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Efeito da qualidade do carboidrato da dieta sobre o controle glicêmico e a saciedade em pacientes com Diabetes Melito tipo 2

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Doutorado

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Flávia Moraes Silva

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

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"Tenho a impressão de ter sido uma criança brincando à beira-mar, divertindo-me em descobrir uma pedrinha mais lisa ou uma concha mais bonita que as outras, enquanto o imenso oceano da verdade continua misterioso diante de meus olhos".

(Isaac Newton)

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FORMATO DA TESE DE DOUTORADO

A presente tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, sendo apresentada através de dois manuscritos originais acerca do tema estudado:

1. Artigo original referente à revisão sistemática com meta-análise de ensaios clínicos randomizados acerca do efeito das fibras dietéticas no controle glicêmico de pacientes com Diabetes Melito tipo 2, aceito para publicação no periódico Nutrition Reviews*: Silva FM, Kramer CK, Almeida JC, Steemburgo T, Gross JL, Azevedo MJ. Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized clinical trials. Nutrition Reviews. 2013, in press.*

2. Artigo original referente a ensaio clínico randomizado acerca do efeito de desjejuns com diferentes índice glicêmico e conteúdo de fibras na resposta glicêmica e de saciedade em pacientes com Diabetes Melito tipo 2, a ser submetido à publicação no periódico American Journal of Clinical Nutrition.

LISTA DE ABREVIATURAS

ADA = American Diabetes Association

AUC = incremental areas under the curves

BMI = body mass index

DM = Diabetes Melito

ECR = ensaio clínico randomizado

EASD = European Association for the Study of Diabetes

FAO = Food and Agriculture Organization

GEE = generalized estimating equation

GI = glycemic index

HbA1c = hemoglobina glicada/ glycated hemoglobin

HGI-HF = high glycemic index and low fiber

HGI-HF = high glycemic index and high fiber

HOMA-IR = homeostasis model assessment of insulin resistance index

HPLC = high performance liquid column

IG = índice glicêmico

LGI-HF = low glycemic index and high fiber

LGI-LF = low glycemic index and low fiber

LSD = least significance difference.

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT = randomized clinical trial

SD = standard deviation

UAE = urinary albumin excretion

VAS = visual analogue scale

WHO = World Health Organization

WDM = weighted difference mean

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FUNDAMENTAÇÃO TEÓRICA

Importância do problema

O Diabetes Melito (DM) é considerado um problema de saúde pública, cuja prevalência e incidência estão aumentando significativamente, alcançando proporções epidêmicas. De acordo com o Instituto de Diabetes da Austrália, a prevalência mundial de DM entre adultos (20-79 anos) era de 6,4% em 2010, acometendo 285 milhões de pessoas. Estima-se que em 2030 a prevalência de DM aumentará para 7,7%, acometendo 439 milhões de adultos, o que implica em aumento de 69% no número de pessoas com DM nos países em desenvolvimento e de 20% nos países desenvolvidos (1). Em nosso país, dados do VIGITEL (Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico) apontaram prevalência autorreferida de DM igual a 5,6% em 2011 (2). Estima-se um aumento de 30% na prevalência de DM entre 2010 (prevalência = 6,0%) e 2030 (prevalência = 7,8%) na população brasileira (1).

O DM tipo 2 ocorre geralmente na vida adulta e é a forma mais comum de DM, estando associado à obesidade em cerca de 80% dos casos (3). A doença cardiovascular é a principal responsável pela redução da sobrevida de pacientes com DM tipo 2, sendo a causa mais frequente de mortalidade nesse grupo de pacientes (4). Tanto a hiperglicemia de jejum como a pós-prandial são fatores de risco cardiovascular em pacientes com DM, tendo associação com eventos cardiovasculares e com mortalidade (5-7). De fato, a glicemia pós-prandial é um importante determinante do controle glicêmico, avaliado através da hemoglobina glicada (HbA1c), e existe uma correlação positiva forte (r = 0,92) entre os

valores de HbA1c e de glicemia média (8). Ademais, a glicemia pós-prandial pode se responsável por 50% ou mais dos valores de HbA1c, dependendo do grau de compensação glicêmica (9).

