UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA
ÁREA DE CONCENTRAÇÃO: NUTRIÇÃO E METABOLISMO
MESTRADO E DOUTORADO

Padrões alimentares e desfechos de saúde em pacientes com Diabetes tipo 2: avaliação a partir de um questionário de frequência alimentar

Roberta Aguiar Sarmento

Orientadora:
Profª Drª Jussara Carnevale de Almeida

Porto Alegre, dezembro de 2016.

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Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia como requisito parcial para a obtenção do título de doutora

Porto Alegre, dezembro de 2016.

“Have courage and be kind.”

Do filme CINDERELLA. Walt Disney Pictures, 2015.

Dedico este trabalho aos meus pais, Angela
e Roberto, por me tornarem a pessoa que
sou hoje.

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FORMATO DA TESE

Esta tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul, sendo apresentada por uma breve revisão da literatura e dois manuscritos referentes ao tema estudado:

CAPÍTULO I. Referencial teórico, parcialmente publicado em formato de capítulo de livro [*in press;* Editora Rubio]

CAPÍTULO II. Artigo original a ser submetido para publicação no periódico *Public Health Nutrition*, redigido conforme as normas do periódico

CAPÍTULO III. Artigo original a ser submetido para publicação no periódico *Diabetes Care*, redigido conforme as normas do periódico

CAPÍTULO IV. Considerações finais

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LISTA DE ABREVIATURAS E SIGLAS

A1c – hemoglobina glicada

ADA – *American Diabetes Association*

AGS – ácidos graxos saturados

AGMI – ácidos graxos monoinsaturados

AGPI – ácidos graxos poli-insaturados

BMI – *body mass index*

CI – *confidence interval*

DASH – *Dietary Approaches to Stop Hypertension*

ECR – ensaio(s) clínico(s) randomizado(s)

FFQ – *food frequency questionnaire*

GI – *glycemic index*

GL – *glycemic load*

HbA1C – hemoglobina glicada

HDL – *high density lipoprotein*

IMC – índice de massa corporal

IC – intervalo de confiança

LDL – *low density lipoprotein*

OR – *odds ratio*

PAS – pressão arterial sistólica

PAD – pressão arterial diastólica

PR – *prevalence ratio*

QFA – questionário de frequência alimentar

RRR – regressão por redução de posto

r – coeficiente de correlação

RDA – *Recommended Dietary Allowance*

SBD – Sociedade Brasileira de Diabetes

SD – *standard deviation*

TACO – Tabela de Composição dos Alimentos

T2DM – type 2 diabetes mellitus

UAE – urinary albumin excretion

VCT – valor calórico total

WDR – *weighed diet record*

CAPÍTULO I

REFERENCIAL TEÓRICO

DIABETES

O diabetes é uma doença crônica que acomete parte significativa da população mundial - cerca de 415 milhões de pessoas - e estima-se que para o ano de 2040 ocorra um aumento para 642 milhões de pessoas com a doença[1]. No Brasil, a prevalência de diabetes no ano de 2015 foi de 14,3 milhões de pessoas, correspondendo a 8,1% da população nacional[1]. O diabetes constitui um importante problema de saúde pública em razão da elevada prevalência e morbi-mortalidade[2,3], além dos custos envolvidos no seu tratamento[1].

O diabetes tipo 2 é a forma mais comum da doença e ocorre geralmente na vida adulta, estando associado ao excesso de peso. A hiperglicemia sustentada, resultado da resistência à ação da insulina e da incapacidade pancreática em suplantar essa resistência, associada a fatores genéticos e ambientais é uma das principais responsáveis pelo desenvolvimento das complicações crônicas microvasculares, neuropáticas e macrovasculares[1,4].

A redução das complicações crônicas do diabetes é usada como alvo terapêutico no tratamento da doença e as incidências de retinopatia, nefropatia e neuropatia estão diretamente associadas com o grau de hiperglicemia[4]. Modificações no estilo de vida a partir de um plano alimentar saudável e individualizado com a prática regular de exercícios físicos associadas ao tratamento farmacológico são recomendadas para o manejo rigoroso da hiperglicemia[4], embora este controle intensivo possa aumentar em duas vezes o risco de episódios graves de hipoglicemia[5]. Assim, a melhor estratégia farmacológica para reduzir a glicemia em pacientes com diabetes tipo 2 tem sido constantemente avaliada[6] e muitos pacientes não conseguem atingir os alvos terapêuticos estabelecidos[7] reforçando a importância de aspectos relacionados ao estilo de vida, em especial o manejo da dieta, no controle do diabetes.

Tratamento dietoterápico

A proporção de macronutrientes que deve ser respeitada em um plano alimentar vem sendo constantemente modificada. Inicialmente, pensava-se que os carboidratos, deveriam ser abolidos da dieta do paciente com diabetes, e o plano alimentar era composto basicamente de proteínas e lipídeos[8]. Mas, com o passar dos anos, essa proporção de macronutrientes veio se aproximando cada vez mais da dieta de indivíduos sem diabetes – população geral[8]. O que os estudos mais recentes mostram é que não existe uma proporção ideal para o consumo de calorias a partir de carboidratos, proteínas e lipídeos em pacientes com diabetes[4]. As recomendações dietoterápicas mais atuais estão descritas no **quadro 1**.

Os carboidratos são os nutrientes que mais afetam a glicemia. De uma maneira geral, todo o carboidrato ingerido é convertido em glicose dentro de 15 minutos a duas horas após a ingestão. A recomendação da Sociedade Brasileira de Diabetes (SBD) é de que os carboidratos correspondam a 45-60% do valor calórico total da dieta ou pelo menos 130 g/dia[9]. Esse valor foi baseado na quantidade mínima de glicose utilizada pelo cérebro e é a *Recommended Dietary Allowance* - RDA - para crianças e adultos[10]. Já a diretriz americana não traz uma recomendação específica sobre a quantidade de carboidratos, mas reforça que o consumo desse nutriente seja a partir de frutas, vegetais, grãos integrais, legumes e laticínios[4,11]. Dietas com baixo índice glicêmico e carga glicêmica devem ser consideradas na elaboração do plano alimentar do paciente com diabetes[4,9,11] por melhorarem a hemoglobina glicada dos pacientes[12]. A sacarose pode estar presente no plano alimentar, desde que não ultrapasse 10% do valor calórico total[9]. Na prática clínica, costuma-se restringir o consumo de sacarose para não estimular o consumo de alimentos ricos em açúcares e doces. Ainda, o uso racional é orientado somente em pacientes que utilizam a terapia nutricional de contagem de carboidratos.

O consumo de fibras deve ser de 30 a 50 g/dia ou 14 g/1000 kcal (recomendação mínima), segundo a SBD[9]. A ingestão de fibras solúveis tem sido associada a picos glicêmicos pós-prandiais menores e o consumo de dietas ricas em fibras tem mostrado benefício na redução da glicemia de jejum e da hemoglobina glicada[13]. Entretanto, não é recomendada a suplementação com módulos de fibras, desde que seja estimulado o seu consumo a partir de cereais integrais, hortaliças, leguminosas e frutas[4,9,11].

A recomendação para o consumo de lipídeos em pacientes com diabetes ainda é inconclusiva, devendo ser individualizada. A SBD recomenda que os ácidos graxos saturados (ASG) não ultrapassem 7% do valor calórico total da dieta. No caso dos ácidos graxos monoinsaturados (AGMI), a ingestão recomendada é de 5 a 10% do valor calórico total, pois promove melhor controle glicêmico e redução no risco cardiovascular[9]. O consumo dos AGMI é especialmente elevado na dieta Mediterrânea (rica em óleo de oliva), padrão alimentar que será discutido a seguir. Em relação aos ácidos graxos poli-insaturados (AGPI), o consumo recomendado é de 10% do valor calórico total. Para atingir um consumo adequado de AGPI da série ômega-3, incentiva-se o consumo de duas ou mais porções de peixe por semana[9]. O efeito benéfico da suplementação de ômega-3 não é sustentado pelas publicações científicas atuais[4,9,11], não sendo recomendando por nenhuma organização. Já em relação ao consumo de colesterol, o limite máximo preconizado é de 300 mg/dia e de ácidos graxos

trans-insaturados, 1% do VCT - tanto pela SBD[9] quanto pela *American Diabetes Association* (ADA)[4,11].

A SBD sugere que a adoção de limites mais rígidos para o consumo de gorduras têm o intuito de reduzir colesterol total e LDL-colesterol, e consequentemente, prevenir a incidência de DCV nessa população[9,14]. Entretanto, recente metanálise não demonstrou benefício sobre o consumo elevado de AGPI ômega-3 e da série ômega-6 bem como no consumo reduzido de ácidos graxos saturados na redução de desfechos coronários na população em geral[15].

Com relação ao aporte proteico da dieta, em pacientes com função renal normal, a SBD recomenda um consumo de 0,8 a 1 g/kg ou 15-20% do valor calórico total[9]. A ingestão de proteínas tem sido associada a um aumento na resposta insulínica sem aumento na glicemia pós-prandial e consequentemente, melhor controle glicêmico[16].

O consumo de sódio não deve ultrapassar 2.000 mg/dia[9] ou 2.300 mg/dia[4,11], dependendo da diretriz consultada. Alguns estudos têm mostrado que deficiências de cromo, magnésio e vitamina D podem agravar a intolerância à glicose e a resistência à insulina[9]. Entretanto, a suplementação de vitaminas e minerais não está indicada para pessoas sem deficiências específicas. Além disso, a suplementação de antioxidantes com o intuito de reduzir o risco de doenças cardiovasculares também não está indicada[4,9,11], já que não possui estudos suficientes acerca deste tema[17].

O papel dos nutrientes no controle metabólico, bem como no desenvolvimento de complicações crônicas do diabetes ainda não está completamente esclarecido. Nesse contexto, a avaliação da ingestão alimentar a partir de padrões alimentares parece representar o método mais adequado para avaliar essa relação, já que os indivíduos ingerem refeições, e não nutrientes ou alimentos isoladamente, havendo possibilidade de interação entre os diferentes componentes da alimentação[18].

Padrões alimentares

Padrões alimentares são definidos como um conjunto ou grupos de alimentos consumidos por uma determinada população[19]. A identificação de padrões alimentares pode ser feita *a priori* ou *a posteriori*. Na definição de padrões alimentares *a priori*, são propostos índices que permitem avaliar a qualidade da dieta com base em critérios conceituais de nutrição saudável, de diretrizes e recomendações nutricionais[19]. Diferentes índices dietéticos têm sido elaborados e/ou adaptados de acordo com as recomendações nutricionais de populações específicas e seus guias alimentares[20]. Já na definição de padrões alimentares *a*

posteriori, parte-se de dados empíricos de alimentos que são agregados com base em análise estatística, com posterior avaliação, ou seja, identificação de um ou mais padrões alimentares[19]. A seguir, serão discutidos os principais padrões alimentares *a priori* e seus efeitos nos desfechos de saúde e doença nestes pacientes.

Dieta Mediterrânea

Um padrão alimentar de estilo mediterrâneo, com base nos estudos revisados, é composto por um maior consumo de legumes, cereais integrais, frutas, legumes, oleaginosas, peixes e consequentemente, de AGMI e AGPI. Por outro lado, observa-se um consumo reduzido de carne vermelha e AGS em comparação com uma dieta tradicional. A dieta Mediterrânea também caracteriza-se pelo consumo moderado de vinho[21].

