional consultations (Table 4) was positive in both groups but lower in those that performed CC (model 3) (0.13 ± 0.28 kg vs. 0.53 ± 0.24 kg, p value = 0.024), and this difference was also constant throughout the follow-up period (p for interaction = 0.226). In an additional adjustment for pregnancy using only data from adult and adolescent women, the difference, although still significant, was not constant throughout the follow-up period (p for interaction = 0.035).

Performing the same analyses, but excluding consultations during pregnancy, one patient was excluded from the CC group and the statistical difference for ethnicity was not maintained between groups [whites: 48 (100%) in CC vs. 161 (89.4%) in not CC; p = 0.051]. All other results were similar to those conducted with the entire sample (data not shown).

Among the variables analyzed, insulin dose, nutritional status, other autoimmune diseases, fasting glucose levels and retinopathy were associated with the HbA1c target. This effect was constant over time for insulin dose, nutritional status and other autoimmune diseases (p value = 0.043, p value = 0.008 and 0.044, respectively), but varied for fasting glucose levels and retinopathy (p for interaction = 0.014 and 0.008, respectively). After adjustments (Supplementary Table 1), it was found that the chance of attaining the HbA1c target in the absence of other autoimmune diseases was 4 times the chance of those with other autoimmune diseases in addition to DM1 (OR = 4.09; 95% CI 1.4–11.93), while a 1 unit increment of insulin/kg in the insulin dose resulted in a 76% lower chance of attaining the HbA1c target (OR = 0.24; 95% CI 0.08-0.7). On the other hand, having no retinopathy was an outcome predictor at follow-up times 1 and 3, while an increase of 1 mg/dl in fasting glucose reduced the chance of good glycemic control at follow-up times 1, 3 and 4. This relationship was inverted at time 10, ie, there was a greater chance of attaining the HbA1c target with higher fasting glucose. Nutritional status was not a predictor in the multivariate model.

Adherence to CC was reported in 69,2% of the CC consultations (Figure 2). The number of absences during follow-up, thyroid disease, BMI, fasting glucose and HbA1c values were significantly associated with CC adherence, and, with the exception of HbA1c, the effect of the others was inconsistent over time (p for interaction = 0.017; 0.002; 0.019, 0.000 and p value = 0.011, respectively). In the multivariate model (Supplementary Table 2), a 1% increase in HbA1c was associated with a 34% lower chance of CC adherence (OR = 0.66; 95% CI 0.44-0.93), each additional absence during follow-up reduced the chance of CC adherence by 96% at follow-up time 3 (OR = 0.04, 95% CI 0.006-0.28), while a 1 unit increase of BMI increased the odds of adherence by 80% at time 4 (OR = 1.8; 95% CI 1.08-2.98).

Discussion

In this real-life study in a public health system environment, T1D patients in the CC group had better glycemic control and less variation in body weight than the standard nutritional monitoring group, showing a difference in HbA1c with potential clinical impact (≈ -0.7%).

According to previous studies, the effects of the CC method are somewhat divergent in patients with T1D (13-23, 26). Of the randomized controlled trials (RCT) that compared CC to a control group, several (17-20) found that the intervention optimized glycemic control, while others did not (13-16).

Additionally, studies from 2020 and 2021 found that CC was only effective in the short term. In the 2020 study, CC resulted in a lower mean HbA1c during 1 year of follow-up, although when the analysis was performed separately at 3, 6, 9 and 12 months, the benefit was

maintained only in the first evaluation (26). The 2021 study found that CC had a positive effect on HbA1c after 3 months of treatment, but not after 12 months (43). In the Brazilian population, a 4-month clinical trial of 28 adolescents from Goiás found that HbA1c was lower in the CC group than the control group (22). A cross-sectional study of children and adolescents in Rio de Janeiro in which 80% of the sample performed CC found that the technique was associated with lower HbA1c values (21). According to our results, CC optimized HbA1c, corroborating some of these data (17-22, 26) with a longer follow-up time (13-16, 18-20, 26, 43) and superior sample size (13-18, 20, 26, 43) to most other studies.

Adjusting for pregnancy reduced the number of consultations in the analysis, and although the difference in HbA1c was maintained, it did not remain statistically significant. However, the difference was clinically relevant, so perhaps if a larger sample size had been included, CC would have had a significant benefit. Analyses that excluded consultations during pregnancy did not significantly change the results obtained with the entire sample.

A meta-analysis that included the above-mentioned RCTs (except for those from 2020 and 2021) investigated the effects of CC on HbA1c in T1D. Although the quality of evidence was moderate, lower HbA1c values were found with the intervention. Nevertheless, there was a low magnitude of effect [mean difference (MD) = -0.35%]. In the subgroup analysis, although CC did not differ from other DM diets, the association was maintained when it was compared to dietary education in diabetes (MD = -0.68%) (44). This strategy was similar to that of the present study, in which patients on fixed doses of insulin were educated about healthy eating in DM but did not receive strict eating plans.