A resposta glicêmica assim como a resposta insulinêmica ao consumo de uma refeição ou alimento também apresenta relação estreita com a homeostase pós-prandial de fome e saciedade (10-12), a qual pode ser avaliada subjetivamente através de escalas validadas para esse fim (13) ou objetivamente pela dosagem de hormônios envolvidos nesse mecanismo, dentre os quais a grelina (14). Metanálise de sete ensaios clínicos sobre refeições envolvendo 136 indivíduos saudáveis demonstrou associação entre concentrações plasmáticas de glicose e, especialmente, concentrações plasmáticas de insulina e sensações de apetite avaliadas subjetivamente (10). Do mesmo modo, correlação entre concentrações plasmáticas de glicose e insulina e concentrações plasmáticas de grelina é descrita na literatura (15). A grelina é um hormônio secretado pelas células endócrinas do trato gastrintestinal, especialmente localizadas no estômago. As concentrações plasmáticas de grelina aumentam antes do consumo de alimentos e tendem a reduzir após as refeições. Sugere-se que a grelina desempenhe um importante papel no controle da ingestão alimentar, do balanço energético, do metabolismo da glicose e possivelmente da regulação da insulina (16).

Determinantes dietéticos da resposta glicêmica pós-prandial

A resposta glicêmica e insulinêmica pós-prandial é influenciada especialmente pelos carboidratos da dieta vez que os mesmos são convertidos quase que em sua totalidade em glicose nas primeiras horas após serem consumidos. Essa influência é dependente da velocidade de liberação dos carboidratos para a corrente sanguínea, do seu tempo de depuração consequente à síntese e secreção de insulina e da sensibilidade tecidual periférica à ação desse hormônio (17). Tais efeitos são determinados tanto pela quantidade como pela

qualidade do carboidrato consumido. Entre outros fatores (18), a qualidade do carboidrato presente nos alimentos (determinante de seus efeitos fisiológicos e benefícios à saúde) pode ser avaliada pelo teor de fibras e pelo índice glicêmico (IG).

Fibras dietéticas e índice glicêmico: aspectos gerais

Fibra alimentar é definida como a parte não digerível do alimento de origem vegetal, a qual resiste à digestão e absorção intestinal e sofre fermentação completa ou parcial no intestino grosso. Apesar de discussões entre grupos de pesquisadores, a maioria deles concorda que oligossacarídeos, celulose, hemicelulose, pectinas, gomas, lignina, polissacarídeo indigeríveis e não amilosos, além de ceras e outras substâncias inerentes às plantas, devem ser classificadas como fibras alimentares (19). A FAO/WHO (Food and Agriculture Organization/ World Health Organization) recomenda o consumo de pelo menos 25 gramas de fibras totais por dia a fim de auxiliar na prevenção do aparecimento de doenças crônicas (18). A recomendação para pacientes com DM não difere daquela definida para a população geral (3).

O IG é uma medida do impacto relativo do carboidrato presente nos alimentos sobre a concentração de glicose plasmática. É determinado pela relação entre a área abaixo da curva de resposta glicêmica duas horas após o consumo de uma porção do alimento teste e a área abaixo da curva de resposta glicêmica correspondente ao consumo de uma porção do alimento referência (com a mesma quantidade de carboidrato que a porção do alimento teste). O valor obtido nessa relação é multiplicado por 100 e o IG é expresso em porcentagem (20). Em geral, o alimento referência é o pão branco ou a glicose, sendo esta preferida por possibilitar maior padronização e comparação de resultados. Os alimentos que provocam maior aumento na resposta glicêmica apresentam elevado IG (IG >70%), enquanto que aqueles que estão associados a uma menor resposta glicêmica apresentam valores menores de IG (IG <55%)

(www.glycemicindex.com). Para calcular o IG de refeições mistas e/ou dieta determina-se primeiramente a porcentagem de cada alimento em relação ao carboidrato total da refeição, multiplica-se este valor pelo IG de cada alimento e divide-se esse valor por 100. Somam-se os valores obtidos para estimar o IG da refeição (20).