Um estudo transversal[22] e um estudo caso-controle[23] examinaram a associação entre a adesão a um padrão alimentar de estilo Mediterrâneo e controle metabólico em pacientes com diabetes. Não houve diferenças significativas entre os tercis de aderência a este padrão para hemoglobina glicada[22,23], colesterol total[22,23], ou LDL-colesterol[22]. Já o HDL-colesterol foi significativamente maior e os valores de triglicerídeos foram significativamente menores no maior tercil de aderência ao padrão alimentar estilo Mediterrâneo[22]. Ainda, o maior tercil de adesão ao padrão Mediterrâneo também foi associado com uma redução de 56% no risco de doença arterial periférica[23].

Em uma revisão sistemática de cinco ECR realizados em indivíduos com diabetes tipo 2[24], a melhora no controle glicêmico e na sensibilidade a ação da insulina foi maior nos participantes que seguiram a dieta Mediterrânea do que aqueles que seguiram as dietas controle, embora a magnitude dos resultados tenha que ser interpretada com cautela porque a restrição de calorias também foi incluída em dois[25,26] dos cinco estudos avaliados. A dieta Mediterrânea com reduzido teor de carboidratos reduziu a necessidade de medicamentos antidiabéticos em indivíduos com excesso de peso e diabetes recém-diagnosticada em comparação com aqueles que seguiram uma dieta com baixo teor de gordura[26] e, após quatro anos de seguimento, demonstrou também uma maior redução na hemoglobina glicada destes pacientes[27]. Em um estudo com 322 participantes moderadamente obesos com diabetes[25], a dieta Mediterrânea com restrição calórica resultou em concentrações menores de glicose plasmática em jejum e insulina ao final de dois anos de seguimento do que a dieta hipolipídica.

Em um subgrupo de participantes com diabetes do estudo PREDIMED (n = 3.614), a dieta Mediterrânea suplementada com azeite de oliva extra-virgem (~1 litro por semana) ou uma mistura de oleaginosas (15 g de nozes; 7,5 g de avelã e 7,5 g de amêndoas), sem restrição calórica, reduziu significativamente a incidência de eventos cardiovasculares após um seguimento médio de 4,8 anos, com *Hazard Ratio* de 0,71 (IC95% 0,53 – 0,96)[28].

Recentemente, duas metanálises foram publicadas e comprovaram o benefício da dieta Mediterrânea no controle glicêmico em pacientes com diabetes[29,30]. Esposito *et al* realizaram uma revisão sistemática com metanálise que incluiu três ECR com duração superior a seis meses e encontrou benefício da dieta Mediterrânea na redução na hemoglobina glicada (-0,47%; IC 95% -0,56 a -0,38) quando comparada a dieta controle ou pobre em gorduras[29]. Posteriormente, Huo *et al* publicaram uma metanálise que incluiu nove ECR (n = 1.178 indivíduos com diabetes tipo 2) com duração que variou de quatro semanas a quatro anos e encontrou evidências que sugerem que a dieta Mediterrânea melhora o controle glicêmico, o peso corporal e os fatores de risco cardiovascular. A redução média na hemoglobina glicada foi de -0,30% (IC 95% -0,46 a -0,14), na glicemia de jejum foi de -12,96 mg/dl (IC 95% -22,32 a -3,78) e no IMC foi de -0,29 kg/m^2 (IC 95% -0,46 a -0,12). Da mesma forma, foram demonstradas reduções nas concentrações de colesterol (-5,41 mg/dl; IC 95% -7,34 a -3,48) e triglicerídeos (-25,68 mg/dl; IC 95% -41,62 a -8,85), e aumento nos valores de HDL-colesterol (2,32 mg/dl; IC 95% 0,77 a 3,86) nesta população. Além disso, a dieta Mediterrânea foi associada com declínio na pressão arterial sistólica e diastólica (cerca de -1,41 a 1,45 mmHg, respectivamente)[30].

De acordo com a literatura atual, podemos concluir que a dieta Mediterrânea, independentemente da restrição calórica, promove melhora no controle glicêmico e reduz os fatores de risco para doenças cardiovasculares em comparação com uma dieta convencional para o controle do diabetes[31].

Dietary Approaches to Stop Hypertension - DASH

A dieta DASH foi desenvolvida inicialmente para reduzir a pressão arterial em pessoas sem diabetes ou em pacientes com diabetes, mas com bom controle glicêmico[32,33]. Essa dieta possui um conteúdo elevado de potássio, magnésio, cálcio e fibras e um baixo aporte de gorduras totais, AGS, colesterol e sódio. Em termos de grupos alimentares, é uma dieta que preconiza o consumo de vegetais, frutas, produtos lácteos desnatados, grãos integrais, aves, peixes, carnes magras e oleaginosas e é pobre em carne vermelha, doces, sobremesas e

bebidas açucaradas. Em um ECR cruzado com oito semanas de duração, a dieta DASH teve efeitos favoráveis no controle da glicemia, colesterol total, frações HDL- e LDL-colesterol, pressão arterial[34] e marcadores inflamatórios[35] em 31 pacientes com diabetes tipo 2, quando comparada a uma dieta controle.

ECR com quatro semanas de duração foi realizado em 40 pacientes hipertensos com diabetes tipo 2 em nosso meio. O grupo intervenção recebeu orientações para seguir um plano alimentar estilo DASH e para aumentar o número de passos ao dia (caminhada). O grupo controle recebeu uma dieta com base nas recomendações da ADA. A intervenção no estilo de vida (dieta DASH e caminhada) causou uma maior redução na pressão arterial sistólica e diastólica que o grupo de controle. Já a hemoglobina glicada reduziu de forma semelhante em ambos os grupos[36].

Estudo multicêntrico avaliou a relação entre a aderência a dieta DASH e fatores de risco cardiovascular em 2.130 jovens (idade entre 10 e 22 anos) com diabetes tipo 1 e tipo 2. Os autores observaram que, entre os jovens com diabetes tipo 1, a maior aderência à dieta DASH foi significativa e inversamente associada com a razão LDL/HDL (-0,07) e hemoglobina glicada (-0,2%). Entre os jovens com diabetes tipo 2, as associações foram observadas com colesterol total (-13,2 mg/dL) e IMC (-0,26 escore-Z)[37].

O papel de cada componente alimentar da dieta DASH na pressão arterial foi avaliado em 225 pacientes com diabetes tipo 2 em um estudo transversal. E, a partir de modelos de regressão logística multivariada, os autores observaram que a ingestão diária de frutas e vegetais foi associada a menor chance do paciente apresentar valores de pressão arterial média acima de 92 mmHg: OR de 0,781 (IC 95% 0,617 a 0,987) para frutas (80 g/1000 kcal) e OR de 0,781 (IC 95% 0,618 a 0,988) para vegetais (50 g/1000 kcal)[38].

Conforme observado, as evidências são limitadas em relação aos efeitos da dieta DASH sobre os desfechos de saúde em indivíduos com diabetes. Embora a maioria das evidências seja em indivíduos hipertensos e sabendo que há uma grande parcela de pacientes com hipertensão e diabetes, o seu efeito ainda precisa ser testado nos outros parâmetros além dos pressóricos. Somente três ECR demostraram melhora no controle metabólico[34,35] e no controle pressórico[36] desses pacientes em relação a uma dieta convencional.

Dieta Vegetariana

Segundo a Sociedade Vegetariana Brasileira[39], é considerado vegetariano todo aquele que exclui de sua alimentação todos os tipos de carne, aves e peixes e seus derivados,

podendo ou não utilizar laticínios ou ovos. O vegetarianismo inclui o veganismo, que é a prática de não utilizar produtos oriundos do reino animal para nenhum fim (alimentar, higiênico, de vestuário *etc.*). O indivíduo que segue a dieta vegetariana pode ser classificado de acordo com o consumo de subprodutos animais (ovos e laticínios): ovolactovegetariano, lactovegetariano, ovovegetariano ou vegetariano estrito[39].

O efeito da dieta vegetariana tem sido avaliado em pacientes com diabetes, entretanto, uma melhora no controle glicêmico ou nos fatores de risco cardiovascular não tem sido consistentemente reportada[16,31]. Dois ECR cruzados realizados em nosso meio com pacientes com diabetes tipo 2 micro[40] e macroalbuminúricos[41] não demonstraram benefício no consumo de um padrão alimentar lacto-vegetariano na melhora do controle glicêmico, na pressão arterial e nas frações HDL- e LDL-colesterol. No entanto, o colesterol total[40] e a excreção urinária de albumina[41] diminuíram significativamente em comparação com uma dieta habitual ou à base de frango.

Um ECR com 74 semanas de duração comparou um padrão alimentar vegetariano com baixo teor de gordura e uma dieta convencional e observou que ambas as dietas reduziram o peso (-4,4 kg e -3,0 kg, respectivamente; P = 0,25) e a hemoglobina glicada (-0,34 e -0,14, respectivamente; P = 0,43) sem diferença significativa entre os grupos[42]. Recentemente, uma metanálise que incluiu seis estudos com duração de quatro a 74 semanas, encontrou que o consumo de dietas vegetarianas foi associado com uma redução significativa na hemoglobina glicada (-0,39%; IC 95% -0,62 a -0,15; P = 0,001), porém, os próprios autores relacionam esse beneficio a uma menor ingestão calórica (-139,75 kcal/dia; IC 95% -232,77 a -46,73) e consequente perda de peso, embora a perda de peso não tenha sido mensurada neste estudo[43].

O efeito do padrão alimentar vegetariano no controle glicêmico e os fatores de risco para doença cardiovascular de pacientes com diabetes precisa ser melhor investigado em futuros ensaios clínicos. Nestes, o acompanhamento da regularidade do consumo calórico precisa ser uma variável de confusão a ser controlada.

Dieta Paleolítica

Na última década, também tem sido investigado os possíveis efeitos benéficos de outro padrão alimentar chamado de “dieta Paleolítica”, ou dieta “da idade da pedra” (*stone age*) ou “de caçadores e coletores” (*hunter - gatherer*). Este tipo de padrão alimentar consiste no consumo de alimentos originados de animais e plantas silvestres como, por exemplo, carnes magras, peixes, vegetais, frutas, raízes, ovos e nozes. A dieta exclui grãos (cereais e

leguminosas), laticínios, sal, açúcar refinado e óleos processados, os quais não eram disponíveis antes que os humanos começassem a cultivar plantas e domesticar animais[44]. Estima-se que a composição nutricional deste padrão alimentar tenha um elevado consumo de proteínas (34% do total de calorias), AGMI (18% do total de calorias) e AGPI (15% do total de calorias) e baixo consumo de carboidratos (45% do total de calorias)[45,46].

A dieta paleolítica parece ter benefício na redução dos fatores de risco para doença cardiovascular (IMC, circunferência da cintura, pressão arterial e LDL-colesterol), quando comparada a uma dieta controle, conforme observado em um ECR cruzado com 13 pacientes com diabetes tipo 2[47]. Outro benefício sugerido é que a dieta paleolítica parece promover uma maior saciedade devido a sua composição de macronutrientes e fibras[48].

Em 2015, foi realizada uma comparação entre os resultados de 14 participantes que consumiram uma dieta paleolítica com 10 participantes que consumiram uma dieta baseada nas recomendações da ADA. Ao final dos 14 dias de intervenção, ambos os grupos apresentaram melhora no peso corporal e hemoglobina glicada, mas o grupo que consumiu a dieta paleolítica obteve maiores benefícios sobre a glicemia de jejum (-23,4 ± 25,2 mg/dl), colesterol total (-26 ± 27 mg/dl) e LDL-colesterol (-15 ± 22 mg/dl)[49].

A dieta paleolítica é um padrão alimentar que vem sendo estudado mais recentemente, mas, até o momento, são poucos os estudos feitos em pacientes com diabetes. Além disso, o pequeno tamanho amostral dos estudos (13 – 24 participantes) e o curto tempo de seguimento (máximo três meses)[47-49] são limitações importantes e a adoção deste padrão alimentar na prática clínica ainda requer mais estudos com melhor delineamento.