Since CC makes feeding more flexible (18, 23, 24) its impact on weight have also been studied (29), and it could be inferred that it leads to increased weight. However, most RCT have not found a change in weight or BMI after CC, and no difference in weight

variation compared to controls was found at the end of these studies (16-18, 20, 26, 43). BMI was reduced in the CC group and increased in the control group in only one RCT, with a modest but significant difference between the groups (23). Although the authors could not provide a concrete explanation for this, they suggested that CC might provide weight loss benefits, such as improved nutrition or increased physical activity. These data partially corroborate those of the present study, since we also observed less weight variation in the CC group despite our observational design.

In the literature on patient adherence to CC, there is no uniformity regarding assessment, no gold standard method, and no method that has been validated for the Brazilian population. In a Brazilian cross-sectional retrospective study on self-reported adherence to different T1D diets, of the 967 patients in CC, 626 reported being adherent (45). These data corroborate our results, since we estimated adherence in 69,2% of consultations in CC. Our data also associated CC adherence with fewer absences from nutritional consultations and with increased BMI - which was unrelated to insulin dose (which could be influenced by the degree of CC adherence and impact on body weight) because the association between TDID and CC adherence was not significant in the univariate analysis. Although no data were found specifically for CC, the above-mentioned study found an association between a greater number of medical consultations and diet adherence, but higher BMI was associated with lower adherence. This study also found lower adherence among adolescents (45), while there was no association between age and adherence in our results. In the present study, higher HbA1c levels were associated with lower CC adherence and, although the literature associates adherence to T1D treatment with glycemic control, the assessment usually considers adherence as a predictor variable (46).

Several factors have also been investigated as predictors of glycemic control in T1D. Data from the Type 1 Diabetes Exchange Registry show that individuals with HbA1c < 7% used less insulin than those with HbA1c ≥ 9%, which corroborates our results, although the authors only assessed children and adolescents (47). Our study also found an association between good glycemic control and no retinopathy and other autoimmune diseases. Most of the literature assessing HbA1c and autoimmune diseases have studied celiac disease, and there seems to be no difference in glycemic control between individuals with T1D and those with T1D and celiac disease who are treated with a gluten-free diet (48, 49). However, autoimmune diseases were grouped together in our analyses, which makes it difficult to compare our results with such studies. Regarding retinopathy, although the literature relates it to HbA1c, the assessments usually consider glycemic control a predictor of this complication (9, 50). Despite the fact that our analysis showed a significant difference, the 95% CI amplitude at time 1 denotes imprecision in the estimation of the effect. In our study, the direction of the association between fasting glucose and glycemic control also varied during follow-up, and although at most time points the increase in glycemic values was associated with worsening HbA1c, the opposite occurred at time 10. One explanation for this could be that since HbA1c results from the glycemic mean (fasting, pre-prandial, and post-prandial values), one isolated parameter cannot fully explain it (51).

The study has some limitations. Its retrospective design does not exclude the possibility of bias, since the measurements were performed during routine consultations. Although adjustments were made, the observational design may have led to a confounding bias. Furthermore, the fact that few patients had a large number of nutritional consultations made it impossible to properly assess the variables associated with good glycemic control and

CC adherence. The fact that we did not use suitable adherence questionnaires also limits our data on this topic.

However, our study also had a number of strengths. The sample selection was not biased, since all eligible patients with nutritional consultations between 2014 and 2018 were included. Given that all patients were treated by the same dietitian, we believe there was good uniformity of care. Although the study was observational, the favorable effects of CC were verified during a longer follow-up period (median ~2 years) than most RCTs [duration between 3.5 – 30 months; only two > 1 year (17, 20)].

Conclusion

We can conclude that, as a nutritional strategy, CC had a positive impact on the glycemic control of patients with T1D treated in the Brazilian public health system, resulting in less body weight variation than conventional nutritional monitoring. We also found that greater effort should be made so that more patients can benefit from this technique.

Acknowledgements

We would like to thank the Hospital de Clínicas de Porto Alegre and Coordination for the Improvement of Higher Education Personnel (CAPES) for supporting the development of the research project.

Funding statement

This work was supported by the Research Incentive Fund of Hospital de Clínicas de Porto Alegre (FIPE - HPCA) and National Council for Scientific and Technological Development – CNPq (#310167/2020-5) and AC received a scholarship from CAPES.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contribution

AC: Conceptualization, methodology, formal analysis, investigation, writing original draft

CN: Conceptualization, writing reviewing and editing

MVB: Writing reviewing and editing

TCR: Conceptualization, methodology, writing reviewing and editing, supervision, project administration

References

1. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993 Jun;328(23):1676-85. doi: 10.1056/NEJM199306103282306.