Fibras dietéticas e índice glicêmico: efeitos no controle glicêmico

A literatura acerca da influência das fibras dietéticas no controle glicêmico de pacientes com DM é vasta e consistente na demonstração de benefício do consumo de fibras dietéticas na redução da glicemia e/ou HbA1c. Recentemente, nosso grupo demonstrou em ensaio clínico randomizado (ECR) envolvendo 42 pacientes com DM tipo 2 e síndrome metabólica o efeito da suplementação com goma-guar (10g/dia) por um período de seis semanas. A suplementação de fibra solúvel reduziu a HbA1c, a excreção urinária de albumina e os ácidos graxos trans séricos (21). Uma revisão sistemática com metanálise, publicada há cerca de 10 anos, compilou resultados de 24 estudos conduzidos em pacientes com DM tipo 1 e tipo 2 e demonstrou redução significativa de todos os marcadores glicêmicos ao comparar dietas com elevado conteúdo de carboidrato e de fibra com dietas com baixo conteúdo de carboidrato e de fibras (22). Outra revisão sistemática com metanálise de 15 ECR (324 participantes e em sua maioria ECR cruzados, com duração entre três e 12 semanas) demonstrou uma diferença de 15 mg/dl na glicemia de jejum e de 0,26% na HbA1c com dietas ricas em fibras em comparação a dietas controle em pacientes com DM tipo 2 (23).

A literatura também contempla estudos acerca do efeito agudo do consumo de refeições com conteúdo aumentado de fibras ou com adição de suplementos de fibras na resposta glicêmica pós-prandial. A maioria desses estudos foi realizada em indivíduos sem DM e em geral demonstrou redução da glicemia e insulinemia com alimentos ou refeições enriquecidas com fibras, seja através de suplementação ou através de alimentos fontes (24-

28). Em pacientes com DM tipo 2 também é demonstrado benefício na resposta glicêmica e insulinêmica aguda atribuído ao consumo de fibras dietéticas. Ensaio clínico randomizado cruzado com 60 pacientes com DM tipo 2 demonstrou redução significativa da glicemia, insulinemia e concentrações plasmáticas de peptídeo C apenas após o consumo da barra de cereal com maior quantidade de fibras (8g) em comparação ao consumo de barra de cereal com menor conteúdo de fibras (29). Redução na glicemia de 14% (após desjejum) a 20% (após jantar) com adição de *Psyllium* em comparação ao consumo das refeições controles foi demonstrada em outro ECR controlado com placebo conduzido em pacientes com DM tipo 2 (30).

Da mesma forma, o benefício das dietas de baixo IG no controle glicêmico de pacientes com DM já está bem documentado na literatura (34), inclusive em metanálises sobre o tema (35-37). Brand-Miller e colaboradores compilaram resultados de 14 ECR (203 pacientes com DM tipo 2 e 153 pacientes com DM tipo 1) que compararam o efeito de dietas com baixo IG e de dietas com elevado IG na resposta glicêmica. A redução média no IG em 22 unidades promoveu uma diminuição na HbA1c de aproximadamente 0,50% (35). Tal benefício foi confirmado por metanálises publicadas posteriormente (36,37).

O IG da refeição também parece influenciar a resposta glicêmica e insulinêmica aguda, embora sejam escassos os estudos conduzidos em pacientes com DM. Em ECR envolvendo 12 mulheres obesas sem DM foram testadas em ordem aleatória duas refeições com baixo IG (elevado e reduzido aporte calórico) e duas refeições com alto IG (elevado e reduzido aporte calórico). Maior resposta glicêmica com a refeição de elevado aporte calórico e alto IG em comparação à refeição de elevado aporte calórico e baixo IG foi demonstrada (38). Outro estudo envolvendo 12 adultos saudáveis também demonstrou melhora da resposta glicêmica pós-prandial com alimentos de baixo IG (cereais matinais integrais) ao comparar dois desjejuns (39). Em ECR conduzido em pacientes com DM tipo 2 foi demonstrada

redução das concentrações plasmáticas de glicose após o consumo de cereais enriquecidos com β-glucano de baixo IG em comparação ao consumo de pão branco (40).

