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Dissertação de Mestrado

Efeitos da Ingestão de Fibra Alimentar na Saúde do Metabolismo – Associação com Inflamação em Pacientes com Diabetes Melito Tipo 1

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Diabetes Melito Tipo 1

Aluna: Fernanda Sarmento Rolla Bernaud

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SUMÁRIO

FORMATO DA DISSERTAÇÃO DE MESTRADO

Esta dissertação de Mestrado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Metabolismo e Nutrição da Faculdade de Medicina da UFRGS, sendo apresentada na forma de 2 artigos científicos. Um artigo de revisão em português e um artigo original em inglês a ser submetido para publicação em periódicos Qualis A Internacional na Classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior- (CAPES).

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LISTA DE ABREVIATURAS

Capítulo I

DAC: doença arterial coronariana

AVC: acidente vascular cerebral

DM: diabetes melito

PNA: polissacarídeos não amido

AR: amido resistente

FA: fibra alimentar

PCR: proteína C-reativa

US: ultra-sensível

SM: síndrome metabólica

DASH: dietary approaches to stop hypertension

LISTA DE ABREVIATURAS

Capítulo II

T1D: type 1 diabetes

CRP: C-reactive protein

T2D: type 2 diabetes

WC: waist circumference

hs: high sensitive

UAE: urinary albumin excretion

DR: diabetic retinopathy

NPDR: non-proliferative diabetic retinopathy

BMI: body mass index

IHD: ischaemic heart disease

CVD: cardiovascular disease

MS: metabolic syndrome

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Artigo de Revisão

Fibra alimentar – ingestão adequada e efeitos sobre a saúde do metabolismo

FIBRA ALIMENTAR – INGESTÃO ADEQUADA E EFEITOS SOBRE A SAÚDE DO METABOLISMO

Título abreviado: Fibras e metabolismo

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Resumo

Os efeitos positivos da fibra alimentar estão relacionados, em parte, ao fato de que uma parcela da fermentação de seus componentes ocorre no intestino grosso, o que produz impacto sobre a velocidade do trânsito intestinal, sobre o pH do cólon e sobre a produção de subprodutos com importante função fisiológica. Indivíduos com elevado consumo de fibra parecem apresentar menor risco para o desenvolvimento de doença coronariana, hipertensão, obesidade, diabetes e câncer de cólon. O aumento na ingestão de fibras reduz os níveis séricos de colesterol, melhora a glicemia em pacientes com diabetes, reduz o peso corporal e foi associado com menor nível sérico de proteína C reativa ultra-sensível. Maior consumo de fibras e a ingestão de mais fibras do que o atualmente recomendado (14 g/1000 kcal) poderá trazer maior benefício à saúde, incluindo a redução de processos inflamatórios de baixo grau.

Descritores: fibras alimentares, doença crônica, inflamação.

Abstract

The positive effects of dietary fiber are related, in part, to a portion of the fermentation of components that occurs in the large intestine, which has an impact on the speed of digestion, on the pH of the colon and in the production of elements with important physiological function. Individuals with high fiber intake seem to have lower risk for developing coronary artery disease, hypertension, obesity, diabetes and colon cancer. The increase in fiber intake reduces serum cholesterol, improves blood glucose in patients with diabetes, reduces body weight and it was associated with lower serum C reactive protein ultrasensitive level. Increased fiber intake and eating more fiber than the currently recommended (14 g/1000 kcal) can bring greater health benefits, including reducing low-grade inflammation.

Keywords: dietary fibers, chronic disease, inflammation.

Introdução

O papel da ingestão das fibras tornou-se mais estudado nos últimos anos (1,2). O consumo adequado de fibras na dieta usual parece reduzir o risco de desenvolvimento de algumas doenças crônicas como: doença arterial coronariana (DAC) (3), acidente vascular cerebral (AVC) (4), hipertensão arterial (5), diabetes melito (DM) (6) e algumas desordens gastrointestinais (7). Além disso, o aumento na ingestão de fibras melhora os níveis dos lipídeos séricos (8,9), reduz os níveis de pressão arterial (5), melhora o controle da glicemia em pacientes com diabetes melito (DM) (10), auxilia na redução do peso corporal (11) e ainda atua na melhora do sistema imunológico (12).

A fibra alimentar (FA), também denominada fibra dietética, é resistente à ação das enzimas digestivas humanas e é constituída de polímeros de carboidratos, com três ou mais unidades monoméricas, e mais a lignina – um polímero de fenilpropano (13,14). Os componentes da FA dividem-se nos grupos: polissacarídeos não amido, oligossacarídeos, carboidratos análogos (amido resistente e maltodextrinas resistentes), lignina, compostos associados à FA (compostos fenólicos, proteína de parede celular, oxalatos, fitatos, ceras, cutina e suberina) e fibras de origem não vegetal (quitina, quitosana, colágeno e condroitina) (15).

De forma simplificada, as fibras são classificadas como fibras solúveis, viscosas ou facilmente fermentáveis no cólon, como a pectina, ou como fibras insolúveis como a celulose que tem ação no aumento de volume do bolo fecal, mas com limitada fermentação no cólon (13). Os efeitos positivos da FA estão relacionados, em parte, ao fato de que uma parcela da fermentação de seus componentes ocorre no intestino grosso, o que produz impacto sobre a velocidade do trânsito intestinal, sobre o pH do cólon e sobre a produção de subprodutos com importante função fisiológica (16).

As recomendações atuais de ingestão de FA na dieta variam de acordo com a idade, o sexo e o consumo energético, sendo a recomendação adequada em torno de 14g de fibra para cada 1.000 kcal ingeridas (17).

O objetivo deste artigo é fornecer informações sobre as FAs, seus diferentes tipos e fontes, seu papel no organismo e efeito sobre algumas doenças crônicas, com particular atenção para o seu efeito sobre a inflamação crônica em pacientes com DM, que reconhecidamente apresentam um estado crônico de inflamação de baixo grau (18).

Tipos de fibra alimentar e classificação quanto à sua solubilidade

As diversas frações da FA agrupam-se de acordo com seus componentes e características, determinando o tipo de fibra. Estes componentes são encontrados principalmente em alimentos de origem vegetal, como cereais, leguminosas, hortaliças e tubérculos, conforme apresentados na Tabela 1.

As fibras solúveis dissolvem-se em água, formando géis viscosos. Não são digeridas no intestino delgado e são facilmente fermentadas pela microflora do intestino grosso. São solúveis as pectinas, as gomas, a inulina e algumas hemiceluloses. As fibras insolúveis não são solúveis em água, deste modo não formam géis, e sua fermentação é limitada. São insolúveis a lignina, celulose e algumas hemiceluloses. A maioria dos alimentos que contêm fibras é constituída de um terço de fibras solúveis e dois terços de insolúveis (19).

Fisiologia e efeitos gastrointestinais das fibras

As características físico-químicas das fibras promovem efeitos locais e sistêmicos no organismo humano. As diferenças quanto à capacidade de retenção de água, viscosidade, fermentação, adsorção, entre outras, são responsáveis por implicações metabólicas (efeitos sistêmicos), bem como no trato gastrointestinal (efeitos locais) (20).

Os principais grupos de fibras que chegam ao intestino grosso são os polissacarídeos não amido (PNA), substâncias associadas a estes polissacarídeos, os amidos resistentes (AR) e oligossacarídeos (21). Estes componentes são parcialmente ou totalmente fermentados e utilizados como fonte energética pela microflora no cólon, convertidos em gases (hidrogênio, metano e dióxido de carbono) e ácidos graxos de cadeia curta (AGCCs), principalmente acetato, propionato e butirato. A disponibilidade de substrato no cólon resulta no aumento do número de bactérias e consequentemente no aumento do bolo fecal (22).

O incremento na produção de AGCCs, como resultado da fermentação, resulta na diminuição do pH intracelular e colônico. O meio mais ácido inibe a proliferação de organismos patogênicos bem como a formação de produtos de degradação tóxicos (23), além de reduzir a solubilidade dos ácidos biliares (24) e facilitar a absorção de cálcio, interferindo no metabolismo ósseo (24,25).