2. Rawshani A, Sattar N, Franzén S, Hattersley AT, Svensson AM, Eliasson B, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug;392(10146):477-86. doi: 10.1016/S0140-6736(18)31506-X.

3. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. 2014 Sep;130(13):1110-30. doi: 10.1161/CIR.0000000000000034.

4. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016 Apr;12(4):222-32. doi: 10.1038/nrendo.2016.15.

5. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018 May;41(5):917-28. doi: 10.2337/dci18-0007.

6. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care. 2020 Apr;43(4):867-74. doi: 10.2337/dc19-2292.

7. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):31-8. doi: 10.2337/dc13-2114.

8. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):24-30. doi: 10.2337/dc13-2113.

9. Aiello LP; DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):17-23. doi: 10.2337/dc13-2251.

10. American Diabetes Association. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S53-S72. doi: 10.2337/dc21-S005.

11. Anderson EJ, Richardson M, Castle G, Cercone S, Delahanty L, Lyon R, et al. Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial.

The DCCT Research Group. J Am Diet Assoc. 1993 Jul;93(7):768-72. doi: 10.1016/0002-8223(93)91750-k.

12. Sociedade Brasileira de Diabetes. Diretrizes Sociedade Brasileira de Diabetes 2019-2020 [Internet]. São Paulo: Clannad; 2019. p 97-129, 179-188, 206-219 and 318-337. (Accessed February 4, 2021, https://www.diabetes.org.br/profissionais/images/DIRETRIZES-COMPLETA-2019-2020.pdf)

13. Enander R, Gundevall C, Strömgren A, Chaplin J, Hanas R. Carbohydrate counting with a bolus calculator improves post-prandial blood glucose levels in children and adolescents with type 1 diabetes using insulin pumps. Pediatr Diabetes. 2012 Nov;13(7):545-51. doi: 10.1111/j.1399-5448.2012.00883.x.

14. Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, et al. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care. 2012 May;35(5):984-90. doi: 10.2337/dc11-2044.

15. Gilbertson HR, Brand-Miller JC, Thorburn AW, Evans S, Chondros P, Werther GA. The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes. Diabetes Care. 2001 Jul;24(7):1137-43. doi: 10.2337/diacare.24.7.1137.

16. Kalergis M, Pacaud D, Strychar I, Meltzer S, Jones PJ, Yale JF. Optimizing insulin delivery: assessment of three strategies in intensive diabetes management. Diabetes Obes Metab. 2000 Oct;2(5):299-305. doi: 10.1046/j.1463-1326.2000.00107.x.

17. Trento M, Trinetta A, Kucich C, Grassi G, Passera P, Gennari S, et al. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes managed by Group Care. J Endocrinol Invest. 2011 Feb;34(2):101-5. doi: 10.1007/BF03347038.

18. Dafne Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ. 2002 Oct 5;325(7367):746. doi: 10.1136/bmj.325.7367.746.

19. Scavone G, Manto A, Pitocco D, Gagliardi L, Caputo S, Mancini L, et al. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in Type 1 diabetic subjects: a pilot study. Diabet Med. 2010 Apr;27(4):477-9. doi: 10.1111/j.1464-5491.2010.02963.x.

20. Gökşen D, Atik Altınok Y, Ozen S, Demir G, Darcan S. Effects of carbohydrate counting method on metabolic control in children with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol. 2014;6(2):74-8. doi: 10.4274/Jcrpe.1191.

21. Fortins RF, Lacerda EMA, Silverio RNC, do Carmo CN, Ferreira AA, Felizardo C, et al. Predictor factors of glycemic control in children and adolescents with type 1 diabetes mellitus treated at a referral service in Rio de Janeiro, Brazil. Diabetes Res Clin Pract. 2019 Aug;154:138-45. doi: 10.1016/j.diabres.2019.05.027.

22. de Albuquerque IZ, Stringhini MLF, Marques RMB, Mundim CA, Rodrigues MLD, Campos MRH. Contagem de carboidratos, estado nutricional e perfil metabólico em adolescentes com diabetes *mellitus* tipo 1. Scientia Medica. 2014;24(4):343-52. Brazilian. doi:10.15448/1980-6108.2014.4.18381

23. Laurenzi A, Bolla AM, Panigoni G, Doria V, Uccellatore A, Peretti E, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). Diabetes Care. 2011 Apr;34(4):823-7.doi: 10.2337/dc10-1490.