Diante do exposto, observa-se que o benefício de dietas com elevado teor de fibras no controle glicêmico pode ser em parte atribuído ao fato de essas dietas, de uma maneira geral, apresentarem também baixo IG. De fato, relação inversa entre conteúdo de fibras e IG é descrita na literatura (31,32). Recentemente demonstramos em estudo transversal realizado em pacientes com DM tipo 2 uma correlação inversa entre o conteúdo de fibras totais e o IG da dieta (r = -0,441) e das refeições principais (desjejum, r =-0,442; almoço, r = -0,550 e jantar, r = -0,398) (31). Ademais, as fibras dos alimentos/ refeições parecem exercer influência sobre o seu IG. A adição de uma fibra viscosa a um biscoito resultou em redução superior a 60% no IG do biscoito em estudo envolvendo 10 indivíduos saudáveis e nove pacientes com DM tipo 2 (33). Além disso, uma metanálise publicada recentemente (41) demonstrou que a redução de marcadores glicêmicos parece ser mais acentuada com dietas de baixo IG e elevado conteúdo de fibras. Destaca-se, contudo, que a maioria dos estudos supracitados apresenta intervenções que contemplam ambas as manipulações dietéticas, dificultando a identificação do efeito isolado da redução do IG em comparação ao aumento do conteúdo de fibras.

Fibras dietéticas e índice glicêmico: efeitos na saciedade

A grelina é considerada um hormônio “sinalizador da fome”, cuja secreção é influenciada pelo consumo de alimentos, sendo observada maior redução da grelina após consumo de carboidrato em comparação à proteína e à gordura, sendo a gordura o macronutriente que parece exercer menor influência na resposta pós-prandial da grelina (14, 42,43). Ainda, o efeito dos macronutrientes parece ser similar quando avaliadas as

modificações nas concentrações plasmáticas de grelina total ou de grelina acilada, a qual representa a forma ativa da grelina (42).

O papel das fibras alimentares na liberação de grelina já foi avaliado por alguns estudos descritos na literatura, em indivíduos sem DM. Ensaio clínico, envolvendo 14 mulheres saudáveis, demonstrou influência positiva da adição de fibra ao pão nas concentrações de grelina no período pós-prandial (44). Recentemente, em ECR envolvendo 30 adultos saudáveis, a adição de capsaicina (suplemento de fibra) a um almoço não teve efeito na resposta subjetiva da saciedade, mas reduziu as concentrações plasmáticas de grelina, embora tal redução não tenha atingido a significância estatística (45).

Por outro lado, o papel do IG de uma dieta ou refeição na secreção de grelina foi pouco explorado na literatura até o momento, não sendo encontrados estudos sobre esse tema conduzidos em pacientes com DM tipo 2. Sugere-se benefício do consumo de alimentos com baixo IG em prolongar a saciedade, uma vez que o consumo de alimentos com alto IG em uma refeição parece aumentar o consumo de alimentos em refeições subsequentes (46). Além disso, o efeito das dietas de baixo IG em prolongar a saciedade parece estar associado a menor resposta glicêmica e insulinêmica observada após o consumo de alimentos com baixo IG (11). De fato, em recente ECR envolvendo 12 indivíduos saudáveis foi observada uma associação positiva entre refeições de baixo IG e menores concentrações plasmáticas de glicose e insulina e as concentrações plasmáticas de grelina foram inversamente correlacionadas com as concentrações de insulina (47).

Justificativa e objetivo geral da tese

Embora metanálise publicada recentemente tenha demonstrado redução média de 0,26% na HbA1c com dietas ricas em fibras em pacientes com DM tipo 2, a magnitude do efeito dessa intervenção não está completamente elucidada. Destaca-se que nessa revisão os

autores incluíram estudos de curta duração e com tamanho amostral reduzido, compararam os valores finais de glicemia e HbA1c dos estudos ao invés de comparar a mudança ocasionada pelas intervenções, não diferenciaram efeito de fibras provenientes de alimentos ou de suplementos e não identificaram qual a quantidade de fibras dietéticas necessária para que redução dos marcadores glicêmicos seja obtida. Além disso, benefícios agudos na resposta glicêmica e insulinêmica atribuídos ao consumo de carboidratos podem ser decorrentes da redução do IG e/ou do aumento do conteúdo de fibras das refeições. Considerando-se que existe uma correlação entre IG e conteúdo de fibras de refeições, a diferenciação do efeito de intervenções com diferentes IG e conteúdos de fibras é necessária para o melhor entendimento da modulação dietética da resposta metabólica pós-prandial. Entretanto, não foram identificados na literatura estudos que tenham avaliado o efeito específico dessas manipulações dietéticas na resposta glicêmica e insulinêmica. Ainda, o efeito do IG e das fibras dietéticas na saciedade pós-prandial de pacientes com DM tipo 2 tem sido pouco estudada.