Prebiótico

Denominam-se prebióticos os ingredientes alimentares não digeríveis que afetam beneficamente o hospedeiro por estimular seletivamente o crescimento e/ou atividade de uma ou de um número limitado de bactérias no cólon, e desta forma beneficiam a saúde do hospedeiro (26).

A microbiota intestinal é formada por microorganismos benéficos, patogênicos e neutros, sendo 90% anaeróbios, bacteroides e bifidobactérias. Comparados a outros carboidratos resistentes à digestão, os prebióticos podem ser distintos por seu padrão de fermentação e estímulo seletivo do crescimento de bifidobactérias, capazes de produzir as vitaminas B1, B2, B6, B12, ácido nicotínico, ácido fólico e biotina (27).

No intestino grosso, as bifidobactérias fermentam os carboidratos não digeridos no intestino delgado, formando gases (hidrogênio, oxigênio, dióxido de carbono, amônia e metano) e produzindo AGCCs, principalmente butirato, utilizado preferencialmente como fonte de energia pelos colonócitos. A inulina e os frutoligossacarídeos são típicos prebióticos, naturalmente presentes em frutas e vegetais como banana, ameixa, chicória, yacón, cebola, alho, alho poró e trigo (28).

Fibra alimentar e Doenças Crônicas

Doença Cardiovascular (DCV)

O maior consumo de fibras na dieta foi associado com menor prevalência de DAC, AVC e doença vascular periférica (3,29,30). Os fatores de risco ligados a DCV como hipertensão, diabetes, obesidade e dislipidemia são também menos frequentes em indivíduos com maior consumo de fibras (31).

Resultados de estudos epidemiológicos mostraram que o consumo de grãos integrais está associado com menor risco para desenvolvimento de DAC (32). Estudo de coorte prospectivo com duração de 14 anos envolvendo um grande número de indivíduos do sexo masculino (n=42.850), com idade entre 40-75 anos mostrou que o quintil com maior consumo de grãos integrais foi associado a menor risco de desenvolvimento de DAC, *hazard ratio* = 0,82 (IC 95%: 0,70 – 0,96). O mesmo estudo comparou grupos com e sem adição de farelos de grãos integrais à dieta e o risco de desenvolvimento de DAC foi significativamente menor no grupo com maior adição de farelos, *hazard ratio* = 0,70 (IC 95%: 0,60 – 0,82) (33). Os autores sugerem que o farelo presente nos grãos integrais pode ser um fator chave nesta relação de redução de risco de DAC.

Dados de quatro estudos, incluindo 134.000 indivíduos indicaram uma redução de risco para AVC isquêmico em torno de 26% entre indivíduos com maior ingestão de FA ou grãos integrais (maior quintil) quando comparados com aqueles com menor consumo (menor quintil) (4,36). Outros estudos sugerem que a ingestão de frutas e vegetais está associada com menor risco para AVC isquêmico (37) e a efeitos favoráveis na inibição do processo de progressão da aterosclerose (38).

Uma revisão incluindo 10 coortes prospectivas, com seguimento de 6 a 10 anos, analisou a estimativa de associação entre ingestão de fibras e risco de DAC. Após o ajustamento para fatores demográficos, índice de massa corporal

(IMC) e estilo de vida, o incremento de 10 g/dia de fibra total ingerida foi associado respectivamente com uma redução de 14% e 27% no risco relativo para todos os eventos coronarianos e para morte decorrente destes eventos (39).

Hipertensão arterial

Estudos observacionais sugerem uma relação inversa entre a ingestão de fibras e níveis de pressão arterial (40,41). Alguns ensaios clínicos randomizados identificaram uma redução nos níveis de pressão arterial decorrente da ingestão de fibras na dieta (42, 43).

Uma meta-análise que incluiu 25 ensaios clínicos randomizados (5) observou uma variação na ingestão de fibras entre os grupos intervenção e controle entre 3,8 g e 125 g/dia. A ingestão de fibras na dieta foi associada a uma redução nos níveis da pressão arterial diastólica (média de quase 2 mm Hg). Entretanto, não se observou redução nos níveis de pressão arterial sistólica. Esta mesma meta-análise mostrou uma redução média em ambas, pressão arterial sistólica (quase 6 mm Hg) e diastólica (quase 5 mm Hg) em um subgrupo de estudos que avaliaram pacientes hipertensos e com pelo menos oito semanas de intervenção.

Recentemente, a *Dietary Approaches to Stop Hypertension* (conhecida como dieta DASH), que entre outros alimentos prioriza o consumo de frutas e vegetais, alimentos ricos em fibras, mostrou-se associada a uma redução dos níveis de pressão arterial em indivíduos com DM tipo 2, quando comparados a pacientes com DM tipo 2 sem este tipo de dieta (44).

Obesidade

Na década de 70, Heaton (45) propôs a ação das fibras como um obstáculo fisiológico ao consumo energético por três possíveis mecanismos: (1) as fibras ocupam o lugar das calorias e nutrientes da dieta; (2) aumentam a mastigação, o que limita a ingestão através da promoção e secreção de saliva e suco gástrico, resultando na expansão do estômago e aumento da saciedade; e (3) as fibras reduzem a eficiência da absorção de outros alimentos no intestino delgado. Ainda, os alimentos ricos em fibras têm uma densidade energética menor em comparação aos alimentos ricos em gorduras. Desta forma, alimentos ricos em fibras poderiam estrategicamente substituir a energia (calorias) dos demais alimentos que apresentam maior densidade energética (46).

A ingestão de fibras e vegetais mostrou efeito protetor contra o excesso de peso corporal em uma população com grande variedade de etnias (47). A avaliação de 16 ensaios clínicos randomizados sobre o efeito da suplementação de fibras na redução de peso corporal mostrou uma redução média de peso de 1,7 kg (grupo placebo) vs. 3,0 kg (grupo intervenção) em 4 semanas; enquanto que ao longo de 8 semanas a redução foi de 2,4 kg (grupo placebo) vs. 4,9 kg (grupo intervenção) (48). A maioria desses estudos utilizou fibras insolúveis, na forma de tabletes com doses médias de 2,5 g, fornecidos três vezes ao dia. As fibras solúveis goma-guar ou glucomannan foram utilizados em alguns ensaios.

Estudo recente mostrou que as fibras com características mais viscosas (pectinas, ß-glucanas e goma-guar) tiveram um efeito melhor na redução do apetite e ingestão energética aguda, quando comparadas às fibras com menor viscosidade (49)

Lipoproteínas

De forma geral os estudos relacionados às fibras abordam a utilização de fibras solúveis como aveia, psyllium, pectina, goma-guar, sugerindo que este tipo de fibra reduz os níveis séricos de colesterol total e LDL colesterol (50, 51). Uma meta-análise (8) mostrou que a ingestão de 2-10 g/dia de fibra solúvel foi associada a uma redução no colesterol total e LDL colesterol, -0,045 $mmol.L^{-1}$ (-1,73 mg/dl) e -0,057 $mmol.L^{-1}$ (-2,21 mg/dl), por cada grama de fibra/dia ingerida, respectivamente. Contudo, o efeito das diversas fibras solúveis nos lipídios plasmáticos não diferiu significativamente e os níveis de triglicerídeos e HDL colesterol não foram modificados (8).

Ensaios clínicos de maior duração com fibras solúveis, utilizando psyllium por seis meses e goma-guar por 12-24 meses, mostraram que o uso de psyllium por seis meses manteve uma redução nos níveis de LDL colesterol ao redor de 6,7% (52) enquanto o uso da goma-guar por 12 meses sustentou uma redução ao redor de 16,1% nos valores de LDL colesterol e de 25% ao longo de 24 meses (37,53).

Neoplasia Intestinal

A redução de risco de câncer provavelmente está envolvida com o consumo de frutas e hortaliças, ricos em fibra alimentar (FA) (54, 55).

Resultados do estudo *European Prospective Investigation on Cancer* que envolveu 510.978 indivíduos, com idade entre 25-70 anos, reportaram uma redução do risco de neoplasia colorretal ao redor de 40% quando sujeitos com uma ingestão de elevada de FA [maior quintil de ingestão de fibras (35 g/dia)] foram comparados àqueles com menor ingestão (15 g/dia) (56). Neste estudo o efeito protetor foi referido para todo tipo de fibra ingerida, sugerindo que o tipo e a escolha da fibra talvez sejam irrelevantes em relação aos benefícios observados.