24. Elise R, Lisa GC, Charles S, Elysabeth BS, Frédérique G, Antoine T, et al. Variation of carbohydrate intake in diabetic children on carbohydrate counting. Diabetes Res Clin Pract. 2019 Apr;150:227-35. doi: 10.1016/j.diabres.2019.03.010.

25. Rodrigues TC, Veyna AM, Haarhues MD, Kinney GL, Rewers M, Snell-Bergeon JK. Obesity and coronary artery calcium in diabetes: the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. Diabetes Technol Ther. 2011 Oct;13(10):991-6. 10.1089/dia.2011.0046

26. Donzeau A, Bonnemaison E, Vautier V, Menut V, Houdon L, Bendelac N, et al. Effects of advanced carbohydrate counting on glucose control and quality of life in children with type 1 diabetes. Pediatr Diabetes. 2020 Nov;21(7):1240-1248. doi: 10.1111/pedi.13076.

27. Sociedade Brasileira de Diabetes. Manual de Contagem de Carboidratos para Pessoas com Diabetes [Internet]. São Paulo; 2016. (Accessed February 4, 2021, at https://www.diabetes.org.br/publico/images/manual-de-contagem-de-carboidrato2016.pdf).

28. Schmidt S, Nørgaard K. Bolus calculators. J Diabetes Sci Technol. 2014 Sep;8(5):1035-41. doi: 10.1177/1932296814532906.

29. Tascini G, Berioli MG, Cerquiglini L, Santi E, Mancini G, Rogari F, et al. Carbohydrate Counting in Children and Adolescents with Type 1 Diabetes. Nutrients. 2018 Jan 22;10(1). doi: 10.3390/nu10010109.

30. Sociedade Brasileira de Diabetes. Posicionamento Oficial SBD nº 01/2020. Conduta Terapêutica no Diabetes Tipo 1: Algoritmo SBD 2020 [Internet]. 2020. (Accessed February 4, 2021,https://www.diabetes.org.br/publico/images/Posicionamento_Oficial_Sbd_N012020v6_brLC.PDF?fbclid=IwAR0SsEnS6znmOt7bb5UvjSdSZkc9EFSVMPXUV8vRIjKFI5kkxi4cB-m3XcU).

31. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and

adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:115-35. doi: 10.1111/pedi.12718.

32. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502. Pubmed PMID: 4337382

33. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter., Suppl. 2013; 3: 19-62. doi:10.1038/kisup.2012.64

34. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995; 854:1-452. PMID: 8594834.

35. Lipschitz DA. Screening for Nutritional Status in the Elderly. Prim Care. 1994 Mar; 21(1):55 - 67. PMID:8197257

36. Atalah E, Castillo C, Castro R, Aldea A. Proposal of a new standard for the nutritional assessment of pregnant women. Rev Med Chil. 1997 Dec;125(12):1429-36. PMID: 9609018.

37. WHO Anthro for personal computers, version 3.2.2, 2011: Software for assessing growth and development of the world's children. Geneva: WHO, 2010 (Accessed July 17, 2021, at http://www.who.int/childgrowth/software/en/).

38. WHO AnthroPlus for personal computers Manual: Software for assessing growth of the world's children and adolescents. Geneva: WHO, 2009. (Accessed July 17, 2021, at http://www.who.int/growthref/tools/en/).

39. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S73-S84. doi: 10.2337/dc21-S006.

40. American Diabetes Association. Children and Adolescents: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S180-S99. doi: 10.2337/dc21-S013.

41. American Diabetes Association. Older Adults: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1: S168-S79. doi: 10.2337/dc21-S012.

42. American Diabetes Association. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44 Suppl 1:S200-S10. doi: 10.2337/dc21-S014.

43. Sterner Isaksson S, Bensow Bacos M, Eliasson B, Thors Adolfsson E, Rawshani A, Lindblad U, et al. Effects of nutrition education using a food-based approach, carbohydrate counting or routine care in type 1 diabetes: 12 months prospective randomized trial. BMJ Open Diabetes Res Care. 2021 Mar;9(1). doi: 10.1136/bmjdrc-2020-001971.

44. Fu S, Li L, Deng S, Zan L, Liu Z. Effectiveness of advanced carbohydrate counting in type 1 diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2016 Nov 14;6:37067. doi: 10.1038/srep37067.

45. Davison KA, Negrato CA, Cobas R, Matheus A, Tannus L, Palma CS, et al. Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. Nutr J. 2014 Mar;13:19. doi: 10.1186/1475-2891-13-19.

46. Gloaguen E, Bendelac N, Nicolino M, Julier C, Mathieu F. A systematic review of non-genetic predictors and genetic factors of glycated haemoglobin in type 1 diabetes one year after diagnosis. Diabetes Metab Res Rev. 2018 Nov;34(8):e3051. doi: 10.1002/dmrr.3051.