Padrões alimentares definidos a posteriori

A associação entre padrões alimentares definidos *a posteriori* e desfechos de saúde em indivíduos com diabetes tem sido estudada mais recentemente. Desde 2010, 15 estudos já foram publicados acerca do tema em diversas partes do mundo. A maioria dos estudos é do tipo transversal[50-61] e a forma mais predominante para identificação dos padrões alimentares foi análise fatorial[50,52,55-59,62,63]. O tamanho amostral variou de 73[57] a 1.153[53] indivíduos tanto com diabetes tipo 1[53,54,58,61] como diabetes tipo 2[50,52,55-57,59,60,62,63]. Dentre os desfechos avaliados, podemos citar: controle glicêmico, valores pressóricos e perfil lipídico, variáveis antropométricas, função cognitiva, marcadores inflamatórios e de rigidez arterial, calibre vascular da retina, presença de doença renal crônica, retinopatia e eventos cardiovasculares,

bem como mortalidade por todas as causas. As principais características de cada estudo encontrado estão descritas no **quadro 2**.

JUSTIFICATIVA

Parece não haver um padrão alimentar ideal que irá beneficiar todas as pessoas com diabetes. Mas os estudos existentes mostram que existem padrões alimentares que estão associados a melhores desfechos globais de saúde e que são ricos em vegetais, frutas, cereais integrais, frutos do mar, legumes e nozes, contêm quantidades moderadas de produtos lácteos, e são pobres em carne vermelha e processada, açúcar e grãos refinados[64].

O conhecimento do padrão alimentar da população a ser assistida se faz importante para elaborar estratégias terapêuticas mais específicas a partir das evidências cientificas existentes[65]. Em epidemiologia nutricional, a avaliação do consumo alimentar a partir de inquéritos dietéticos de indivíduos ou grupos é fundamental para o estabelecimento de padrões alimentares e para determinar a relação de causalidade entre dieta e doenças[19]. No entanto, a complexidade da dieta humana representa um grande desafio para qualquer estudo que contemple sua relação com a doença[66].

Independente da finalidade, é necessário mensurar a ingestão dos alimentos a partir de instrumentos que combinem facilidade na aplicação ou na coleta da informação, validade e precisão[19]. Dentre os inquéritos dietéticos mais utilizados para a obtenção de dados sobre consumo alimentar em epidemiologia estão os inquéritos recordatórios, registros alimentares e o questionário de frequência alimentar (QFA)[19]. O princípio do QFA é estimar a dieta habitual praticada ao longo de semanas, meses ou anos, pois esse hábito é um fator de exposição mais importante do que a estimativa da dieta pontual. Essa premissa justifica a utilização de informações menos precisas, mas relacionadas ao consumo habitual, em detrimento da precisão de dados relativos à ingestão pontual de alimentos obtida a partir de recordatórios ou registros alimentares[19].

A lista de alimentos de um QFA deve refletir o hábito regional[66] e características da população como idade, etnia/origem, gênero, escolaridade e estado de saúde podem afetar o seu desempenho[67]. Portanto, a avaliação de sua validade e reprodutibilidade precisa ser testada na população de interesse antes de relacionarmos as informações da dieta obtidas no QFA com desfechos de saúde ou doença da população investigada[19]. Em 2012, nosso grupo construiu um QFA[68] que foi validado e sua reprodutibilidade em curto prazo (um mês) foi testada[69] para avaliar o consumo alimentar de pacientes com diabetes tipo 2 no sul do Brasil, entretanto, este instrumento precisa ser calibrado e a sua reprodutibilidade em longo prazo (um ano) ainda precisa ser testada.

OBJETIVOS DA TESE

1. Avaliar o desempenho de um QFA construído previamente para estimar o consumo alimentar de pacientes com diabetes tipo 2;
    a. Avaliar a reprodutibilidade em longo prazo de um QFA construído para avaliar a dieta usual de pacientes com diabetes tipo 2;
    b. Calibrar o QFA comparando a informação obtida pelo instrumento com registro alimentar com pesagem dos alimentos (método de referência);
2. Identificar a possível existência de padrões alimentares em uma amostra de pacientes com diabetes tipo 2;
3. Avaliar a associação entre os padrões alimentares identificados e a obtenção de alvos terapêuticos preconizados (peso corporal, controle glicêmico, níveis pressóricos e perfil lipídico) em pacientes com diabetes tipo 2;

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Quadro 1. Sumário das diretrizes nacionais e internacionais

	***American Diabetes Association*[4,11]**	**Sociedade Brasileira de Diabetes[9]**
Carboidratos	Prescrição individualizada	45-60% do VCT* >130 g/dia
Sacarose	-	Até 10% do VCT*
Frutose	-	Não adicionar nos alimentos
Fibra alimentar	Seguir as recomendações da população sem diabetes	14g/1000 kcal Diabetes tipo 2: 30 a 50 g/dia
Lipídeos	Prescrição individualizada	25-35% do VCT*
Ácido graxo saturado	Seguir as recomendações da população sem diabetes	<7% do VCT*
Ácido graxo *trans*	Seguir as recomendações da população sem diabetes	<1% do VCT*
Ácido graxo poli-insaturado	-	Até 10% do VCT*
Ácido graxo monoinsaturado	-	5-15% do VCT*
Colesterol	Seguir as recomendações da população sem diabetes	< 300 mg/dia
Proteínas	Não reduzir o consumo habitual	15 a 20% do VCT*
Vitaminas e minerais	Não suplementar	Seguir as recomendações da população sem diabetes
Sódio	Até 2.300 mg	Até 2.000 mg

VCT = valor calórico total; *Para definição do valor calórico total da dieta, considerar as necessidades individuais, utilizando parâmetros semelhantes à população sem diabetes, em todas as faixas etárias.

Quadro 2. Principais estudos que avaliaram padrões alimentares definidos *a posteriori* em indivíduos com diabetes

Autor, revista e ano	População e país de origem	Delineamento	Forma de análise dos padrões	Padrões encontrados	Desfechos avaliados
Lim JH, *et al*. *J Korean Med Sci* (2011)[50]	n = 680 Idade = 61 ± 11 anos Diabetes tipo 2 Coreia do Sul	Transversal	Recordatório alimentar de 24 horas (1 dia); Análise fatorial	(1) Pão, carne e álcool (2) Macarrão de frutos do mar (3) Arroz e vegetais (4) Saudável	PAS e PAD, A1c, glicemia de jejum, triglicerídeos, colesterol total e HDL, IMC e circunferência da cintura
Iimuro S, *et al*. *Geriatr Gerontol Int* (2012)[62]	n = 912 Idade = 71 ± 4 anos Diabetes tipo 2 Japão	Coorte prospectiva (duração = 6 anos)	Questionário de frequência alimentar; Análise fatorial	(1) Saudável (2) Lanches (3) Gorduras	Características clínicas, antropométricas e laboratoriais e causas de mortalidade
Davis NJ, *et al*. *Am J Clin Nutr* (2013)[51]	n = 235 Idade = 56 ± 12 anos Tipo de diabetes não especificado Estados Unidos	Transversal	Questionário de frequência alimentar; Análise de componentes principais	(1) Pizza e doces (2) Carnes (3) Alimentos fritos (4) Frutas e vegetais (5) Amido do Caribe	Características sócio demográficas
Hsu C-C, *et al*. *Clinical Nutrition* (2014)[52]	n = 635 Idade = 61 ± 8 anos Diabetes tipo 2 Taiwan	Transversal	Questionário de frequência alimentar; Análise fatorial	(1) Rico em gordura (2) Vegetais e peixe (3) Lanches tradicionais chineses	Características clínicas, antropométricas e laboratoriais e indicadores de função renal

Autor, revista e ano	**População e país de origem**	**Delineamento**	**Forma de análise dos padrões**	**Padrões encontrados**	**Desfechos avaliados**
Lamichhane AP, *et al*. *European Journal of Clin Nutr* (2014)[53]	n = 1153 Idade = 10 ± 3 anos Diabetes tipo 1 Estados Unidos	Transversal	Questionário de frequência alimentar; Regressão por redução de posto (RRR)	(1) Rico em bebidas adoçadas com açúcar e refrigerante diet, ovos, batatas e carne gorda, e pobre em doces, sobremesas e laticínios desnatados	PAS, A1c, triglicerídeos, LDL-colesterol, proteína C-reativa, circunferência da cintura e marcadores de rigidez arterial
Jaacks LM, *et al*. *J Diabetes Complications* (2015)[54]	n = 99 Idade = 42 ± 16 anos Diabetes tipo 1 China	Transversal	Recordatório alimentar de 24 horas (3 dias); Regressão por redução de posto (RRR)	(1) Pobre em produtos de trigo e bolos e rico em feijão e legumes em conserva (2) Pobre em bolos, nozes, sementes, peixes, mariscos, chás e café, e rico em arroz e ovos	A1c e LDL-colesterol
Darani Zad ND, *et al*. *J Diabetes Metab Disord* (2015)[55]	n = 400 Idade = 40–60 anos Diabetes tipo 2 Irã	Transversal	Questionário de frequência alimentar; Análise fatorial	(1) Legumes e aves (2) Ocidental (3) Semi saudável	A1c, glicemia de jejum, triglicerídeos, colesterol total, HDL e LDL, IMC e circunferência da cintura
Ghane Basiri MG, *et al*. *Int J Vitam Nutr Res* (2015)[56]	n = 728 Idade = 35–65 anos Diabetes tipo 2 Irã	Transversal	Questionário de frequência alimentar; Análise fatorial	(1) Saudável (2) Não saudável	IMC e circunferência da cintura

Autor, revista e ano	**População e país de origem**	**Delineamento**	**Forma de análise dos padrões**	**Padrões encontrados**	**Desfechos avaliados**
Enomoto M, *et al*. *J Int Med Res* (2015)[57]	n = 73 Idade = 72 ± 5 anos Diabetes tipo 2 Japão	Transversal	Registro alimentar de três dias; Análise fatorial	(1) Óleos, nozes, sementes, açúcares e ovos (2) Cereais e carnes (3) Frutas e batatas (4) Vegetais e peixe (5) Leguminosas	Características clínicas, antropométricas e laboratoriais e função cognitiva
Ahola AJ, *et al*. *J Diabetes Complications* (2016)[58]	n = 874 Idade = 46 ± 13 anos Diabetes tipo 1 Finlândia	Transversal	Questionário de frequência alimentar; Análise fatorial	(1) Saudável (2) Tradicional (3) Vegetais (4) Doces (5) Moderno (6) Queijos brancos (7) Peixe e ovos	Razão cintura-quadril, A1c, PAS e PAD, LDL-colesterol, triglicerídeos, doença renal crônica, retinopatia e eventos cardiovasculares
Shi Z, *et al*. *Acta Diabetol* (2016)[63]	n = 102 Idade = 56 ± 12 anos Diabetes tipo 2 China	Coorte prospectiva (duração 10 anos)	Questionário de frequência alimentar; Análise fatorial	(1) Masculino (2) Tradicional (3) Guloso (4) Rico em vegetais	Mortalidade
Osonoi Y, *et al*. *Nutr J* (2016)[59]	n = 726 Idade = 58 ± 8 anos Diabetes tipo 2 Japão	Transversal	Questionário de história alimentar; Análise fatorial	(1) Algas, vegetais, produtos de soja e cogumelos (2) Peixe e carne (3) Macarrão e sopa (4) Carne, gorduras e óleos, temperos e ovos (5) Frutas, produtos lácteos e doces (6) Sopas de arroz e *missô*	Características clínicas, antropométricas e laboratoriais e fatores de risco para doença cardiovascular

Autor, revista e ano	**População e país de origem**	**Delineamento**	**Forma de análise dos padrões**	**Padrões encontrados**	**Desfechos avaliados**
Mathe N, *et al*. *Can J Diabetes* (2016)[60]	n = 196 Idade = 59 ± 8 anos Diabetes tipo 2 Canadá	Transversal	Questionário de frequência alimentar; Análise de componentes principais	(1) Frituras, bolos e sorvetes (2) Peixe e legumes (3) Massas, batatas e pães	PAS e PAD, A1c, colesterol total e LDL e triglicerídeos
Keel S, *et al*. *Acta Ophthalmol* (2016)[61]	n = 83 Idade = 14 ± 3 anos Diabetes tipo 1 Austrália	Transversal	Questionário de frequência alimentar; Análise de componentes principais	(1) Alimentos processados (2) Alimentos de origem vegetal (3) Recusa vegetais e peixes	Calibre vascular da retina

A1c = hemoglobina glicada; PAS = pressão arterial sistólica; PAD = pressão arterial diastólica.