Em relação às diferentes fontes de fibras, uma meta-análise que incluiu 25 estudos prospectivos mostrou que uma elevada ingestão de FA (3 porções/dia =90 g a mais na dieta usual), em especial as encontradas em cereais e grãos integrais, foi associada a uma redução de risco de câncer colorretal (RR=0,83; IC 95%: 0,78-0,89) (57).

Constipação

O aumento no consumo de FA é comumente utilizado na prevenção e tratamento da constipação. O farelo de trigo, os cereais integrais e suplementos de fibras são amplamente utilizados pelos consumidores, o que sinaliza um conhecimento comum dos efeitos benéficos das fibras (13).

Cummings (58) tabulou o efeito de diferentes fibras em relação ao aumento no peso fecal (em gramas) por cada grama de fibra ingerida, conforme segue: farelo de trigo, 5,4 g; frutas ou vegetais, 4,7 g; psyllium, 4,0 g; celulose, 3,5 g; aveia, 3,4 g; milho, 3,2 g; leguminosas, 2,2 g e pectina, 1,2 g. Terapias de primeira linha para a constipação geralmente incluem um aumento na ingestão de FA e líquidos (59). Psyllium é a única fibra viscosa que resiste à total fermentação através do transito intestinal, o que lhe confere efeito laxativo, pois as demais fibras viscosas são extensivamente fermentadas (60).

Por outro lado, uma inadequada ingestão de FA foi associada à constipação, um problema clínico comum na adolescência (61). Em estudo envolvendo 52 crianças com constipação crônica, Morais e colaboradores (62) identificaram que a ingestão de fibras destas crianças era significativamente menor quando comparadas àquelas com hábito intestinal normal (9,7 vs. 12,6 g/dia). Em outro estudo, crianças em idade pré-escolar, 10 gramas de farelo de fibras adicionadas ao consumo diário por quatro semanas, na forma de 2 porções de cereal integral com passas de uva, aumentou o peso do bolo fecal em 60%, além de aumentar a frequência das evacuações (63).

Diabetes Melito

O consumo de fibra solúvel parece reduzir a resposta glicêmica pós-prandial após as refeições ricas em carboidratos (64). Este efeito poderia ser explicado pela viscosidade e/ou propriedade geleificante das fibras solúveis, que desse modo retardam o esvaziamento gástrico e a absorção de macronutrientes a partir do intestino delgado. Entretanto, estudos prospectivos revelaram não ser a fibra solúvel a responsável, mas principalmente, o consumo de fibra insolúvel de cereais e grãos integrais que está consistentemente associado ao risco reduzido de DM tipo 2 (65, 66).

Uma meta-análise que incluiu 328.212 sujeitos, não mostrou associação entre redução de risco para DM tipo 2 e ingestão de fibras provenientes de frutas e vegetais, risco relativo (RR) para o quintil mais extremo 0,96 (IC 95%: 0,88-1,04) e 1,04 (IC 95%: 0,94-1,15) respectivamente (65). No entanto, um consumo elevado de fibras de cereais integrais foi associado significativamente com redução de risco para DM na maioria dos estudos avaliados (RR=0,67; IC 95%: 0,62-0,72) (65). Já um estudo prospectivo recente com duração de 11 anos, 3.704 participantes, mostrou que uma dieta caracterizada por uma ingestão com maior quantidade de vegetais e maior variedade de frutas e vegetais combinados, foi associada com redução de risco para DM tipo 2 (67).

Um ensaio clínico randomizado com pacientes com DM tipo 1 (n=63) aninhado a um estudo maior multicêntrico, avaliou por 24 semanas o efeito de uma dieta com alta ingestão de fibras, > 30 g/dia (DAF) sobre os níveis séricos da glicose e a incidência de hipoglicemia comparadas a uma dieta com baixa ingestão de fibras < 20 g/dia (DBF). A DAF reduziu os níveis da glicemia média diária em relação aos seus valores basais (média de 9% de redução) e também em relação aos valores observados no grupo com DBF (68). O número de eventos hipoglicêmicos no grupo DAF foi metade do observado no grupo com DBF (0,73 vs. 1,5 eventos por paciente por mês, respectivamente) (68).

Estudo observacional de caráter transversal (69) (n=175; DM tipo 2) mostrou maior presença de síndrome metabólica (SM) no grupo com consumo de alimentos com maior índice glicêmico (IG) (60% ± 6,3% vs. 57,5% ± 6,4%) e menor ingestão de fibras (17,0 ± 6,6 g vs. 21,2 ± 8,0 g) em comparação ao grupo de maior ingestão de fibras.

Resultados de uma meta-análise recente com 15 ensaios clínicos randomizados, envolvendo aumento na ingestão de fibras na dieta usual como intervenção, apontaram uma diferença global com redução média de 0,85 mmol/L (15,32 mg/dl) na glicose sérica de jejum a favor do grupo intervenção. Entretanto, os níveis de hemoglobina glicada não foram tão significativos, com uma redução de 0,26% (IC 95%: -0,02 e -0,51) (70).

Em estudo com 44 pacientes com DM tipo 2 e com SM, a suplementação de 10 g/dia de goma-guar por seis semanas (n=23) reduziu após seis semanas em relação aos níveis basais: hemoglobina glicada (inicial: 6,88 ± 0,99%; final: 6,57 ± 0,84%), ácidos graxos trans-insaturados [inicial: 7,08 mg/dl (4,6-13,68); final: 5,71 mg/dl (3,0-10,95)], circunferência da cintura (inicial: 103,5 ± 9,5 cm; final: 102,3 ± 9,7 cm) e excreção urinária de albumina (inicial: 6,8 mcg (3,0-17,5); final: 6,2 mcg (3,0-9,5) (71). Em outro estudo, com 214 pacientes com DM tipo 2, as fibras solúveis provenientes dos grãos integrais e das frutas foram negativamente associadas à presença de SM em pacientes diabéticos tipo2, sugerindo papel protetor nesta amostra (72).

A ingestão diária de 80 g de frutas/1.000 kcal ou 50 g de vegetais/1.000 kcal reduziu em 22% a chance de pacientes com diabetes tipo 2 apresentarem valores de pressão arterial média acima de 92 mm Hg (44).

Ingestão de Fibra Alimentar e processo inflamatório

A presença de inflamação está altamente correlacionada com o desenvolvimento de DAC (73). A DAC não é mais considerada apenas um resultado do armazenamento de colesterol sérico, mas também um processo inflamatório importante no desenvolvimento da aterosclerose (73).

Níveis elevados de proteína C-reativa (PCR) ultra-sensível (US), considerado um marcador inflamatório chave (74), têm sido relacionados à resistência à ação da insulina, ao desenvolvimento de DM e SM, assim como outros fatores de risco para DCV (75). Estudos demonstraram associação inversa entre a ingestão de fibras e níveis séricos de alguns marcadores inflamatórios (76, 77).

Ensaio clínico randomizado encontrou uma redução nos níveis de PCR US quando o consumo de FA foi aumentado na dieta. Esposito e colaboradores (76) estudaram 120 mulheres pré-menopáusicas e obesas; e uma dieta Mediterrânea (à base de vegetais, frutas, grãos integrais, oleaginosas, leguminosas, peixe e azeite de oliva) foi aplicada como intervenção em 60 destas mulheres. O grupo controle foi apenas instruído com informações gerais sobre as melhores escolhas de alimentos saudáveis. Após 24 meses, os níveis de PCR US do grupo intervenção tiveram significativa redução, em relação aos seus valores basais (inicial: 3,2 mg/L e final: 2,1 mg/L respectivamente), o mesmo não aconteceu no grupo controle (76).

Outro estudo, com 24 mulheres e 7 homens, mostrou que a ingestão de 30 g/dia de fibras contidas em uma dieta naturalmente rica em fibras (DASH) ou sob a forma de suplemento (psyllium), reduziu os níveis de PCR US, independente da forma de reposição das fibras. Entretanto, quando o grupo foi estratificado, esta redução não foi significativa para o grupo de obesos hipertensos (77).