47. Campbell MS, Schatz DA, Chen V, Wong JC, Steck A, Tamborlane WV, et al. A contrast between children and adolescents with excellent and poor control: the T1D Exchange clinic registry experience. Pediatr Diabetes. 2014 Mar;15(2):110-7. doi: 10.1111/pedi.12067.

48. Taler I, Phillip M, Lebenthal Y, de Vries L, Shamir R, Shalitin S. Growth and metabolic control in patients with type 1 diabetes and celiac disease: a longitudinal observational case-control study. Pediatr Diabetes. 2012 Dec;13(8):597-606. doi: 10.1111/j.1399-5448.2012.00878.x.

49. Creanza A, Lupoli R, Lembo E, Tecce N, Della Pepa G, Lombardi G, et al. Glycemic control and microvascular complications in adults with type 1 diabetes and long-lasting treated celiac disease: A case-control study. Diabetes Res Clin Pract. 2018 Sep;143:282-7. doi: 10.1016/j.diabres.2018.07.031.

50. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86. doi: 10.1056/NEJM199309303291401.

51. Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr MetabCardiovasc Dis. 2013 Jul;23(7):591-8. doi: 10.1016/j.numecd.2013.03.007.

Figures

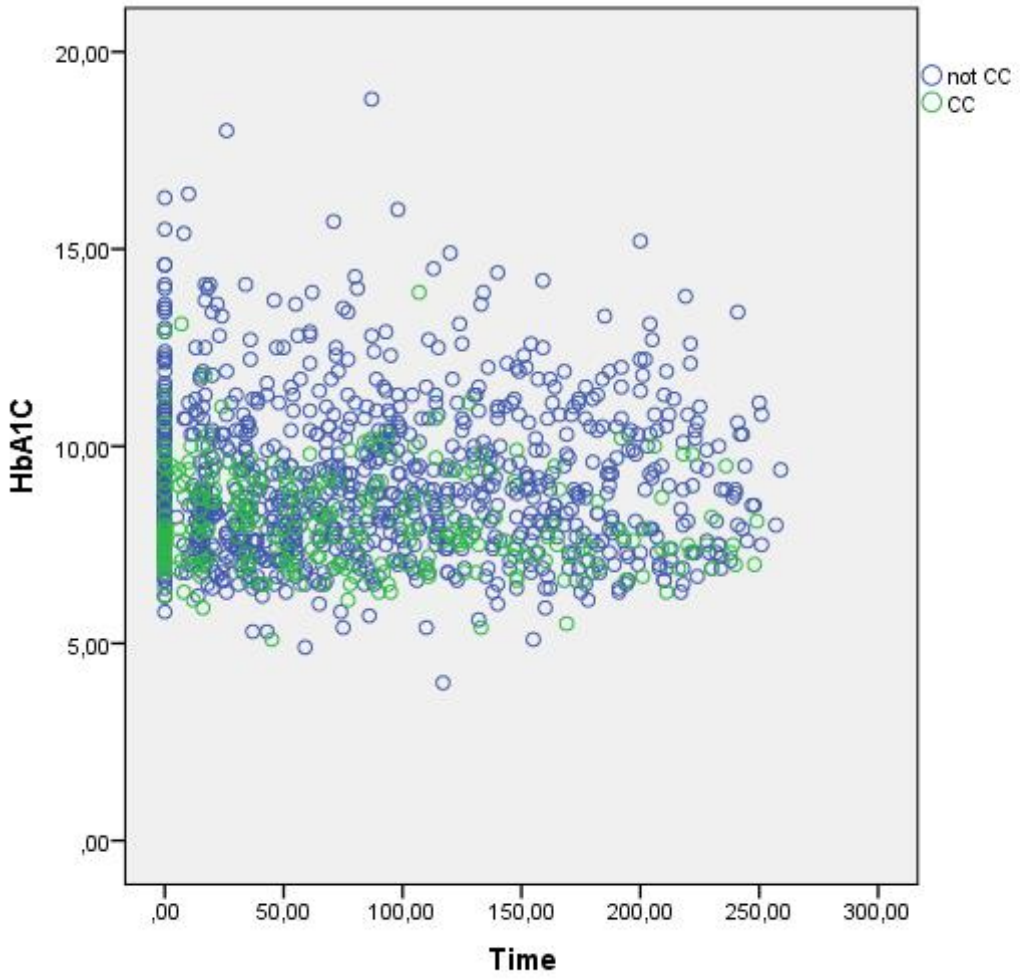


Figure 1: HbA1c in both groups during the follow-up period. Values collected at each nutritional consultation analyzed between 2014 and 2018. Time = weeks from baseline. HbA1c: Glycated Hemoglobin.