CAPÍTULO II

Artigo original a ser submetido para publicação no periódico *Public Health Nutrition*, redigido conforme as normas do periódico

LONG-TERM REPRODUCIBILITY AND CALIBRATION OF A QUANTITATIVE FOOD FREQUENCY QUESTIONNAIRE DESIGNED FOR PATIENTS WITH TYPE 2 DIABETES MELLITUS FROM SOUTHERN BRAZIL

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ABSTRACT

Objective: To evaluate the long-term reproducibility and calibration of a previously validated FFQ to assess the usual diet of patients with type 2 diabetes mellitus (T2DM).

Design: Cross-sectional survey using two quantitative FFQ (1-year interval) supported by a food photograph portfolio and 5-day weighed diet records (WDR).

Setting: Group of Nutrition in Endocrinology, southern Brazil.

Subjects: Out-patients with T2DM.

Results: From a total of 88 eligible patients in the original study, 70 were included in the evaluation of FFQ reproducibility and 57 provided data for the calibration study. Mean nutrient intake values reported in the second FFQ did not differ from those of the first FFQ. Only protein, monounsaturated fatty acids, sodium, and iron were different from corresponding values between the first and second FFQs ($P<0.05$). All correlation coefficients were significant before and/or after adjustment for energy ($P<0.05$), ranging from 0.627 (potassium) to 0.243 (cholesterol). Calibration coefficients estimated by linear regression of the 5-day WDR on the second FFQ measurements ranged from 0.11 (glycaemic load) to 0.57 (calcium).

Conclusions: Results confirm that this FFQ had adequate reproducibility to assess past-year intakes of energy, nutrients, glycaemic index, and glycaemic load, and will enable the conduction of prospective studies to evaluate the relationship between food intake, achievement of recommended therapeutic targets, and development of complications in patients with T2DM in southern Brazil. Furthermore, the use of calibration coefficients is recommended to correct the measurement error of the FFQ.

Keywords: type 2 diabetes mellitus, nutritional epidemiology, food frequency questionnaire, food records, reproducibility, calibration.

INTRODUCTION

The influence of diet on the development of human disease has been the central focus of nutritional epidemiology[1]. In the case of diabetes, the importance of individual nutrients and foods for disease management has been demonstrated in clinical trials[2-4], but the overall effect of diet in achieving recommended therapeutic targets is not fully elucidated[5].

To investigate the association between dietary components and diabetes management and/or development of chronic complications, the dietary evaluation should cover a long period (months or years), as is the case of the food frequency questionnaire (FFQ)[1]. The FFQ should be based on a specific population, and its validity, calibration, and reproducibility should always be tested[1]. Validity is examined by comparing FFQ data with a reference method, biomarkers, or both[6]. To evaluate reproducibility, the FFQ should be tested at least on two separate occasions[7]. Finally, calibration is used to correct intake data obtained by the FFQ (test method) according to the reference method[8].

Recently, a quantitative FFQ was constructed[9] and validated[10] in patients with type 2 diabetes mellitus (T2DM) from Southern Brazil, and the short-term reproducibility (1-month) of this instrument was evaluated[10]. The present study continues this research and was designed to calibrate and evaluate the long-term reproducibility (1-year) of the FFQ for assessment of the usual diet of patients with T2DM.

METHODS

Patients

The present study was conducted in patients with T2DM, defined as individuals over 30 years of age at onset of diabetes, with no previous episode of ketoacidosis or documented ketonuria, and with initiation of insulin therapy (when present) at least 5 years after diagnosis[11]. The study recruited out-patients who consecutively attended the Endocrinology Division of the Hospital de Clínicas de Porto Alegre (Brazil) and who had not previously undergone any dietary assessment.

The inclusion criteria were: age <80 years, serum creatinine <2.0 mg/dL and body mass index <40.0 kg/m^2. Patients using corticosteroid drugs and with orthostatic hypotension or gastrointestinal symptoms suggestive of autonomic diabetic neuropathy were excluded. The study was conducted according to the guidelines laid down in the Declaration of Helsinki

and all procedures involving patients were approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre. Written informed consent was obtained from all patients.

Patients underwent clinical, lifestyle and anthropometric evaluation. Information about clinical data (co-morbidities associated with diabetes and medication use) was collected from the patients' most recent medical records. Increased urinary albumin excretion (UAE) was considered in the presence of UAE ≥14 mg/l in a random spot urine collection, or ≥30 mg/24 h. This diagnosis was always confirmed[5]. Patients were classified as current smokers or not (former and non-smokers) and self-identified as white or non-white. Economic status was evaluated by a standardized Brazilian questionnaire[12] and physical activity level was classified according to the short version of the International Physical Activity Questionnaire[13], culturally adapted to the Brazilian population[14]. Physical activity was graded into three levels: low, moderate and high, according to activities during a typical week[13]. The body weight and height of patients (wearing light clothing and no shoes) were obtained, with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. Body mass index (kg/m^2) was then calculated. Waist circumference was measured at the midpoint between the iliac crest and the last floating rib, using a flexible and non-stretchable fiberglass tape.

Dietary assessment

The patients' usual diet was assessed by the FFQ (study factor), previously constructed[9] and validated[10] in patients from Southern Brazil, and by 5-day weighed diet records (WDR), used as a relative reference. The FFQ consisted of the 98 most commonly consumed food items and covered the past 12 months[9,10]. A portfolio with photographs of each included food item and its portion sizes was used to assist the patients in identifying the consumed portions.

The FFQ was applied by a nutritionist in an interview, twice, with a 1-year interval. Between these visits, the patients underwent a 5-day WDR (four non-consecutive weekdays and one day off) as previously standardized[15]. Compliance with the WDR technique was confirmed by comparison between the protein intakes estimated from the WDR and the 24 h urinary urea-N output[16]. To be included in calibration of the FFQ, misreporting should be excluded. Misreporting was defined when the ratio of protein intake estimated from the WDR to protein intake estimated by urinary urea-N was <0.79 or >1.26, as defined previously[17].

The food intakes reported in the dietary instruments (FFQ and 5-day WDR) were converted into daily intakes and their nutritional composition was calculated in the Nutribase Clinical® software (CyberSoft Inc., Phoenix, AZ, USA), which is based on food composition data from the U.S. Department of Agriculture[18]. The amount of trans-fatty acids was derived from the Tabela de Composição dos Alimentos – TACO[19], the US Department of Agriculture[20], Slover *et al*[21] and the TRANSFAIR Study[22]. The total, soluble and insoluble dietary fibre contents were estimated from data available in the CRC Handbook of Dietary Fiber in Human Nutrition[23]. The glycaemic index (GI) and glycaemic load (GL) were obtained from international tables[24]. When the GI of foods present in the instruments was not found, we used data for food with a similar composition.

Laboratory evaluation

Blood samples were obtained after a 12 h fast. Plasma glucose was determined by the glucose oxidase method; serum and urinary creatinine level by Jaffé's reaction; HbA1c was tested by HPLC (Tosoh 2.2 Plus HbA1c; Tosoh Corporation, Tokyo, Japan; reference value: 4.8 to 6.0%); total cholesterol and triglycerides were measured by enzymatic colorimetric methods; and HDL-cholesterol was determined by the homogeneous direct method. LDL-cholesterol was calculated using the Friedewald formula[25], only for patients with triglyceride values <400mg/dl.

On the third day of the WDR, urea was measured in a 24 h urine collection. Collection started on the morning of the third day with the second morning urine and lasted until the fourth day, at the same hour, with the first morning urine. Completeness of urine collection was confirmed by 24 h creatinine measurements: 700 to 1500 mg/24h for women and 1000 to 1800 mg/24h for men[26]. Protein intake was estimated from 24 h urinary urea-N output and calculated using Maroni's formula[16]. Urinary albumin excretion was measured by immunoturbidimetry (MicroAlb Sera-Pak® Immunomicroalbuminuria; Bayer, Tarrytown, NY, USA) in a Cobas Mira Plus® system (Roche, Indianapolis, IN, USA), and urinary urea was measured by an enzymatic UV method.

Statistical analysis

Results are expressed as mean and standard deviation or as median and interquartile range. Gaussian distribution was verified by the one-sample Shapiro-Wilk test. For descriptive analysis, the chi-squared test, Student's *t*-test and the Mann-Whitney test for

independent samples were used to test for differences in demographic, lifestyle and metabolic parameters of patients included in the reproducibility study, as compared with those included in calibration study. Data analyses were performed in SPSS Version 20.0 and SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC), version 9.4. The type I error rate was fixed at $P<0.05$ (two-tailed).

To evaluate the FFQ reproducibility, data from the first and second FFQs were compared by Student's *t*-test or Wilcoxon's *U* test for paired samples, and Pearson correlation coefficients were calculated with crude data and data adjusted for energy intake according to the residual method[1]. Data were log-transformed before analyses to normalize distributions.

In the calibration study, data from the second FFQ and 5-day WDR were evaluated. Calibration was performed using a linear regression model. Energy and nutrient intake values from WDR were used as dependent variables, and estimates based on data from the FFQ were used as independent (predictor) variables. Values for each nutrient were calibrated using the following equation: $calibrated\ value = \alpha + \lambda Q$, where α is the regression constant, λ is the slope of the regression line or "calibration factor", and Q is the estimated energy and nutrient intake from the FFQ.

RESULTS

Patients

Out of a total of 88 participants eligible for the original study[10], 18 patients (20.4%) agreed to participate but did not return for another visit to complete the second FFQ. Furthermore, 13 patients (14.8%) performed an unsatisfactory WDR and were not included in the calibration evaluation. Therefore, 70 patients were included for the reproducibility evaluation and 57 patients provided complete data for the calibration study. The demographic, clinical, anthropometric and laboratory characteristics of the patients included in each study are shown in **Table 1**. We did not observe differences in characteristics between the patients included in the reproducibility study and patients included in the calibration evaluation ($P>0.100$ for all analyses).

Reproducibility study (long term)

The daily intake data obtained from the first and second FFQs were compared and are shown in **Table 2**. The mean values of nutrient intake reported from the first FFQ for protein

(5.8%), monounsaturated fatty acids (6.7%), sodium (5.9%), and iron (6.7%) were different than corresponding values from the second FFQ ($P<0.05$ for all comparisons).

The reported intakes of other macro- and micronutrients were not different between the two applications of the FFQ. The correlation coefficients between the nutrients reported in the first FFQ and second FFQ were calculated and are also shown in **Table 2**. All correlation coefficients were significant before and/or after energy adjustment ($P<0.05$ for all analyses). Most nutrients showed moderate correlation values: the highest value was for potassium (r = 0.627), and the lowest was for cholesterol (r = 0.243).