Estudo aninhado ao *Nurses' Health Study,* com 902 mulheres com diabetes, observou que aquelas com o maior quintil de ingestão de grãos integrais apresentavam menores níveis de PCR em relação aquelas mulheres com o menor quintil de ingestão (5,52 mg/L vs 6,60 mg/L), que apresentavam respectivamente 35,4 g/dia e 4,75 g/dia de ingestão de fibras. A mesma tendência foi observada quando comparados os quintis de maior e menor ingestão de farelos de grãos integrais e de fibras de cereais (78). De maneira interessante, a diferença nos níveis de PCR foi de 18% para o maior quintil de fibras de cereais. Neste estudo, a ingestão de fibras totais e fibras de outros alimentos/fontes, incluindo frutas e vegetais não foi associada à diferença nos níveis de PCR.

Conclusão

A ingestão de fibras da dieta parece estar associada a uma redução significativa dos níveis de glicose, pressão arterial e de lipídeos séricos. Adicionalmente, há dados sobre redução de doenças crônicas, incluindo DCV, DM e neoplasia de cólon em indivíduos com maior ingestão de fibras.

Em pacientes com DM, a ingestão de fibras esta associada à redução dos níveis de pressão arterial, glicose e presença de SM e/ou seus componentes.

Em relação à inflamação de baixo grau, a ingestão parece estar associada a menores valores dos marcadores inflamatórios e poderia ser uma ferramenta no seu tratamento.

Uma ingestão de fibras de pelo menos 30 g/dia, bem como a variedade de alimentos fontes de fibras (frutas, verduras, grãos integrais e farelos) são fatores relevantes para que os benefícios descritos sejam alcançados.

Apesar de notáveis evidências de estudos epidemiológicos e experimentais sobre os benefícios da FA, ainda é limitada a indicação mais precisa da quantidade e o tipo de fibra a ser ingerida.

Estudos adicionais que envolvam intervenção e diferentes populações são ainda necessários para melhor confirmar estas observações.

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Tabela 1- Tipos de FA, grupos, componentes e principais fontes.

Tipo	Grupos	Componentes	Fontes
Polissacarídeos não amido	Celulose	Celulose (25% da fibra de grãos e frutas e 30% em vegetais e oleaginosas)	Vegetais (parede celular das plantas), farelos
	Hemicelulose	Arabinogalactanos, ß-glicanos, arabinoxilanos, glicuronoxilanos, xiloglicanos, galactomananos,	Aveia, cevada, vagem, abobrinha, maçã com casca, abacaxi, grãos integrais e oleaginosas
	Gomas e mucilagens	Galactomananos, goma guar, goma locusta, goma karaya, goma tragacanto, alginatos, agar, carragenanas e psyllium	Extratos de sementes: Alfarroba, semente de locusta; exudatos de plantas, algas, psyllium
	Pectinas	Pectina	Frutas, hortaliças, batatas, açúcar de beterraba
Oligossacarídeos	Frutanos	Inulina e frutoligossacarídeos (FOS)	Chicória, cebola, Yacón, alho, banana, tupinambo
Carboidratos análogos	Amido resistente e maltodextrina resistentes	Amido + produtos da degradação de amido não absorvidos no intestino humano saudável	Leguminosas, sementes, batata crua e cozida, banana verde, grãos integrais, polidextrose
Lignina	Lignina	Ligada à hemicelulose na parede celular. Única fibra estrutural não polissacarídeo – polímero de fenilpropano	Camada externa de grãos de cereais e aipo

Substâncias associadas aos polissacarídeos não amido	Compostos fenólicos, proteína de parede celular, oxalatos, fitatos, ceras, cutina, suberina	Componentes associados à FA que confere ação antioxidante a esta fração	Cereais integrais, frutas, hortaliças
Fibras de origem não vegetal	Quitina, quitosana, colágeno e condroitina	Fungos, leveduras e invertebrados	Cogumelos, leveduras, casca de camarão, frutos do mar, invertebrados

Adaptado de Tungland e Mayer (15).

Capítulo II

Artigo Original

Fiber intake and inflammation in type 1 diabetes subjects

FIBER INTAKE AND INFLAMMATION IN TYPE 1 DIABETES SUBJECTS

Running title: Dietary Fiber and inflammation

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ABSTRACT

Higher intake of dietary fiber is associated with lower risk of coronary heart disease, the leading cause of mortality among people with type 1 diabetes (T1D). Population-based studies have shown an inverse association between nutrition and high sensitivity C-reactive protein (hs-CRP). Few studies report the nutrition in individuals with T1D. We aimed to ascertain the association between fiber intake and hs-CPR levels. This cross-sectional study was conducted with 106 outpatients T1D; age 40 ± 11 years; diabetes duration of 18±8.8 years. Dietary intake was evaluated by 3-day weighed-diet records. Patients were categorized in 2 groups, according fiber intake (>20 g/day and <20 g/day). The group with fiber intake > 20 g/day had lower hs-CRP levels [median ($25^{th-}75^{th}$ 0.7 mg/dl (0.4-2.4) vs. 1.9 mg/dl (1.0-4.4); P = 0.002], than the other group. Controlled for HbA1c and energy intake, an inverse relation was observed between hs-CRP levels and total fiber [ß = - 0.030 (SE: 0.0120), P = 0.02], soluble fiber [ß = - 0.078 (SE: 0.0421), P = 0.06] and insoluble fiber [ß = - 0.039 (SE: 0.01761), P = 0.026]. Even, after additional adjustment fibers remained associated with lower hs-CRP levels. Total fibers were stratified in 4 groups: < 10 g/day, from 10 to 20 g/day, from 20 to 30 g/day and > 30 g/day; adjusted for HbA1c stratified in tertiles. Compared to the group who ingested < 10 g/day of total fiber (referent group), the group who consumed > 30 g/d had significantly lower hs-CRP levels [-2.45 mg/L, P=0.012] independent of the HbA1c values. Also, in comparison to the lowest tertile of HbA1c (the referent group), the subjects in the highest tertile had higher hs-CRP levels [1.387 mg/L, P=0.006], independent of the fiber intake. The present study suggests that an increased consumption of dietary fiber > 30 g/day may play a role in reducing inflammation and, thus the risk of CHD in individuals with T1D.

Keywords: Type 1 diabetes, fiber intake, inflammation.

INTRODUCTION

The consumption of dietary fiber, a group of polysaccharides and lignins of plant origin, has been associated with a lower risk of coronary heart disease (CHD) (1, 2), the leading cause of mortality among people with type 1 diabetes (T1D) (3). Epidemiologic studies have consistently shown that greater fruits and vegetables intakes are associated with a lower risk of incident cardiovascular events (4, 5).

Individuals that consumed more than 5 fruits and vegetables servings/d had a 26% reduction in risk of stroke (6) and a 17% reduction in risk of coronary heart disease (7) compared with those consuming less than 3 servings/d. Potential mechanisms for the protective effect of this class of food include its anti-inflammatory properties. Some population-based studies have shown an inverse association between nutrition and C-reactive protein (CRP), a marker of systemic inflammation (8-10). Particularly, a prudent dietary pattern characterized by high intakes of vegetables, fruit, and whole grains has shown to be related to lower concentrations of circulating CRP (11, 12).

In type 2 diabetes (T2D) individuals, the intake of soluble fibers, mostly from whole-grain foods and fruits, had a protective role for the presence of metabolic syndrome (MS) (13). Further, among women with T2D, intakes of whole grains, bran and cereal fiber were associated with lower levels of CRP (14).

It’s also well known that patients with diabetes have a low grade-inflammation status (15), and it has been speculated if this low-grade systemic inflammation could be implicated not only in the pathogenesis of insulin resistance and the metabolic syndrome (16), but also in the pathogenesis of diabetic microvascular complications (17, 18) and cardiovascular disease (17-19) in T1D.

Few studies account about the nutrition in individuals with T1D (20-22). In men with T1D, an increased saturated fat intake and a lower intake of cereal fiber predicted a higher waist circumference (WC), a lower polyunsaturated fat intake and a lower glycemic index of the diet determined lower WC (20).