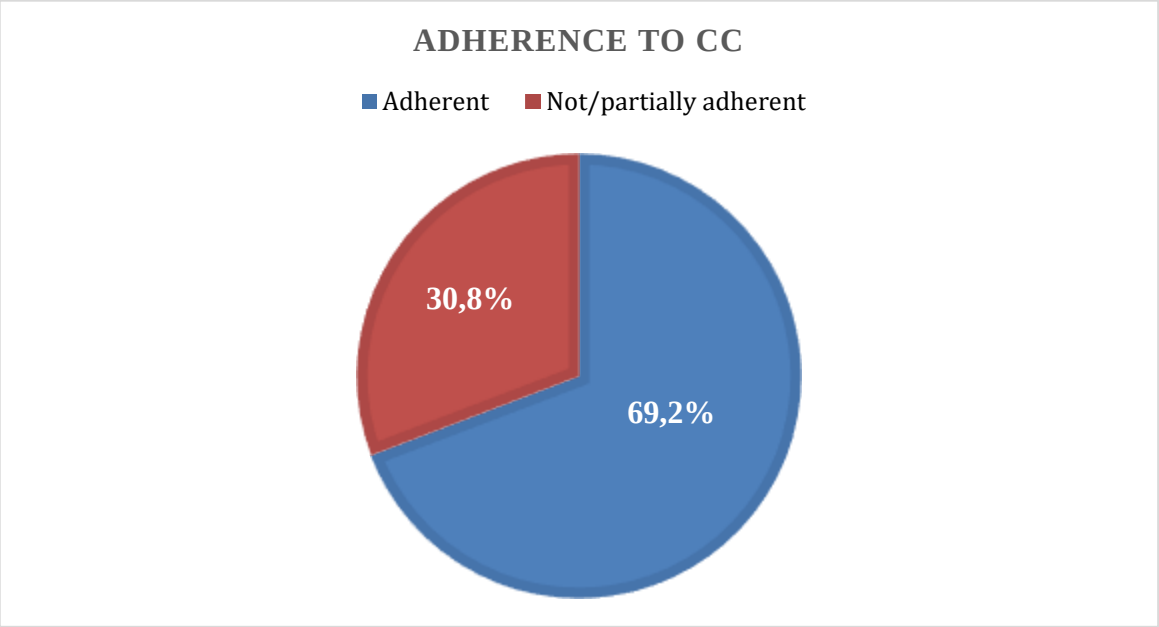


Figure 2: Adherence to CC. Frequency (%) of consultations (among those in which CC was performed) in which patients were classified as compliant or not/partially compliant. CC: Carbohydrate Counting.

Tables

Table 1. Sociodemographic and clinical characteristics, number of pregnant women and number of consultations in the study population (single-measure variables).

Variable	**CC (n = 49)**	**Not CC (n = 180)**	**p-value**
Age, years §	32.91 ± 11.31	30.7 ± 16.26	0.275
Nutritional follow-up time, months §	97 (5.5 – 129.5)	43.5 (0 -126.75)	0.045
Diabetes duration, months §	195 (112 – 265)	147 (33.5 – 266.55)	0.1
Age at DM diagnosis, years	16 (10.5 – 24.5)	14 (8.25 – 25)	0.588
Males (n, %)	20 (40.8)	84 (46.7)	0.570
Ethnicity (n, % white)	49 (100)	161 (89.4)	0.045
Maximum education (n, %)			0.001
Ignored/≤ complete elementary	15 (30.7)	86 (47.8)	
High school	15(30.6)	68 (37.7)	
≥ Incomplete higher education	19 (38.7)	26 (14.5)	
Pregnant women (n, %)$^{+}$	5 (10.2)	1 (0.55)	0.003
Number of consultations$^{\#}$	10 (6 - 14)	5 (3 - 9)	0.000
DKD (n, %)*	1 (2)	14 (7.8)	0.202
GFR < 60 (ml/min/1.73 m²) (n, %)*	1 (2)	15 (8.3)	0.204
Positive albuminuria (n, %)*	38 (77.6)	127 (70.6)	0.431
Neuropathy (n, %) *	2 (4.1)	15 (8.3)	0.538
Retinopathy (n, %) *	23 (46.9)	60 (33.3)	0.112
Cardiovascular events (n, %)*	1 (2)	1 (0.6)	0.383

Ocular diseases (n, %)*	1 (2)	15 (8.3)	0.204
Autoimmune diseases (n, %)*	10 (20.4)	34 (18.9)	0.972
Psychiatric disorders (n, %)*	10 (20.4)	41 (22.8)	0.873
Thyroid diseases (n, %)*	13 (26.5)	38 (21.1)	0.539
Hypertension (n, %)*	8 (16.3)	42 (23.3)	0.391

CC: carbohydrate counting; DKD: diabetic kidney disease; DM: diabetes mellitus; GFR: glomerular filtration rate; SD: standard deviation

Data are presented as mean ± SD, median (interquartile range P25 – P75) or number and percentage of cases (n, %).