Calibration study

The results of calibration are presented in **Table 3**. Values ranged from 0.11 (glycaemic load) to 0.57 (calcium). Calibration results were statistically significant for most nutrients. As expected, the mean calibrated values based on data from the FFQ were very similar to the energy-adjusted mean values from the 5-day WDR, and were associated with a considerable reduction in standard deviation.

DISCUSSION

The present FFQ, constructed to evaluate the usual diet of Brazilian patients with T2DM, had adequate reproducibility to assess past-year intakes of energy, most nutrients, GI, and GL. This is the first FFQ developed on the basis of usual dietary intake of patients with T2DM in Brazil.

In our study, some methodological precautions were taken into account: we selected a sample of patients with diabetes and without previous experience in dietary records; we used reference standards (WDR and urinary urea-N output) previously standardized in patients with diabetes[15,17]; we included the influence of seasonality on reproducibility evaluation of the FFQ, applying the tested instrument throughout the year[27]; and, finally, the nutrients were adjusted for energy using the residual method[1]. Adjustment for energy is recommended both by the need to consider isocaloric models and to control embedded error in the methods[1].

Analysis of reproducibility revealed that mean intake of energy, macro- and micronutrients, fibre, glycaemic index and glycaemic load estimated from the two FFQs were not different. We observed statistical differences between the two FFQ for protein,

monounsaturated fatty acids, sodium, and iron (see **Table 2**). However, the differences were small (<7%) and not clinically relevant.

Reproducibility was also analysed using Pearson correlations. All nutrients with crude data and/or data adjusted for energy showed coefficients between 0.24 and 0.62, although the energy adjustment method reduced correlation values in the reproducibility study (see **Table 2**). Possibly, this occurs when the variability of the nutrient is affected by systematic errors of under-recording or over-reporting of food consumption[1].

In the literature, correlation coefficients between 0.40 and 0.70 are considered indicative of good reproducibility of the FFQ[1]. This is due to the fact the reproducibility may be affected by the time elapsed between FFQ applications[1]. If the interval is too short, such as a few days or weeks, reproducibility could be overestimated, as the participant remembers the answers of the first questionnaire. On the other hand, long intervals can reduce correlations as a consequence of a real change in dietary patterns or response variability[28]. In this study, the average time interval between interviews was 1 year, and this range could imply moderate correlation coefficients. Our results were similar to those of other studies that evaluated FFQ performance[29-31].

Calibration is useful for correcting errors in estimating food intake, particularly when dietary intake is the exposure variable of an association study between diet and disease[32]. This statistical method provides the coefficients required to correct the average values of energy intake and nutrients estimated by the test method (FFQ), resulting in values similar to those obtained by the reference method, the WDR[33]. In calibration by a linear regression model, the method used in this study, it is desired that the slope, represented by λ, be approximately 1.0. This indicates absence of bias in the questionnaire, i.e., average intake estimated through the FFQ will be equal to the average estimated by the reference method[33]. As in other calibration studies[34-37], slope values less than 1.0 were observed in the present study (see **Table 3**).

To obtain greater λ coefficients, either the number of replicates of the reference method or the sample size must be increased[35]. The number of replicates used in our study (5 days) is greater than that commonly used in the literature[34-37], but less than "ideal". Capturing the daily variability of certain nutrients could take more than 5 days, as demonstrated by Basiotis *et al*, who reported that the number of days of diet observation range from 3 (for calories) to 44 (for vitamin A)[38].

In fact, we chose to use the WDR in this study because it is widely recommended in the literature as the reference method for FFQ validation, because it discloses independent errors in the collection of diet information[27], even though it demands greater effort of the participants, who may cause changes in food intake to facilitate its registration[39]. Furthermore, we believe that the use of a 5-day WDR may increase the possibility of loss to follow-up, as was the case in this study. However, individuals lost to follow-up did not demonstrate significant differences in characteristics as compared with those who remained in the study (data not shown).

In conclusion, reproducibility results confirm that this FFQ will enable the conduction of prospective studies to evaluate the relationship between food intake, achievement of recommended therapeutic targets, and development of complications in patients with T2DM in southern Brazil. The use of calibration coefficients is recommended to correct for the measurement error of the FFQ, which can make it a more useful tool for studies designed to test for associations between diet and health outcomes.

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Table 1. Demographic, clinical, anthropometric, and laboratory characteristics of patients included in reproducibility and calibration studies

Characteristics	Reproducibility study	Calibration study	*P* value
n	70	57	
Female sex	42 (60.0)	30 (52.6)	0.469*
Age (years)	62.6 ± 8.7	62.3 ± 8.5	0.832†
Diabetes duration (years)	10.0 (4.0-17.5)	11.0 (4.0-20.0)	0.665‡
White skin colour (self-reported)	49 (70.0)	40 (70.2)	0.980*
Years of education	6.5 (5.0-11.0)	8.0 (5.0-11.0)	0.539‡
Hypertension	63 (90.0)	50 (87.7)	0.657*
Increased UAE	21 (30.4)	17 (30.4)	0.943*
Diabetes treatment			
Diet	1 (1.4)	1 (1.8)	
Oral agents	32 (45.7)	22 (38.6)	0.826*
Insulin and oral agents	37 (52.9)	34 (59.6)	
Economic status: middle class	30 (42.8)	20 (35.1)	0.877*
Current smoking	4 (5.7)	2 (3.5)	0.787*
Physical activity: low level	38 (55.9)	30 (53.6)	0.896*
Body mass index (kg/m²)	29.7 ± 4.4	29.8 ± 4.6	0.954†
Waist circumference (cm)			
Male	102.9 ± 10.9	103.2 ± 11.3	0.934†
Female	99.4 ± 9.9	99.8 ± 10.9	0.853†
Fasting plasma glucose (mg/dl)	142.7 ± 55.0	145.1 ± 55.6	0.818†
HbA1c (%)	8.5 ± 2.0	8.6 ± 2.0	0.699†
Total cholesterol (mg/dl)	184.2 ± 48.4	182.9 ± 48.0	0.892†
HDL-cholesterol (mg/dl)			
Males	41.3 ± 12.3	46.4 ± 16.4	0.203†
Females	49.9 ± 13.4	45.6 ± 11.0	0.175†
LDL-cholesterol (mg/dl)	109.2 ± 38.2	109.1 ± 39.1	0.984†
Triglycerides (mg/dl)	120.0 (94.0-177.5)	124.5 (95.3-181.0)	0.733‡
Serum creatinine (mg/dl)	0.9 ± 0.3	0.9 ± 0.3	0.806†
Urinary albumin excretion (mg/dl)	8.2 (3.0-23.5)	13.7 (3.2-52.1)	0.936‡

Data are expressed as means ± standard deviation, median (interquartile range), or n (%).

*Chi-square test; †Student's *t*-test; ‡Mann-Whitney test.

Table 2. Energy intake, macro- and micronutrients, fibre, glycaemic index, and glycaemic load estimated from the two food frequency questionnaires (FFQ) at a 1-year interval, in patients with type 2 diabetes mellitus (reproducibility study, *n* = 70)

Nutrient	First FFQ	Second FFQ	*P* value[†]	Pearson correlations[‡]	
				Crude data	Adjusted[§]
Energy (kcal)	2105.3 ± 700.7	2113.9 ± 617.7	0.914	0.517*	-
Protein (g)	92.2 ± 16.2	86.8 ± 13.1	**0.011**	0.596*	0.310*
Carbohydrate (g)	259.3 ± 38.4	263.0 ± 44.1	0.537	0.438*	0.233
Total fibre (g)	25.1 ± 6.6	24.7 ± 7.1	0.613	0.560*	0.457*
Soluble fibre (g)	8.8 ± 2.3	8.4 ± 2.2	0.177	0.531*	0.346*
Insoluble fibre (g)	16.1 ± 5.0	16.2 ± 5.3	0.819	0.507*	0.424*
Total lipids (g)	79.1 ± 14.3	81.9 ± 17.6	0.242	0.449*	0.345*
Saturated fatty acids (g)	23.5 ± 5.9	22.8 ± 6.4	0.462	0.580*	0.431*
Monounsaturated fatty acids (g)	26.2 ± 5.5	28.1 ± 7.1	**0.031**	0.556*	0.430*
Polyunsaturated fatty acids (g)	21.4 ± 7.6	23.3 ± 8.8	0.110	0.234	0.415*
Trans-unsaturated fatty acids	1.9 ± 0.6	1.7 ± 0.6	0.245	0.501*	0.334*
Glycaemic index (%)	55.7 ± 4.6	55.2 ± 5.1	0.425	0.464*	0.440*
Glycaemic load (g)	127.8 ± 26.8	123.7 ± 29.2	0.378	0.452*	0.082
Cholesterol (mg)	243.1 ± 79.4	223.6 ± 75.3	0.079	0.579*	0.243*
Vitamin C	202.9 (132.3-259.8)	202.8 (127.3-252.8)	0.736	0.599*	0.572*
Calcium (mg)	895.4 ± 309.0	850.2 ± 289.0	0.191	0.585*	0.573*
Magnesium (mg)	335.5 ± 61.6	343.5 ± 70.3	0.275	0.547*	0.561*
Sodium (mg)	1998.7 ± 463.6	1881.0 ± 442.3	**0.049**	0.529*	0.423*
Iron (mg)	15.0 ± 2.2	14.0 ± 2.5	**0.003**	0.559*	0.363*
Potassium (mg)	3512.0 ± 715.6	3528.9 ± 752.8	0.842	0.627*	0.486*

Data are expressed as means ± standard deviation or median (interquartile range). [†]Student's *t*-test for paired samples or Wilcoxon *U*-test for paired samples. [‡]Energy and nutrient values were log-transformed to normalize distribution and calculate correlation coefficients. [§]Data adjusted for energy intake according to the residuals method[(1)]. *$P < 0.05$

Table 3. Energy intake, macronutrients, fibre, glycaemic index, and glycaemic load estimated from the second food frequency questionnaire (FFQ) *versus* a 5-day mean of weighed diet records (WDR) in patients with type 2 diabetes mellitus (calibration study, *n* = 57)