Therefore, our main aims were to describe the nutritional pattern of our sample with T1D subjects by fiber intake status and to report, if present, a possible association between high sensitive (hs)-CRP levels and fibers intake.

SUBJECTS AND METHODS

Subjects

This cross-sectional study was performed with patients with T1D who consecutively attended the Endocrine Division's outpatient clinic of the Hospital de Clínicas de Porto Alegre, Brazil. T1D was defined as: onset before 40 years of age, presence of ketonuria or ketonemia in the diagnosis and use of insulin to maintain life. The patients were selected based on the following criteria: no dietary counseling by a registered dietitian during the previous six months, age > 18 years, duration of diabetes over five years. Patients with renal failure, symptomatic heart failure (class III or IV) or acute cardiovascular event in the preceding 6 months (stroke, heart attack as myocardial infarct and pulmonary acute edema), and incapacity to perform weighed diet records were excluded from the study. Medications in current use were maintained, except for statins.

Patients with hs-CRP≥ 10 mg/L were also excluded this analyze, because there was the possibility of other inflammatory condition.

All participants gave their written informed consent to the protocol, which was approved by the ethics committee of Hospital de Clínicas de Porto Alegre. The recruitment process occurred from January 2011 to December 2011.

Clinical evaluation

Medical history was taking by a physician, subjects undergone to questions regarding current lifestyle, demographic information, and medication. Patients were self-identified as white or non-white (mixed or black) and they were classified as current smokers or noncurrent smokers. Current alcohol intake was categorized as present for the consumption of any kind of alcoholic beverage. The frequency of exercise, according to activities during a typical day was graded into four levels based on a standardized questionnaire as described previously (23). Level one was considered as sedentary.

Sitting blood pressure was measured twice after a 10-min rest, in the left arm, using a digital sphygmomanometer (Omron® HEM-705 CP). Hypertension was defined as blood pressure ≥ 140/90 mmHg measured on two occasions or use of antihypertensive drugs (24). Complete physical examination was performed for all patients.

Patients were classified according presence of nephropathy using a random spot urine sample or 24-h timed urine collection (at least two sample 6 months apart), normoalbuminuria was considered when urinary albumin excretion rate (UAE) < 17 mg/L or < 20 µg/min; microalbuminuric when UAE was 17-174 mg/L or 20-200 µg/min, and macroalbuminuric when UAE was > 176 mg/L or UAE > 200 µg/min at least twice in a 6-month period apart (25).

Diabetic retinopathy (DR) was evaluated by direct and indirect ophthalmoscopy after mydriasis by an ophthalmologist, and the severity was classified using the Global Diabetic Retinopathy Group scale (26). Patients were classified as: 'absence of DR', 'mild non-proliferative DR' (NPDR), 'moderate NPDR', 'severe DR', and proliferative DR' (PDR). For the analyses the patients were divided in two groups: absence of DR and presence of any degree of DR.

Nutritional evaluation

The body weight and height of patients (without shoes or coats) were obtained using an anthropometric scale (Filizola®, Filizola Balanças Industriais S.A. Brazil) with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. Then body mass index (BMI) (kg/m²) was calculated. Waist circumference was measured midway between the lowest rib margin and the iliac crest, near the umbilicus. Flexible, non-stretch fiberglass tape was used for measurements.

The patient's usual diet was assessed by means of 3-day weighed diet records (two non-consecutive week days and one weekend day, with an interval of about seven days between them) as previously standardized (27) Patients were issued commercial scales (1-2000 g; CUORI®/CE-cuo-840, Italy) and measuring cups (25-250 mL; Marinex®, Brazil) and detailed explanation and demonstration were given to each participant. Patients were considered adherent when the ratio of protein intake estimated by weighed diet records to protein intake estimated by nitrogen output (protein intake-weighed diet records/protein intake-nitrogen ratio) was 0.79 to 1.26 (28). Completeness of urine collection was confirmed by 24-h urinary creatinine measurements.

Nutrients from the dietary records were analyzed using the Nutribase 2007 Clinical Nutritional Manager software version 7.14 (Cybersoft, Phoenix, AZ., USA) and updated (29). Data were collected from January/2011 until December/2011. Data from nutrients were expressed as a percentage of total daily energy (%), in crude amounts (g/day) and g/kg weight. Nutrient data on frequently consumed foods were updated if necessary and/or complemented with data obtained from local manufacturers of specific industrialized foods.

The total, soluble and insoluble fiber content was estimated according to data provided in the CRC Handbook of Dietary Fiber in Human Nutrition (30). To analyze the consumption of fiber according to origin, foods were classified as whole-grains (included both intact and pulverized forms), beans and legumes, fruits, tuberous (potatoes, sweet potatoes, cassava and yams) and vegetables A and B, according to their carbohydrate content (%) of crude weight: group A (5%), vegetables from group B (10%). The following ingredients in the database were considered whole grains: whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal and whole corn flour, brown rice, whole rye and whole rye flour, whole barley and bulgur (31).

Laboratory methods

UAE rate was measured by immunoturbidimetry [MicroAlb Sera-Pak® immuno microalbuminuria; Bayer, Tarrytown, NY on Cobas Mira Plus (Roche®); mean intra-assay and interassay CVs of 4.5 and 7.6%, respectively]. HbA1c test was measured by a high-performance liquid chromatography system (reference range 4.7 - 6.0%) (Merck- Hitachi 9100; Merck®, Darmstadt, Germany). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica®). Serum creatinine was measured by the Jaffe method, serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (ADVIA® 1800 AutoAnalyzer, Germany), and HDL cholesterol was measured by the homogeneous direct method (ADVIA® 1800 AutoAnalyzer, Germany). LDL cholesterol was calculated using the Friedewald formula (32). CRP-hs was measured by turbidimetry method (ADVIA® 1800 AutoAnalyzer, Germany) and fibrinogen was determined by the Clauss clotting method, which measures the rate of fibrinogen conversion to fibrin in a diluted sample under the influence of excess thrombin. Urinary urea was measured by an enzymatic ultraviolet method (ADVIA® 1800 AutoAnalyzer, Germany).

Statistical analysis

Data are presented as mean ± SD, frequency (%) or median ($P25^{th}$-$P75^{th}$). Baseline characteristics were compared by fiber intake status using the Student's *t* test, Mann-Whitney *U* test or Chi Square (λ^2) test. Pearson correlation was used to describe the correlation between hs-CRP (log transformed) and others variables.

To determine the relationship among hs-CRP levels and fiber we performed a General Linear Model (with gamma regression) with hs-CRP levels as the dependent variable and fiber, glicemic control, and others nutrients as predictor variables.

The analyses were performed in PASW program, (Chicago, IL).

RESULTS

Among 137 consecutive eligible patients, six of them refused to participate; fourteen had hs-CRP levels above 10 mg/L and eleven were excluded due to compliance issues, unable to complete diet records. Thus, 106 patients were included. The laboratory and clinical characteristics of excluded group was not different from the subjects included in this study. The mean age was 40 ± 11 years and diabetes duration of 18 ± 8.8 years, 52.8% (n=56) were men, predominantly Caucasian 85.9% (n=91) and noncurrent smokers 91.5% (n=97).

Table 1 shows the main clinical and laboratory characteristics of patients according to median of total fiber intake. The group who had higher fiber intake (> 20 g/day), was more frequently constituted by men (71.2%) and was less frequently sedentary (34.6%); lower insulin dose [(0.6 ± 0.2 UI/kg vs. 0.8 ± 0.3 UI/kg), P=0.012, and had lower hs-CRP levels [median ($25^{th-}75^{th}$), 1.9 mg/dl (1.0-4.4) vs. 0.7 mg/dl (0.4-2.4); P = 0.002], than the group who ingested less fiber (<20 g/day). There were no differences for proportion of Caucasian, current smoking, alcohol intake, presence of hypertension, blood pressure levels, BMI, waist circumference or presence of microvascular complications. Either for plasma glucose, HbA1c test, cholesterol levels.