§ Referring to baseline (first consultation included during the period 2014 - 2018).

+ Number along follow-up consultations.

All consultations between 2014-2018 were considered in the CC group, including those in which patients used fixed doses of insulin.

* Occurring prior to or during the follow-up period.

Table 2. Clinical, laboratory and anthropometric characteristics of the study population (repeated-measures variables)

Variable	CC (n = 49)	Not CC (n = 180)	p-value §	p for interaction ¶
Fasting glucose (mg/dl)*	203.42 ± 11.23 (182.53-226.7)	207.87 ± 5.93 (196.55-219.84)	0.918	0.741
Total cholesterol (mg/dl) *	178.81 ± 7.17 (165.24-193.5)	186.42 ± 3.96 (178.78-194.39)	0.522	0.761
cHDL (mg/dl) *	58.11 ± 2.87 (52.72-64.05)	58.98 ± 1.57 (55.97-62.15)	0.61	0.606
cLDL (mg/dl) *	102.72 ± 5.57 (92.31-114.31)	106.39 ± 3.11 (100.42-112.71)	0.458	0.684
Triglycerides (mg/dl) *	88.44 ± 8.9 (72.53-107.83)	97.31 ± 5.3 (87.41-108.33)	0.91	0.106
GFR (ml/min/1.73m²) *	102.4 ± 4.57 (93.79-111.81)	99.03 ± 2.25 (94.71-103.56)	0.654	0.615
SMBG**			0.005	0.127
Yes	92.2 ± 2.4 (86-95.7)	84.4 ± 1.8 (80.6-87.6)		
Insulin dose* (UI/kg)	0.66 ± 0.03 (0.6-0.73)	0.71 ± 0.02 (0.67-0.75)	0.199	0.607

Basal insulin **			0.055	0.129
Long-acting analogs	60.7 ± 6.8 (46.9-73)	42.4 ± 3.6 (35.6-49.5)		
Bolus insulin **			0.000	0.163
Rapid-acting analogs	100 ± 0 (82.1-100)	77.9 ± 3.1 (71.3-83.4)		
Nutritional status**			0.813	0.653
Excess body weight	40 ± 6.5 (28.4-53.5)	43 ± 3.5 (36.4-50)		

CC: carbohydrate counting; cHDL: high density lipoprotein cholesterol; cLDL: low density lipoprotein cholesterol; GFR: Glomerular filtration rate; SE: Standard error; SMBG: Self-monitoring of capillary blood glucose; UI: Unit of insulin

* Continuous variables presented as mean ± SE and 95% CI

** Dichotomous variables presented as estimated proportion (%) ± SE and 95% CI.

§ p-value of the effect of the variable

¶ p of interaction between the effect of the variable and time

All analyses were adjusted for the nutritional follow-up time that the patients already had at baseline, as well as for the time elapsed between each consultation during the study period (2014-2018) and baseline.

Table 3. Association between CC and glycemic control

HbA1c (%)*	**CC (n=49)**	**Not CC (n=180)**	**p-value §**	**p for interaction ¶**
Model 0	8.2 ± 0.21	9.13 ± 0.12	0.000	0.735
	(7.8 to 8.63)	(8.89 to 9.38)		
Model 1	8.66 ± 0.4	9.36 ± 0.39	0.016	0.841
	(7.9 to 9.5)	(8.62 to 10.16)		
Model 2	8.26 ± 0.58	8.82 ± 0.55	0.107	0.999
	(7.19 to 9.49)	(7.8 to 9.98)		

HbA1c = glycated hemoglobin; CC = carbohydrate counting; SE: Standard error

* HbA1c measured at each nutritional consultation during follow-up (2014-2018); presented as mean ± SE and 95% CI.

Model 0: adjustment for the nutritional follow-up time that the patients already had at baseline and for the time elapsed between each consultation during the study period (2014-2018) and baseline.

Model 1: model 0 + adjustment for ethnicity (white, black, mixed race), education (ignored, none, elementary/high school/ higher education or graduate school - complete or incomplete), total number of consultations between 2014 and 2018, BMI, SMBG (dichotomous), bolus insulin (short-acting or rapid-acting analogs) and physical activity (sufficiently or insufficiently active).