Nutrient	Regression constant α (95% CI)	Calibration factor λ (95% CI)	FFQ[†‡]	WDR[†‡]	Calibrated FFQ[†]
Energy (kcal)	1194.1 (750.5-1637.8)	0.37 (0.17-0.57)	2136.6 ± 577.5	1993.8 ± 480.0	1993.8 ± 216.1
Protein (g)	51.4 (24.3-78.4)	0.51 (0.21-0.81)	88.8 ± 30.3	96.9 ± 29.0	96.9 ± 6.9
Carbohydrate (g)	156.0 (106.4-205.6)	0.30 (0.12-0.48)	268.5 ± 75.4	235.9 ± 70.5	235.9 ± 13.2
Total fibre (g)	10.0 (3.8-16.9)	0.36 (0.12-0.60)	24.7 ± 8.3	18.8 ± 8.0	18.8 ± 2.6
Soluble fibre (g)	3.1 (1.2-5.1)	0.41 (0.18-0.63)	8.5 ± 2.6	6.6 ± 2.5	6.6 ± 0.9
Insoluble fibre (g)	6.4 (2.1-10.8)	0.35 (0.10-0.61)	16.2 ± 6.0	12.1 ± 6.0	12.1 ± 1.9
Total lipids (g)	50.1 (32.8-67.4)	0.28 (0.07-0.49)	80.5 ± 27.4	72.7 ± 18.2	72.7 ± 4.4
Saturated fatty acids (g)	12.1 (7.7-16.5)	0.36 (0.17-0.54)	22.9 ± 10.1	20.3 ± 6.5	20.3 ± 2.3
Monounsaturated fatty acids (g)	14.3 (8.2-20.4)	0.35 (0.13-0.56)	28.1 ± 10.6	24.0 ± 7.0	24.0 ± 2.3
Polyunsaturated fatty acids (g)	12.8 (8.0-17.6)	0.39 (0.18-0.60)	21.8 ± 8.3	21.4 ± 6.7	21.9 ± 2.6
Trans-unsaturated fatty acids	1.1 (0.4-1.7)	0.49 (0.13-0.84)	1.7 ± 0.8	1.9 ± 0.9	1.9 ± 0.3
Glycaemic index (%)	40.3 (20.3-60.4)	0.31 (-0.05-0.67)	55.5 ± 4.5	57.4 ± 6.1	57.4 ± 1.4
Glycaemic load (g)	105.5 (82.2-128.9)	0.11 (-0.08-0.29)	125.7 ± 38.2	118.8 ± 34.7	118.8 ± 3.0
Cholesterol (mg)	194.5 (109.3-279.8)	0.17 (-0.18-0.53)	230.7 ± 112.9	234.8 ± 127.9	234.8 ± 12.6
Vitamin C	50.6 (13.6-87.5)	0.23 (0.07-0.39)	206.1 ± 102.8	97.6 ± 69.9	97.6 ± 23.1
Calcium (mg)	216.9 (6.2-427.7)	0.57 (0.34-0.81)	856.1 ± 343.1	709.2 ± 372.1	709.2 ± 163.4
Magnesium (mg)	123.9 (41.5-206.3)	0.55 (0.31-0.78)	348.6 ± 103.0	314.3 ± 105.2	314.3 ± 37.8
Sodium (mg)	1439.9 (915.3-1964.5)	0.32 (0.04-0.59)	1876.9 ± 619.7	2031.6 ± 701.2	2031.6 ± 149.4
Iron (mg)	11.4 (6.7-16.1)	0.20 (-0.12-0.53)	14.1 ± 4.0	14.3 ± 4.4	14.3 ± 0.5
Potassium (mg)	1230.5 (289.0-2172.0)	0.46 (0.21-0.72)	3633.2 ± 1089.5	2918.3 ± 1076.4	2918.2 ± 331.9

[†]Data are expressed as means ± standard deviation. [‡]Data adjusted for energy intake according to the residuals method[(1)].

CAPÍTULO III

Artigo original a ser submetido para publicação no periódico *Diabetes Care*, redigido conforme as normas do periódico

EATING PATTERNS AND HEALTH OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Objective: To evaluate the relationship between eating patterns and achieving recommended therapeutic targets in patients with type 2 diabetes.

Research design and methods: In this cross-sectional study, patients underwent clinical, laboratory, and nutritional evaluations. The therapeutic targets defined were: blood pressure <140/90mmHg; BMI <25kg/m^2 (<27kg/m^2 for elderly); waist circumference <94cm for men and <80cm for women; fasting plasma glucose <130mg/dl; HbA1c <7%; triglycerides <150mg/dL; HDL-cholesterol >40mg/dL for men and >50mg/dL for women; LDL-cholesterol <100mg/dL. Dietary intake was assessed by a quantitative food frequency questionnaire and eating patterns identified by cluster analysis.

Results: A total of 197 patients with type 2 diabetes (63.5% women; 62.5±9.1 years; diabetes duration = 10 (5-19) years; HbA1c = 8.5±2.0%) were studied. We identified two eating patterns: "unhealthy" eating pattern (n=100) - high consumption of refined carbohydrates, ultra-processed foods, sweets and desserts (P<0.05); and "healthy" eating pattern (n=97) - high intake of whole carbohydrates, dairy, white meat, fish, fruits and vegetables (P<0.05). The healthy group more frequently achieved therapeutic targets for fasting plasma glucose, HbA1c, and LDL-cholesterol than the unhealthy group. Poisson regression, adjusted to potential confounding, confirmed the association of healthy eating pattern with attaining the therapeutic target for fasting plasma glucose [PR=1.59 (95%CI,1.01-2.34); P=0.018], HbA1c [PR=2.09 (95%CI,1.17-3.74); P=0.013], and LDL-cholesterol [PR=1.37 (95%CI,1.01-1.86); P=0.042].

Conclusions: A healthy eating pattern, including the frequent intake of whole carbohydrates, dairy, white meat, fish, fruits and vegetables is associated with reduced fasting plasma glucose, HbA1c, and LDL-cholesterol levels in patients with type 2 diabetes.

Keywords: type 2 diabetes mellitus, eating pattern, therapeutic targets.

INTRODUCTION

Medical nutrition therapy is one of the cornerstones of diabetes management (1). Evidence from prospective cohort studies and clinical trials has shown the importance of individual nutrients and foods for diabetes prevention and management (2,3), but the overall effect of diet in achieving the recommended therapeutic targets has not been fully elucidated (1).

Eating patterns are defined as the quantities, proportions, variety or combinations of different foods and beverages in diets, and the frequency with which they are habitually consumed (4). The identification of eating patterns can be useful to investigate the relationship between diet and disease, especially when more than one dietary component (nutrients or foods) seem to be involved, as in diabetes (5). This evaluation can be analyzed in two ways: *a priori* - eating patterns are defined based on guidelines and nutritional recommendations, or *a posteriori* - when data from dietary surveys are aggregated through specific statistical analysis (6,7).

Several eating patterns defined *a priori* such as Mediterranean, low glycaemic index, moderately low carbohydrate, or vegetarian diets have been recommended for the management of weight and glucose control in diabetes (1,8). However, recently the American Diabetes Association stated that there is no single ideal dietary distribution of calories from carbohydrates, fats, and protein for diabetes patients (1). In this context, the choice of eating pattern should be individualized, taking into account the patient's current consumption preferences and the goal of metabolic targets (1,9).

The aim of this cross-sectional study was to evaluate the relationship between eating patterns defined *a posteriori* and achieving recommended therapeutic targets (blood pressure, body weight, glycemic control, and lipid profile) in patients with type 2 diabetes in Southern Brazil.

RESEARCH DESIGN AND METHODS

Patients

The current study was conducted in patients with type 2 diabetes, defined as individuals over 30 years of age at onset of diabetes, with no previous episode of ketoacidosis or documented ketonuria and who had not been using insulin in the five years since the

diabetes was diagnosed (10). The study recruited outpatients who consecutively attended the Endocrinology Division of the Hospital de Clínicas de Porto Alegre, Brazil.

The inclusion criteria were: age <80 years, serum creatinine <2.0 mg/dL, and BMI <40 kg/m². Patients on corticosteroid treatment or who had orthostatic hypotension or gastrointestinal symptoms suggestive of autonomic neuropathy were excluded. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre, Brazil. Written informed consent was obtained from all patients.

Clinical and laboratory evaluation

Patients were submitted to clinical, laboratory, and lifestyle evaluation. Information about clinical data (co-morbidities associated with diabetes and medication use) was collected from the patient's most recent medical records. Blood pressure was measured twice ("Digital Blood Pressure Monitor Omron" HEM-705CP model) according to international recommendations (11). Increased urinary albumin excretion (UAE) was considered in the presence of UAE ≥14 mg/l in a random spot urine collection, or ≥30 mg in 24-hour collection and the diagnosis was always confirmed (1,12). Patients were classified as current smokers or not (former and non-smokers) and self-identified as white or non-white. Economic status was evaluated by a standardized Brazilian questionnaire (13) and physical activity level was classified according to the short version of the International Physical Activity Questionnaire (14) culturally adapted to the Brazilian population (15). Physical activity was graded at three levels: low, moderate, and high, according to activities during a typical week (14).

Blood samples were obtained after a 12-hour fast. Serum creatinine level was determined by Jaffe's reaction and estimated glomerular filtration rate by CKD-EPI calculator (Study Group and the Chronic Kidney Disease Epidemiology Collaboration - Calculator © 2000 – 2011). Plasma glucose was measured by a glucose oxidase method, HbA1c test by HPLC (Tosoh 2.2 Plus HbA1c; Tosoh Corporation, Tokyo Japan; reference values 4.8 to 6%), total cholesterol and triglycerides by enzymatic-colorimetric methods, and HDL-cholesterol by homogeneous direct method. LDL-cholesterol was calculated using Friedewald's formula: LDL-cholesterol = total cholesterol - HDL-cholesterol - (triglyceride/5) (16) only for patients with triglyceride values <400 mg/dl. UAE was measured by immunoturbidimetry [MicroAlb Sera-Pak® immuno microalbuminuria; Bayer, Tarrytown, NY on Cobas Mira Plus (Roche®)].

Nutritional evaluation: anthropometric and dietary assessments

The body weight and height of patients (light clothing and without shoes) were obtained with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. BMI was then calculated. Waist circumference was measured at the midpoint between the iliac crest and the last floating rib. A flexible and non-stretch fiberglass tape was used for this measurement.

Information on food intake was collected from a quantitative food frequency questionnaire (FFQ) previously constructed (17) and validated (18) in patients from Southern Brazil. The FFQ consist of 98 food items and covered the past 12 months of food intake. Also, a portfolio with photographs of each food item and its portion sizes was used to support patients in identifying the consumed portion.

The intake report obtained by the FFQ was converted into daily consumption to estimate the nutritional composition (19-21). The glycemic index (GI) and load (GL) were obtained from the international table (22). When the GI of foods present in the instruments was not found, we used data from food with a similar composition. Calculations were performed using the syntax of the Statistical Package for Social Sciences (SPSS) version 20.0 program (SPSS Inc., Chicago, IL, USA).

Therapeutic target definitions

Patients were considered to be within the therapeutic target according to the following criteria: systolic and diastolic blood pressure <140/90 mmHg, respectively; BMI <25 kg/m^2 or <27 kg/m² for the elderly (1,23); waist circumference <94 cm for men and <80 cm for women (24); fasting plasma glucose <130 mg/dl; HbA1c values <7%; serum triglycerides <150 mg/dL; HDL cholesterol >40 mg/dL for men and >50 mg/dL for women; and LDL-cholesterol <100 mg/dL (1).

Statistical analysis

The FFQ foods were aggregated into 18 groups and the amount consumed from each food group was converted into a percentage of total daily caloric intake. We performed a cluster analysis based on food groups to derive two non-overlapping groups (eating patterns) using the K-means method. Median and interquartile range were calculated for each of the 18 food groups and compared by Mann-Whitney *U* test for independent samples.

We examined the assumption of normality for all evaluated variables by Kolmogorov-Smirnov test. Chi-squared test, Student's t-test and Mann-Whitney test for independent samples were used to test differences across the eating patterns. Energy and nutrient intake data were adjusted before analyses for energy intake according to the residual method (5).

To investigate the associations between eating patterns and achieve therapeutic targets we used Poisson regression with robust variance analysis. As the first step of the analysis we estimated the effect of eating patterns on each therapeutic target (dependent variable). The second analysis (Model 1) was adjusted for gender, age, economic status, current smoking, and diabetes duration. The third analysis (Model 2) was additionally adjusted for diabetes treatment, physical activity, BMI, and energy intake. BMI was not included as covariate in the analysis of body weight and waist circumference targets (Model 3).

Analyses were performed using the SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL, USA) and the type I error rate fixed at $P \leq 0.05$ (2-tailed).

RESULTS

Our sample consisted of 197 patients with type 2 diabetes: 63.5% women; 70.6% white; 62.5 ± 9.1 years; diabetes duration = 10 (5-19) years; BMI = 30.9 ± 4.3 kg/m^2; presence of hypertension = 89.8%; presence of increased UAE = 39.1%; HbA1c = 8.5 ± 2.0%; and fasting plasma glucose = 164.7 ± 68.2 mg/dL.