Regarding daily nutrients intake, the group who consumed > 20 g/day of fiber presented significantly higher energy intake (kcal/day and kcal/weight), higher intake (crude and g/kg weight) of carbohydrates and protein than the group that consumed up to 20 g/day. No difference was observed when evaluated the percentage of total energy of protein, carbohydrates and fat (% energy). The difference in intake of total energy of saturated fatty acid was only borderline. Individuals who ingested below of 20 g/day consumed more saturated fat (10.4 ± 2.7%) vs. (9.3 ± 3.5%), $P = 0.06$, than those with higher fiber intake. Even when we included the total energy of saturated and monounsaturated fatty as the same group, we did not find difference by the status of fiber intake.

The mean daily intake of nutrients and total fibers from certain foods according median of total fiber intake is described in Table 2.

The group with total fiber intake higher than 20 g/day consumed more fiber from fruits, vegetables A and B, legumes and beans than the subjects with less consumption.

To determine the relationship between fibers intake and hs-CRP levels we performed additional analyses. First, to understand others variables possibly involved with the inflammation status, correlations between the hs-CRP levels (log transformed) with others variables were performed. The hs-CRP levels were correlated with HbA1c ($r = 0.29$, $P = 0.002$), total energy intake, kcal/day and kcal/weight ($r = -0.26$, $P = 0.008$; $r = -0.31$, $P = 0.001$, respectively), crude intake and weight (g/kg) of protein ($r = - 0.34$, $P = 0.001$; $r = -0.39$, $P <0.001$) and carbohydrate ($r = -0.26$, $P = 0.007$; $r = -0.28$, $P = 0.004$), besides of dietary total fiber intake ($r = -0.30$, $P = 0.002$; $r = -0.33$, $P < 0.001$), soluble fiber ($r = -0.24$, $P = 0.012$; $r = -0.27$, $P = 0.005$) and insoluble fiber ($r = -0.30$, $P = 0.002$; $r = -0.33$, $P = 0.001$). The fatty was not correlated with hs-CRP in this sample.

The regression coefficients of dietary total fiber, soluble fiber and insoluble fiber for predicting hs-CRP levels from a Generalized Linear Model are shown in Table 3. The results of analyses using unadjusted and adjusted for covariates are presented. After control for HbA1c and energy intake, a significant inverse relation was observed between hs-CRP level and total, soluble and insoluble fiber intake. After adjustment for Hba1c and protein or carbohydrates intake, the total, soluble and insoluble fibers remained associated with lower hs-CRP levels. Of note, HbA1c also remained associated with hs-CRP levels in all models studied. We also analysed in separate models including sex, smoking and physical activity, and fiber intake remained inversely associated with hs-CRP level.

Based on these results and to examine potential differences between the amount of fiber intake and the levels of HbA1c in relation to hs-CRP concentrations, we performed models considering the total fibers stratified in 4 groups according with the following intake: < 10 g/day, from 10 to 20 g/day, from 20 to 30 g/day and > 30 g/day; adjusted for HbA1c stratified in tertiles. The regression coefficients of these variables for predicting hs-CRP are presented in Table 4. Compared to the group who ingested < 10 g/day of total fiber (referent group), the subjects who consumed > 30g had significantly lower hs-CRP levels [-2.45 mg/L, P=0.012] independent of the HbA1c values. Also, in comparison to the lowest tertile of HbA1c (the referent group), the subjects in the highest tertile had higher hs-CRP levels [1.387 mg/L, P=0.006], independent of the fiber intake.

We also examined the associations of total, soluble and insoluble fibers intake and HbA1c with hs-CRP levels stratified in tertiles (first from 0.0 to 0.72

mg/L; second from 0.721 to 2.81 mg/L and thirdly from 2.811 to 10 mg/L), as illustrated in Figure 1. Subjects with hs-CRP levels in second and last tertile had significantly lower consumption of total fiber, and soluble fiber (Figure 1-A e B) when compared with individuals in the first tertile of hs-CRP (lowest levels). No difference for ingestion was observed between second and third tertiles. The group in the highest tertile of hs-CRP ingested less insoluble fiber than the subjects in first tertile (Figure 1-C). In addition we observed that the subjects with hs-CRP levels in the third tertile had superior HbA1c levels when compared with second and first tertiles of hs-CRP (Figure 1-D). There was no difference between the second and the first tertile of hs-PCR for HbA1c levels.

DISCUSSION

The present study showed an inverse association between serum concentration of hs-CRP and the consumption of dietary fiber (total, soluble and insoluble fiber) in T1D patients. Subjects consuming higher amounts of dietary fiber had lower hs-CRP levels. After adjusting for possible confounds, the association persisted for all types of dietary fiber intake. When the ingestion of total fiber is higher than 30 g/day, it was demonstrated a still lower association with hs-CRP levels. Of note, the amount of dietary total fiber intake (>30 g/day) found in this study for association with lower hs-CRP levels was not different those recommended to the general population and for subjects with diabetes as American Diabetes Association recommendation (14 g/1000kcal) (33).

In the current study, the median of total dietary fiber intake was 20 g/day. The main sources of dietary fiber, in the group that intakes higher than 20 g/day, were fruits, vegetables (A+B), legumes and beans. A prospective study evaluated the association between quantity and variety of fruit and vegetables intake and incident of T2D (34). Their results indicated that a greater quantity of combined fruits and vegetables intake was associated with 21% lower hazard of T2D [HR 0.79 (95% CI 0.62-1.00)] comparing the extreme tertiles [highest tertile = 5.7 (5.0-6.8) portions/day and the first tertile = 2.1 (1.6-2.5) portions/day], in adjusted analyses including variety. When they compared extremes tertiles of variety of fruits (6.9 ± 1.2 vs. 2.0 ± 1.0 items/week), vegetable (11.4 ± 1.5 vs. 5.5 ± 1.4) and combined fruit and vegetable intake (16.3 ± 8.0 vs. 8.0 ± 1.8), a greater variety of these intakes was associated with lower hazard of T2D, 30%, 22% and 39%, respectively.

The protective role of foods rich in soluble fibers was previously evaluated in T2D patients with metabolic syndrome (13). Total fiber and soluble fiber intake from whole-grain foods and fruits were negatively associated with metabolic syndrome. The mean daily intake of total fiber (20.3 ± 7.8 g/day) of patients without metabolic syndrome in that study was similar to the median ($P25^{th}$- $P75^{th}$) [20.0(14.9-25.5)] of daily total fiber intake in our study with T1D patients.

Data from the EURODIAB Complications Study (20), a cross-sectional in T1D also reported a mean of total fiber intake of 20.0 g/day, and protein (percentage of energy) 17.4%, both similar with our findings. The consumption of total fat intake (percentage of energy, 37.9%) observed in the European study was higher than in our study, independent of fiber intake status 33.6% (fiber < 20 g/day) and 30.7% (fiber > 20 g/day). The difference is explained by higher intake of monounsaturated and saturated fat. Similar finding was also reported in an American population of T1D individuals (21), a higher intake of saturated fat (percentage of energy) was observed in comparison to our results (12.9% vs. 10.4%). Our patients had higher intake of carbohydrates (percentage of energy) than both studies reported before, 48.4% vs. 41.9% (20) and 44% (21). These data show the few literature about fiber intake and the T1D population.

The association of a high intake of fruits and vegetables with a lower risk of mortality from ischaemic heart disease (IHD) was demonstrated in European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart Study (35). In that study, the consumption of at least eight portions (80 g each) of fruits and vegetables a day had a 22% lower risk of fatal IHD compared with those consuming fewer than three portions a day.

The role of inflammation in the etiology of several chronic diseases has been supported by epidemiological evidence and the most notable being cardiovascular disease (CVD), diabetes and several types of cancer (36, 37, 38). The hs-CRP levels consistently predict positive associations with chronic conditions, including malignant disease (39 - 42).

Although several studies have examined associations between dietary fiber intake and serum hs-CRP levels (14, 43, 44, 45) there are no available data in the literature about the effects of dietary fiber on systemic inflammation among T1D patients. Our findings are consistent with previous observational and clinical intervention studies that investigated the relationship between dietary fiber intake and serum hs-CRP levels (14, 43, 45, 46) in general population. In our sample of T1D subjects that consumed >30 g/day of total fiber had lower levels of hs-CRP (-2.450 mg/L) than those that ingested <10 g/day.