Model 2: model 1 + adjustment for pregnancy (dichotomous), only consultations with adult and adolescent women were included in this model.

§ p-value of the effect of the variable

¶ p of interaction between the effect of the variable and time

Table 4. Comparison of weight variation between appointments - CC vs. fixed insulin doses

Weight variation (kg)*	**CC (n = 49)**	**Not CC (n = 180)**	**p-value §**	**p for interaction ¶**
Model 0	0.23 ± 0.13 (-0.033 to 0.492)	0.43 ± 0.07 (0.28 to 0.58)	0.045	0.14
Model 1	0.27 ± 0.29 (-0.3 to 0.85)	0.52 ± 0.25 (0.02 to 1.02)	0.027	0.082
Model 2	0.2 ± 0.29 (-0.378 to 0.79)	0.516 ± 0.25 (0.004 to 1.02)	0.023	0.11
Model 3	0.13 ± 0.28 (-0.42 to 0.69)	0.53 ± 0.24 (0.04 to 1.02)	0.024	0.226

CC = carbohydrate counting; SE = standard error

* Variable measured at each nutritional consultation between 2014 and 2018 and presented as mean ± SE and 95% CI.

Model 0: adjustment for the nutritional follow-up time that the patients already had at baseline and for the time elapsed between each consultation during the study period (2014-2018) and baseline.

Model 1: model 0 + adjustment for ethnicity (white, black, mixed race), education (ignored, none, elementary/high school/ higher education or graduate school - complete or incomplete), number of consultations between 2014 and 2018, BMI, SMBG (dichotomous) and insulin bolus (short-acting or rapid-acting analogs).

Model 2: model 1 + adjustment for physical activity (sufficiently or insufficiently active).

Model 3: model 2 + adjustment for age and sex.

§ p-value of the effect of the variable

¶ p of interaction between the effect of the variable and time

SUPPORTING INFORMATION

Supplementary Table 1. Association between good glycemic control (adequate target of HbA1c) and possible predictors - multivariable model.**

Variable	**Reference category**	**OR (95% CI) §**	**p-value §**	**OR (95% CI) ¶**	**p for interactio ¶**
Retinopathy (no)	Yes			T1: 11.61 (1.09-122.63) T3: 7.32 (1.85-28.84)	0.01
Fasting glucose (mg/dl)	NA			T1: 0.99 (0.98– 0.99) T3: 0.99 (0.98-0.99) T4: 0.99 (0.99-0.99) T10: 1.006 (1.0003-1.01)	0.002
Autoimmune diseases (no)	Yes	4.09 (1.4– 11.93)	0.01		
Total insulin dose (UI/kg)	NA	0.24 (0.08-0.7)	0.009		

Nutritional status (underweight/ eutrophic)	Excess weight	0.65 (0.42-1.01)	0.059

HbA1c: glycated hemoglobin; NA: not applicable; OR: odds ratio; UI: units of insulin

T1, T3, T4 and T10: follow-up points in which there was a significant interaction between time and the predictor variable.

**Analyses adjusted for the nutritional follow-up time that the patients already had at baseline, follow-up time, retinopathy, autoimmune diseases, fasting glucose, total insulin dose and nutritional status.

For continuous variables, the odds ratio of attaining the HbA1c target refers to a 1-unit increase of the variable.

§ OR (95% CI) and p-value of possible predictor variables of good glycemic control (attaining the HbA1c target) referring to the main effect of the variables, not the interaction between the variable and time.

¶ OR (95% CI) and p of interaction between the variable and time for possible predictors of good glycemic control (attaining the HbA1c target).

Supplementary Table 2. Association between CC adherence and possible predictor variables - multivariate model **

Variable	**Reference category**	**OR (95% CI) §**	**p-value §**	**OR (95% CI)¶**	**p for interaction¶**
HbA1c (%)	NA	0.66 (0.44-0.93)	0.018		
BMI (kg/m²)	NA			T4: 1.8 (1.08-2.98)	0.037
Number of absences during follow-up	NA			T3: 0.04 (0.006-0.28)	0.006

CC: carbohydrate counting OR: odds ratio NA: not applicable BMI: Body mass index HbA1c: glycated hemoglobin

T3 and T4: follow-up points at which there was a significant interaction between time and the variable

**Analyses adjusted for the nutritional follow-up time that the patients already had at baseline, follow-up time, HbA1c, BMI and number of absences during follow-up.

For continuous variables, the OR for CC adherence refers to a 1-unit increase of the variable.

§ OR (95% CI) and p-value of variables possibly associated with CC adherence; referring to the main effect of the variables, not the interaction between variable and time.

¶ OR (95% CI) and p of interaction between the variable and time for variables possibly associated with CC adherence.