We identified two eating patterns regarding quality of food groups consumed based on cluster analysis. The first cluster, defined as "healthy" eating pattern (n = 97), had a high intake of whole carbohydrates, dairy, white meat, fish, fruits, and vegetables (P<0.05). The second cluster identified was defined as "unhealthy" eating pattern (n = 100) and was characterized by high consumption of refined carbohydrates, ultra-processed foods, sweets, and desserts (P<0.05).

The median and interquartile range of food group consumption (converted into a percentage of daily caloric intake) according to eating patterns is described in **Table 1**. We observed median equal zero in two food groups: alcoholic beverages and fish, although the fish consumption was different between groups: 67% of patients reported no consumption of fish in the unhealthy cluster and 49.5% in the healthy cluster (P=0.01). Regarding consumption of alcoholic beverages, 59% of patients in the unhealthy cluster and 67% of patients in the healthy cluster reported no consumption (P=0.24).

The nutrient intake according to eating pattern was shown in **Table 2**. Differences in nutrient intake were in accordance with results of cluster analyses. Patients from the healthy eating pattern had significantly lower energy, *trans*-unsaturated fatty acid, and sodium intakes than those in the unhealthy eating pattern ($P<0.05$). The healthy group consumed a diet with a lower index and glycemic load ($P<0.05$) than the unhealthy group. The intake of protein, total, soluble and insoluble fiber, omega-3 fatty acid, calcium, magnesium, iron, potassium, and vitamin C were highest in patients from the healthy eating pattern ($P<0.05$).

Clinical and laboratory characteristics of the eating patterns are shown in **Table 3**. Most clinical and laboratory features did not differ between groups, but there were more women in the healthy group (71.1% *vs* 56.0%; $P = 0.038$), were older (63.9 ± 9.1 *vs* 61.1 ± 9.0; $P = 0.028$), and had lower fasting plasma glucose (150.2 ± 61.5 mg/dL *vs* 179.1 ± 71.1 mg/dL; $P = 0.003$) than the unhealthy group. Men from the healthy group have a smaller waist circumference (102.7 ± 9.3 cm *vs* 107.9 ± 11.4 cm; $P = 0.048$) than men from the unhealthy group.

Results comparing the proportion of patients who achieved therapeutic targets in healthy and unhealthy groups are depicted in **Table 4**. A larger proportion of patients who maintained a healthy eating pattern achieved fasting plasma glucose values <130 mg/dL (47.4 *vs* 31.3%; $P = 0.028$), HbA1c <7% (33.0 *vs* 17.0%; $P = 0.013$), and LDL-cholesterol <100 mg/dL (63.2 *vs* 46.6%; $P = 0.034$). There were no differences between groups in the evaluation of other therapeutic targets (blood pressure, BMI, waist circumference, HDL-cholesterol, and triglycerides).

In the crude analysis of Poisson regression, it was observed that the healthy eating pattern was associated with achieving the therapeutic targets for fasting plasma glucose (PR 1.51; 95% CI 1.06 to 2.17), HbA1c (RP 1.94; 95% CI 1.16 to 3.26) and LDL-cholesterol (PR 1.36; 95% CI 1.03 to 1.79). In Model 1, these associations were confirmed for fasting plasma glucose (PR 1.59; 95% CI 1.01 to 2.34), and HbA1c (PR 2.61; 95% CI 1.51 to 4.53). In Models 2 and 3, HbA1c (PR 2.09; 95 % 1.17 to 3.74) and LDL-cholesterol (PR 1.37; 95% CI 1.01 to 1.86) were the target variables associated with a healthy eating pattern (**Table 4**).

DISCUSSION

In this cross-sectional study, we obtained data from 197 patients with type 2 diabetes and identified two eating patterns by cluster analysis. The healthy eating pattern,

characterized by high consumption of whole carbohydrates, dairy, white meat, fish, fruits and vegetables, was associated with better glycemic and lipid control than the unhealthy eating pattern. Patients in the healthy eating pattern had lower fasting plasma glucose, HbA1c, and LDL-cholesterol and most frequently reached the recommended therapeutic targets for these parameters as compared with patients from the unhealthy eating pattern. As expected, patients in the healthy group had a higher intake of protein, total, soluble and insoluble fiber, omega-3 fatty acid, calcium, magnesium, iron, potassium, and vitamin C. Moreover, the association between the healthy eating pattern and achieving the therapeutic targets for fasting plasma glucose, HbA1c and LDL-cholesterol remained, even when potential confounding factors were taken into account as demonstrated by regression analyses.

It is known that carbohydrates are the nutrients that most affect blood glucose levels. However, up to now there is no consensus evidence about the ideal amount of carbohydrate intake for people with diabetes (1,9). In fact, in the current study, the carbohydrate consumption did not differ between the unhealthy and healthy group. The association between healthy eating pattern and glycemic control could be better explained by the quality of carbohydrate intake than the amount of this macronutrient. In agreement with this, we demonstrated a higher consumption of whole carbohydrates, fruits and vegetables in this group of patients. As a consequence, these patients consumed diets with a lower glycemic index and glycemic load values as compared with patients in the unhealthy eating pattern. Currently, diets with a low glycemic index have been associated with improved glycemic control (25).

Another nutrient probably related to the best observed glycemic control in our study is dietary fiber. Accordingly, in our patients in the healthy eating pattern, a higher total, soluble and insoluble fiber consumption was observed. It has already been demonstrated that a high fiber intake was associated with better glycemic control in patients with diabetes (26,27). However, up to now, the beneficial effects of fiber intake, especially soluble fibers, could not be isolated from the effects of glycemic index and glycemic load since most foods that have a low glycemic index also have a high fiber content (8).

On the other hand, the better lipid profile observed in patients in the healthy eating pattern, as compared with the unhealthy eating pattern, was, at least partially, due to dietary fiber content. A beneficial fiber effect on the lipid profile (28) with reduction of total and LDL-cholesterol and triglycerides (29,30) had already been previously established. In our study, a higher proportion of patients in the healthy group (rich in fibers) had LDL-cholesterol

below 100 mg/dL as compared with patients in the unhealthy group. This result could not be explained by lipid-lowering drugs since the frequency of drug users was not different in healthy and unhealthy groups, nor were BMI and the level of physical activity.

Fat consumption, along with fiber intake, could have influenced the improvement of LDL-cholesterol in a healthy eating pattern. The dietary cholesterol and the saturated fatty acid intake did not differ between healthy and unhealthy groups. However, the *trans*-unsaturated fatty acids intake was lower in patients in the healthy group. In fact, this dietary component was already associated with high LDL-cholesterol levels (31).

Although our study has a cross-section design that allowed us to describe only possible associations, it is worthwhile observing that the healthy eating pattern identified in the current study presents similarities with the DASH diet (Dietary Approaches to Stop Hypertension) which is an *a priori* eating pattern characterized by high consumption of vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and is low in sweets and desserts (32,33). In fact, the beneficial effect of this dietary pattern has already been demonstrated in short-term trials in patients with diabetes (34-36).

The association between eating patterns defined *a posteriori* and health outcomes in individuals with diabetes has been studied more recently in different countries. However, most of these studies, different from ours, used factor analysis to determine eating patterns (37-44). Our study was the first to use cluster analysis, a method that creates patterns that are mutually exclusive (ie. categorical variables) and that are defined by maximizing differences in mean intake of food groups (6). Cluster analysis findings are easier to interpret because an individual is in one cluster only, outcomes are specific to individuals within each cluster, and each cluster has a specific food and nutrient composition (45).

Moreover, in our study, some methodological precautions were also taken into account. We used a food frequency questionnaire previously constructed (17) and validated (18) in patients from Southern Brazil and, the macro- and micronutrient data were adjusted for energy using the residual method (5). Also the sample size we used to analyze a food consumption tool was appropriately calculated (46). We included ten individuals for each food group studied (18 food groups studied and 180 subjects).

A possible limitation of our study was the absence of an actual sodium intake estimate. We used the intrinsic sodium of foods derived from a table (19) instead of measurements of 24-h urinary sodium, a more accurate evaluation of salt consumption (47). Finally, as expected, the adopted cross-sectional design hinders any causal inferences. The associations

of healthy eating patterns as described in our study should be evaluated in different samples of patients with diabetes, in long-term cohorts, and ideally, in randomized clinical trials. The recommendation of a healthy eating pattern, instead of prescribing allowed or forbidden foods should be tested as a useful dietary strategy for patients with diabetes.

CONCLUSIONS

In patients with type 2 diabetes a healthy eating pattern including the frequent intake of whole carbohydrates, dairy, white meat, fish, fruits and vegetables was associated with lower fasting plasma glucose, HbA1c, and LDL-cholesterol levels as compared with an eating pattern with high consumption of refined carbohydrates, ultra-processed foods, sweets and desserts.

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Table 1. Daily consumption of food groups in patients with type 2 diabetes according to eating patterns

Food Groups (% of total caloric intake)	Eating Patterns		*P* value*
	Unhealthy (*n* = 100)	Healthy (*n* = 97)	
Whole carbohydrates	0.0 (0.0-2.4)	10.1 (3.5-17.5)	**0.001**
Refined carbohydrates	32.3 (27.6-38.5)	14.9 (10.7-18.4)	**0.001**
Fried foods	1.5 (0.1-5.2)	0.9 (0.0-4.3)	0.450
Ultra-processed foods	2.7 (1.0-4.5)	1.4 (0.2-2.6)	**0.001**
Dairy	8.0 (3.9-11.7)	11.0 (7.4-16.1)	**0.001**
Light and diet foods	0.0 (0.0-1.3)	0.4 (0.0-3.1)	0.198
Caffeinated beverages	0.9 (0.4-1.8)	1.0 (0.5-1.7)	0.919
Alcoholic beverages	0.0 (0.0-0.3)	0.0 (0.0-0.4)	0.633
Sweets and desserts	3.2 (0.5-7.2)	2.1 (0.3-4.7)	**0.032**
Red meat	10.0 (6.1-13.6)	11.4 (6.1-14.8)	0.217
White meat	4.3 (2.5-6.9)	5.6 (3.4-8.2)	**0.009**
Fish	0.0 (0.0-0.1)	0.0 (0.0-1.4)	**0.035**
Fruits	12.4 (7.7-16.3)	16.7 (12.5-21.6)	**0.001**
Vegetables	2.3 (1.5-3.6)	3.5 (2.5-5.7)	**0.001**
Beans	3.3 (1.7-4.9)	3.2 (1.5-4.5)	0.919
Natural juices	0.1 (0.0-1.4)	0.2 (0.0-1.5)	0.612
Solid fats	0.4 (0.0-1.5)	0.8 (0.0-1.5)	0.497
Vegetable oils	2.2 (1.3-4.9)	2.5 (0.6-4.6)	0.218

Data are expressed as median (interquartile range). *Mann-Whitney *U* test.