Ma et al. (46) using cross-sectional and longitudinal data from 524 healthy adults, participants of Seasonal Variation of Blood Cholesterol Levels Study (SEASONS), reported an inverse association between intake of total dietary fiber (separately for soluble and insoluble fiber) and hs-CRP concentrations. The coefficient for the cross-sectional effect of dietary total fiber was -0.01, and -0.02 for insoluble dietary fiber, adjusted for covariates. Our findings for the effect were somewhat higher, -0.042 for total fiber, – 0.098 for soluble fiber, and -0.057 for insoluble fiber. When we stratified the total fiber intake, this effect was even higher for the group that consumed > 30 g/day of total fiber. This may be due to the differences in characteristics of studied population, and maybe in T1D subjects the effect of fiber could be higher than in non diabetic individuals.

Ajani et al., from cross-sectional data in general population, reported that the odds ratio (OR) of likelihood of elevated hs-CRP levels was 0.49 (95% CI: 0.37-0.65) for the highest quintile of total fiber intake (32 g/day) compared with the lowest quintile (5.1 g/day) (43).

In a multiethnic cohort of early stage breast cancer survivors, Villaseñor et al. (44) investigated the relationship between intake of total, soluble, and insoluble dietary fiber with the acute phase marker of inflammation, hs-CRP . An inverse association of total fiber intake (ß = -0.029; 95% CI -0.049, -0.008; P= 0.006) and insoluble dietary fiber (ß = -0.039; 95% CI -0.064, -0.013; P = 0.003) with hs-CRP levels. When they considered only hs-CRP (≥3 mg/L) and tertiles of total, soluble and insoluble dietary fiber intake, the association was maintained only for the highest tertile of insoluble fiber (mean = 15.5 ± 3.4 g/day).

F. de Mello et al. observed that after a 3 month dietary intervention with an experimental diet high in fatty fish, bilberries and wholegrain products (Healthy Diet), or a whole-grain-enriched diet (WGED) reduced the hs-CRP levels in individuals with impaired glucose metabolism and features of the metabolic syndrome when compared with a diet low in fiber (control group). They also observed that both diets (Healthy and WGED) reduced the 2h plasma glucose levels in comparison to control diet (mean ± SD: 120.7 ± 30.6 mg/dL vs. 109.9±30.6 mg/dL) and (118.9±28.8 mg/dL vs. 109.9 ± 34.2 mg/dL) respectively (47). They did not report data about HbA1c.

The cross-sectional nature of this study is a limitation that does not allow the evaluation of causality due to uncertain temporality of the associations. Nevertheless, this design allowed assessing the usual diet of T1D patients. Another possible limitation was the high average of HbA1c in this sample. However, the cohort enrolled in this study was represented by unselected adult T1D routinely attending in our endocrine outpatient clinic and can represent the real patients out of clinical trials, as already observed in the multicenter study conduced in different regions of Brazil (48). Finally, the hs-CRP levels are not the same that cardiovascular event and could be an intermediary outcome. On the other hand, it is well known that the description of CV events in T1D patients is very difficult being demonstrated, once that these patients are young and long time studies are needed. In this scenario, the hs-CRP level can be considerate an important marker and predictor of CV risk.

In conclusion, the results of the current study show that a higher consumption of dietary fiber is associated with lower hs-CRP levels in patients with T1D. An increased consumption of dietary fiber, > 30g/day, may play a role in reducing inflammation and, thus the risk of CVD in individuals with T1D. Randomized controlled trials of high and low fiber diets are needed to support public health recommendations.

Disclosure

All authors have no conflict of interest to declare.

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Table 1. Clinical and laboratory characteristics of patients with type 1 diabetes according to the median for total fiber intake.

	< 20g/d	**> 20g/d**	**P**
n	54	52	
Age (years)	39.1 ± 11.6	40.9 ± 10.5	0.426†
Caucasian (%)	92.6	78.8	0.117‡
Male (%)	35.2	71.2	<0.001‡
Diabetes duration (years)	18.2 ± 9.5	17.8 ± 8.1	0.378†
Current smoking (%)	13.0	3.8	0.092‡
Frequency of exercise: level 1* (%)	61.1	34.6	0.028‡
Current alcohol intake (%)	44.4	42.3	0.824
BMI (kg/m²)	24.3 ± 3.6	24.5 ± 3.4	0.549†
Waist circumference (cm)			
Female	78.9 ± 9.2	81.0 ± 8.6	0.448†
Male	84.7 ± 8.4	86.0 ± 9.6	0.607†
Insulin (UI/kg)	0.8 ± 0.3	0.6 ± 0.2	0.012†
Office systolic blood pressure (mmHg)	125.1 ± 15.0	124.6 ± 17.6	0.867†
Office diastolic blood pressure (mmHg)	75.4 ± 11.7	74.3 ± 9.6	0.610†
Hypertension (%)	46.3	32.7	0.152‡
Presence of nephropathy (%)	16.7	11.5	0.449‡
Presence of diabetic retinopathy (%)	44.4	32.7	0.214‡
Fasting plasma glucose (mg/dl)	197.7 ± 132.0	200.2 ± 109.7	0.915†
HbA1c test (%)	9.1 ± 2.1	9.0 ± 1.9	0.752†
Total cholesterol (mg/dl)	190.4 ± 32.5	185.1 ± 36.7	0.434†
HDL cholesterol (mg/dl)			
Female	66.1 ± 14.9	69.1 ± 15.5	0.542†
Male	50.3 ± 10.2	53.4 ± 13.7	0.354†
LDL cholesterol (mg/dl)	112.0 ± 26.3	111.7 ± 38.6	0.959†

Triglycerides (mg/dl)	82.0 (59.8-114.2)	79.5 (57.8-114.8)	0.799†
hs-CRP (mg/L)	1.9 (1.0-4.4)	0.7 (0.4-2.4)	0.002†
Fibrinogen (mg/dl)	361.0 (311.5-448.0)	349.0 (271.0-410.0)	0.062†
UAEr (mg/24-h)	7.9 (0.0-21.9)	6.0 (0.0-12.0)	0.604†
Serum creatinine (mg/dl)	0.9 ± 0.4	0.9 ± 0.3	0.721†

Data are means ± SD or median ($P25^{th}$- $P75^{th}$), or number of patients with the analyzed characteristic (%). *Level 1 = sedentary; hs-CRP, high sensitive C-reative protein; UAEr, urinary albumin excretion rate. † Student's *t* test; ‡ λ^2 test.

Table 2. Daily intake of nutrients of type 1 diabetes according to the median total fiber intake.

	< 20g/d	> 20g/d	P
n	54	52	
Energy (kcal/day)	1842.1 ± 558.7	2376.4 ± 628.7	< 0.001†
Energy (kcal/weight)/day	28.6 ± 8.0	33.0 ± 8.4	0.006†
Carbohydrates			
Crude intake (g)	220.0 ± 66.1	302.1 ± 88.0	< 0.001†
Weight (g/kg)	3.4 ± 1.0	4.2 ± 1.3	< 0.001†
Energy (%)	48.4 ± 8.0	51.4 ± 8.6	0.074†
Protein			
Crude intake (g)	82.6 ± 31.5	108.3 ± 35.3	< 0.001†
Weight (g/kg)	1.3 ± 0.5	1.5 ± 0.4	0.007†
Energy (%)	18.0 ± 3.7	18.3 ± 3.4	0.616†
Total fat			
Crude intake (g)	70.0 ± 31.6	82.4 ± 35.3	0.011†
Weight (g/kg)	1.1 ± 0.4	1.1 ± 0.5	0.394†
Energy (%)	33.6 ± 8.8	30.7 ± 9.6	0.110†
Saturated fatty acid			
Crude intake (g)	22.1 ± 10.4	24.5 ± 10.8	0.247†
Weight (g/kg)	0.3 ± 0.1	0.3 ± 0.1	0.952†
Energy (%)	10.4 ± 2.7	9.3 ± 3.5	0.059†
Monounsaturated fatty acid			
Crude intake (g)	24.6 ± 11.6	28.4 ± 12.7	0.107†
Weight (g/kg)	0.4 ± 0.2	0.4 ± 0.2	0.530†
Energy (%)	11.7 ± 3.5	10.6 ± 3.4	0.098†
Polyunsaturated fatty acid			
Crude intake (g)	11.6 (8.3-19.9)	18.4 (10.6-26.0)	0.026§
Weight (g/kg)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.148§
Energy (%)	6.0 (4.2-10.0)	7.1 (4.6-0.4)	0.733§
Trans fatty acid – crude intake (g)	0.1 (0.0-0.3)	0.1 (0.0-0.4)	0.069§
Cholesterol (mg)	239.9 ± 148.4	239.0 ± 116.3	0.972†
Total fiber (g)			

Crude intake (g)	14.6 ± 3.5	27.2 ± 6.8	< 0.001†
Weight (g/kg)	0.2 ± 0.1	0.4 ± 0.1	< 0.001†
Soluble fiber			
Crude intake (g)	4.3 ± 1.3	7.8 ± 2.1	< 0.001†
Weight (g/kg)	0.1 ± 0.0	0.1 ± 0.0	< 0.001†
Insoluble			
Crude intake (g)	10.5 ± 2.8	19.4 ± 5.1	< 0.001†
Weight (g/kg)	0.2 ± 0.1	0.3 ± 0.1	< 0.001†
Fibers from fruits			
Total fiber (g)	1.4 (0.2-2.7)	3.0 (1.4-4.9)	0.005§
Fibers from vegetables (A+B)			
Total fiber (g)	1.1 (0.5-2.5)	2.8 (1.5-4.0)	0.001§
Fibers from Tuberous			
Total fiber (g)	0.4 (0.0-0.76)	0.2 (0.0-0.8)	0.062§
Fibers from whole-grain foods			
Total fiber (g)	0.4 (0.0-3.8)	1.1 (0.0-4.5)	0.104§
Fibers from legumes and beans			
Total fiber (g)	2.5 (0.1-6.7)	8.4 (5.5-12.7)	< 0.001§

Data are means ± SD or median ($P25^{th}$- $P75^{th}$). † Student's *t* test; § Mann-Whitney *U* test.

Table 3. Regression coefficients Beta (ß) of dietary total, soluble and insoluble fiber for predicting hs-CRP level according to a generalized linear model

	Unadjusted		Adjusted[1]		Adjusted[2]		Adjusted[3]	
	ß (SE)	P	ß (SE)	P	ß (SE)	P	ß (SE)	P
Total fiber (g/day)	-0.039 (0.0118)	0.001	-0.030 (0.0120)	0.02	-0.037(0.0140)	0.007	-0.042 (0.0134)	0.002
Soluble fiber (g/day)	-0.106 (0.0417)	0.011	-0.078 (0.0421)	0.06	-0.092 (0.0426)	0.03	-0.098 (0.0426)	0.022
Insoluble fiber (g/day)	- 0.053 (0.0160)	0.001	-0.039 (0.0176)	0.026	-0.050 (0.0194)	0.009	-0.057 (0.0184)	0.002

[1]Adjusted for HbA1c and energy intake (kcal/weight).

[2]Adjusted for HbA1c, weight (g/kg) of protein.

[3] Adjusted for HbA1c and weight (g/kg) of carbohydrate.

Table 4. Regression coefficients Beta (ß) of different amounts of dietary total fiber and tertiles of HbA1c for predicting hs-CRP levels according to a generalized linear model

	ß (SE)	P
Total fiber		
<10g/day	-	-
10.01-20g/day	-0.507 (0.8407)	0.546
20.01-30g/day	-0.986 (0.8562)	0.250
>30g/day	-2.450 (0.9744)	0.012
HbA1c		
Tertile 1	-	-
Tertile 2	0.186 (0.4992)	0.709
Tertile 3	1.37 (0.5041)	0.006

SE: standard error. First tertile of HbA1c from 6.3 to 8.0 %; second from 8.01 to 9.3%; and thirdly > 9.3%

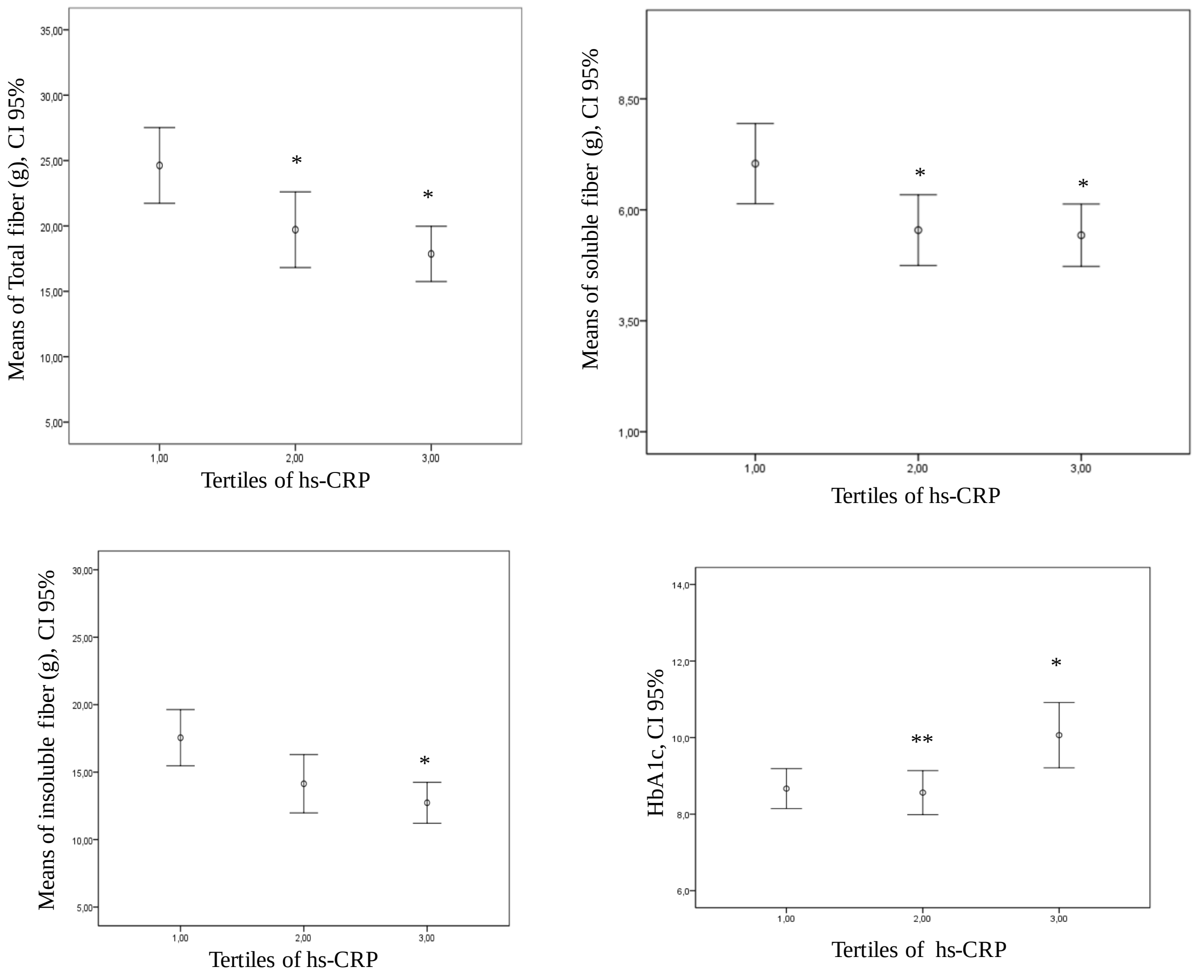

Figure 1. Unadjusted mean total fiber intake (A), soluble fiber intake (B), insoluble fiber intake (C) and HbA1c % (D) in tertiles of hs-CRP (mg/L) for 106 subjects with type 1 diabetes. hs-CRP levels stratified in tertiles (first: 0.0 to 0.72 mg/L; second: 0.721 to 2.81 mg/L and thirdly: 2.811 to 10 mg/L). * for difference to the first tertile and ** for difference to the thirdly tertile, P < 0.001.