Table 2. Daily energy intake, macro and micronutrients, fiber, glycemic index and glycemic load in patients with type 2 diabetes according to eating patterns

Nutrients	Eating Patterns		*P* value
	Unhealthy (*n* = 100)	Healthy (*n* = 100)	
Energy (kcal)	2005.6 ± 788.5	1757.0 ± 649.3	**0.017**[*]
Protein (g)[†]	84.3 ± 19.0	94.1 ± 15.3	**0.001**[*]
Carbohydrate (g)[†]	268.8 ± 42.4	257.7 ± 42.8	0.068[*]
Total fiber (g)[†]	25.0 ± 7.1	30.7 ± 9.9	**0.001**[*]
Soluble fiber (g)[†]	7.0 ± 2.1	8.4 ± 2.8	**0.001**[*]
Insoluble fiber (g)[†]	16.8 ± 5.3	20.4 ± 7.5	**0.001**[*]
Total lipids (g)[†]	53.8 ± 13.4	56.4 ± 13.2	0.178[*]
Saturated fatty acid (g)[†]	19.0 ± 5.7	20.2 ± 5.6	0.157[*]
Monounsaturated fatty acid (g)[†]	17.4 ± 4.9	18.3 ± 5.3	0.247[*]
Polyunsaturated fatty acid (g)[†]	8.8 ± 3.5	9.4 ± 3.2	0.241[*]
Omega-3 fatty acid (g)[†]	0.7 ± 0.3	0.8 ± 0.3	**0.006**[*]
Omega-6 fatty acid (g)[†]	6.9 ± 3.1	7.4 ± 2.8	0.282[*]
Trans-unsaturated fatty acid (g)[†]	1.6 (1.1-2.4)	1.3 (1.0-1.7)	**0.001**[‡]
Cholesterol (mg)[†]	248.5 ± 97.4	271.7 ± 88.4	0.082[*]
Calcium (mg)[†]	751.9 ± 302.7	992.8 ± 358.5	**0.001**[*]
Magnesium (mg)[†]	268.5 ± 54.9	333.3 ± 67.7	**0.001**[*]
Iron (mg)[†]	9.0 ± 2.2	10.2 ± 2.0	**0.001**[*]
Sodium (mg)[†]	1584.2 ± 472.4	1356.5 ± 341.1	**0.001**[*]
Potassium (mg)[†]	3124.9 ± 710.0	3738.3 ± 608.0	**0.001**[*]
Vitamin C (mg)[†]	190.6 (124.8-297.7)	250.4 (195.3-350.7)	**0.001**[‡]
Glycemic index (%)[†]	50.0 ± 5.6	43.7 ± 5.0	**0.001**[*]
Glycemic load (g)[†]	134.3 ± 32.2	113.1 ± 24.7	**0.001**[*]

Data are expressed as means ± standard deviation or median (interquartile range). [†]Data adjusted for energy intake according to the residuals method. [*]Student's *t*-test for independent samples; [‡]Mann-Whitney U test.

Table 3. Clinical and laboratory characteristics of patients with type 2 diabetes, according to eating patterns

Characteristics	Eating Patterns		*P* value
	Unhealthy (*n* = 100)	Healthy (*n* = 97)	
Females	56 (56.0)	69 (71.1)	**0.038**[*]
Age (years)	61.1 ± 9.0	63.9 ± 9.1	**0.028**[†]
Whites	65 (65.0)	74 (76.3)	0.088[*]
Years of study	6.5 (4.0-11.0)	6.0 (4.0-11.0)	0.729[‡]
Economic status: middle class	43 (45.3)	48 (51.7)	0.449[*]
Current smoking	20 (20.0)	8 (8.2)	0.060[*]
Physical activity: low level	59 (60.8)	61 (64.9)	0.568[*]
Diabetes duration (years)	10.0 (4.0-17.7)	10.0 (5.0-19.5)	0.635[‡]
Hypertension	89 (89.0)	88 (90.7)	0.815[*]
Systolic blood pressure (mmHg)	143.3 ± 26.2	140.3 ± 17.8	0.351[†]
Diastolic blood pressure (mmHg)	78.3 ± 13.1	76.9 ± 10.0	0.403[†]
Increased UAE	41 (41.0)	31 (31.9)	0.228[*]
Diabetes treatment			
Diet	1 (1.0)	4 (4.1)	
Oral hypoglycemic drugs	42 (42.0)	46 (47.4)	0.350[*]
Insulin and oral hypoglycemic drugs	50 (50.0)	43 (44.3)	
Anti-hypertensive drugs (number)	2.0 (1.0-4.0)	2.0 (2.0-3.0)	0.892[‡]
Use of ACE inhibitor	68 (68.0)	56 (57.7)	0.143[*]
Use of lipid-lowering drugs	71 (71.0)	64 (66.0)	0.448[*]
Previous cardiovascular event	31 (31.0)	25 (25.8)	0.384*
Body mass index (kg/m²)	31.4 ± 4.6	30.4 ± 3.9	0.098[†]
Waist circumference (cm)			
Male	107.9 ± 11.4	102.7 ± 9.3	**0.048**[†]
Female	103.6 ± 11.1	102.2 ± 8.6	0.442[†]
Fasting plasma glucose (mg/dL)	179.0 ± 71.1	150.2 ± 61.5	**0.003**[†]
HbA1c (%)	8.7 ± 2.0	8.3 ± 2.0	0.230[†]
Total cholesterol (mg/dL)	179.1 ± 37.1	171.4 ± 41.8	0.195[†]
HDL-cholesterol (mg/dL)			
Male	40.3 ± 11.1	39.5 ± 9.6	0.786[†]
Female	43.6 ± 9.0	43.8 ± 12.0	0.907[†]
LDL-cholesterol (mg/dL)	105.0 ± 32.9	97.3 ± 34.4	0.131[†]
Triglyceride (mg/dL)	150.0 (106.0-198.5)	131.0 (98.0-197.0)	0.405[‡]
Serum creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.3	0.806[†]
GFR (mL/min/1.73 m²)	84.9 ± 18.5	81.5 ± 21.4	0.247[†]
UAE (mg/dL)	11.1 (3.8-48.1)	5.6 (3.0-27.0)	0.070[‡]

Data are expressed as means ± standard deviation, median (interquartile range) or number of patients with the analyzed characteristic (%). *Chi-square test; †Student's *t*-test; ‡Mann-Whitney *U* test. UAE = urinary albumin excretion; GFR = glomerular filtration rate.

Table 4. Proportion of patients with type 2 diabetes who achieve therapeutic targets according to eating patterns

Therapeutic Targets	Eating Patterns		*P* value
	Unhealthy (*n* = 100)	Healthy (*n* = 97)	
Blood pressure – n (%)	50 (50.5)	49 (52.1)	0.822*
PR (95% CI)	1	1.03 (0.78-1.36)	0.822
PR adjusted† (95% CI)	1	1.08 (0.80-1.45)	0.628
PR adjusted§ (95% CI)	1	1.07 (0.78-1.47)	0.663
BMI – n (%)	16 (16.0)	14 (14.4)	0.844*
PR (95% CI)	1	0.90 (0.47-1.75)	0.760
PR adjusted† (95% CI)	1	1.08 (0.48-2.44)	0.844
PR adjusted‡ (95% CI)	1	1.07 (0.49-2.36)	0.859
Waist circumference – n (%)	8 (8.0)	6 (6.2)	0.783*
PR (95% CI)	1	0.77 (0.28-2.15)	0.621
PR adjusted† (95% CI)	1	1.40 (0.47-4.17)	0.551
PR adjusted‡ (95% CI)	1	0.93 (0.26-3.27)	0.905
Fasting plasma glucose – n (%)	31 (31.3)	46 (47.4)	**0.028***
PR (95% CI)	1	1.51 (1.06-2.17)	**0.024**
PR adjusted† (95% CI)	1	1.59 (1.01-2.34)	**0.018**
PR adjusted§ (95% CI)	1	1.47 (0.98-2.19)	0.060
HbA1c – n (%)	17 (17.0)	32 (33.0)	**0.013***
PR (95% CI)	1	1.94 (1.16-3.26)	**0.012**
PR adjusted† (95% CI)	1	2.61 (1.51-4.53)	**0.001**
PR adjusted§ (95% CI)	1	2.09 (1.17-3.74)	**0.013**
Triglycerides – n (%)	43 (48.3)	48 (55.2)	0.371*
PR (95% CI)	1	1.14 (0.86-1.52)	0.364
PR adjusted† (95% CI)	1	1.15 (0.86-1.53)	0.344
PR adjusted§ (95% CI)	1	1.11 (0.82-1.50)	0.501
HDL-cholesterol – n (%)	27 (30.3)	25 (28.4)	0.869*
PR (95% CI)	1	0.94 (0.59-1.48)	0.778
PR adjusted† (95% CI)	1	0.91 (0.59-1.40)	0.663
PR adjusted§ (95% CI)	1	0.81 (0.51-1.30)	0.387
LDL-cholesterol – n (%)	41 (46.6)	55 (63.2)	**0.034***
PR (95% CI)	1	1.36 (1.03-1.79)	**0.030**
PR adjusted† (95% CI)	1	1.32 (1.00-1.74)	0.052
PR adjusted§ (95% CI)	1	1.37 (1.01-1.86)	**0.042**

Data are expressed as number of patients with analyzed characteristic (%) and as the prevalence ratio (PR; 95% CI); *Chi-square test. †Model 1: adjusted for gender, age, economic status, current smoking, and diabetes duration. §Model 2: adjusted for gender, age, economic status, current smoking, diabetes duration, diabetes

treatment, physical activity, BMI, and energy intake. ‡Model 3: adjusted for gender, age, economic status, current smoking, diabetes duration, diabetes treatment, physical activity, and energy intake.

Therapeutic target definitions: blood pressure <140/90 mmHg, BMI <25 kg/m^2 or <27 kg/m^2 for the elderly; waist circumference <94 cm for men and <80 cm for women; fasting plasma glucose <130 mg/dl; HbA1c <7%; serum triglycerides <150 mg/dL; HDL-cholesterol >40 mg/dL for men and >50 mg/dL for women; LDL-cholesterol <100 mg/dL.

CAPÍTULO IV

CONSIDERAÇÕES FINAIS

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A importância do manejo dietético no tratamento do diabetes é reconhecida pelas organizações internacionais e nacionais de cuidado desta doença. Assim, a melhor estratégia dietoterápica para reduzir a glicemia em pacientes com diabetes tem sido constantemente avaliada. Diversos estudos foram realizados com o intuito de elucidar o papel dos alimentos e/ou nutrientes no controle metabólico e no desenvolvimento das complicações crônicas do diabetes. Em epidemiologia nutricional, a avaliação do consumo alimentar a partir de inquéritos dietéticos de indivíduos é fundamental para determinar a relação de causalidade entre dieta e doença. Cada vez mais se busca por inquéritos dietéticos que sejam confiáveis para realizar esta avaliação, visto que a complexidade da dieta humana representa um grande desafio para qualquer estudo que contemple sua relação com a doença, como no caso do diabetes e suas complicações.

Quando iniciei minhas atividades no grupo de pesquisa sobre Nutrição em Endocrinologia neste Programa de Pós-Graduação, deparei-me com o desafio de construir e validar um QFA para avaliar a dieta usual de pacientes com diabetes tipo 2. Além disso, a intenção era substituir o instrumento utilizado até então (três dias de registro alimentar com pesagem de alimentos) por um instrumento menos laborioso de avaliação do consumo alimentar, como o QFA.

Durante este doutorado, foi possível avaliar a sua reprodutibilidade em longo prazo e também determinar os seus coeficientes de calibração. A partir disso, aplicamos o QFA e investigamos a relação entre padrões alimentares consumidos usualmente e o controle metabólico de pacientes com diabetes tipo 2. O consumo de padrões alimentares tem sido estudado mais recentemente, considerando que os indivíduos ingerem refeições, e não nutrientes ou alimentos isoladamente, havendo interação entre os diferentes componentes da dieta. De fato, observou-se que os pacientes que consumiam um padrão alimentar saudável, rico em carboidratos integrais, laticínios, carne branca, peixe, frutas e verduras, possuiam menores valores de glicemia, hemoglobina glicada e colesterol-LDL. Por fim, recomendamos que as associações descritas no nosso estudo devam ser avaliadas em diferentes amostras de pacientes com diabetes, em coortes de longo prazo e, idealmente, em ensaios clínicos randomizados.