Com base no exposto, a presente Tese de Doutorado foi desenvolvida com o objetivo geral de avaliar o papel da qualidade do carboidrato, com enfoque no IG e nas fibras dietéticas, no controle glicêmico e na saciedade em pacientes com DM tipo 2.

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Capítulo I

Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized clinical trials

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Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized clinical trials

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ABSTRACT

This systematic review with meta-analysis of randomized clinical trials (RCT) aimed to analyze the effect of fiber intake on glycemic control in patients with type 2 diabetes. Databases were searched up to November 2012 including the following medical subject headings: diabetes, fiber, and RCT. Absolute changes in glycated hemoglobin (HbA1c) and fasting plasma glucose were reported as differences between baseline and end-of-study. Pooled estimates were obtained by random-effects models. From 22,046 identified manuscripts, 11 RCTs (13 comparisons; eight to 24-weeks of duration) fulfilled the inclusion criteria providing data from 605 patients. High fiber diets, including diets with foods rich in fiber (up to 42.5 g/day; four studies) or supplement of soluble fiber (up to 15.0 g/day; nine studies) reduced absolute values of HbA1c by 0.55% (95% CI -0.96 to -0.13) and fasting plasma glucose by 9.97 mg/dl (95% CI -18.16 to -1.78). In conclusion, increased fiber intake improved glycemic control and should be considered as an adjunctive tool in treatment of patients with type 2 diabetes.

Keywords: type 2 diabetes mellitus, glycated hemoglobin, dietary fiber, meta-analysis

INTRODUCTION

Over 180 million people worldwide have diabetes and it is estimated that this number will more than double by 2030.[1] Achieving glycemic control close to the non-diabetic range may reduce both micro[2,3] and macrovascular diabetic complications.[3,4] Despite the fact that drug therapy is mandatory for most patients,[5,6] lifestyle interventions, such as physical exercise[7] and dietary modifications[8-10] are essential in diabetes management.

The main role of diet in glucose control is to decrease the postprandial glucose response because it is an important contributor to glycated hemoglobin (HbA1c)[11] and may also have a role as an independent risk factor for cardiovascular disease in patients with diabetes.[12] In this sense, carbohydrates that are rich in fiber and also have a low glycemic index, such as whole grains, vegetables, and fruits have been recommended to improve glucose control and should be encouraged for people with diabetes.[8,13]

It is hypothesized that dietary fibers form a viscous solution in the stomach that delays gastric emptying and physically inhibit the absorption of macronutrients at the lumen of the small intestine[14]. These effects decrease the glucose absorption and, consequently, can reduce the fasting and post-prandial plasma glucose increment [15-17]. However, the glucose-lowering effect of fiber intake is not consistent in the literature and probably depends on fiber type, amount and/or source.

A substantial number of clinical trials have investigate the fiber intake effects on glycemic profile of patients with diabetes.[18-28] Their results are probably also contradictory due to the trials sample size and duration of intervention, besides the intervention and control diets composition. Although this subject has been already reviewed by others[14,16], the magnitude of a possible favorable effect of fiber intake on glycemic control is still uncertain. Therefore, this systematic review was conducted to analyze the effect of dietary fiber (type and amount) on glycemic control in patients with type 2 diabetes.

METHODS

This systematic review was carried out using a protocol constructed according to the Cochrane Handbook recommendations[29] and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[30]

Search strategy

We searched Medline, Embase, Scopus, and Cochrane electronic databases from 1950 to November 21, 2012 to identify RCTs that reported the effect of fiber intake on glycemic control [glycated hemoglobin (HbA1c) and fasting plasma glucose] of patients with diabetes.

The initial search comprised the MESH terms *diet*, *dietary therapy*, *dietary fiber*, *carbohydrates*, *diabetes*, and related entry terms associated with a high sensitivity strategy for the search of RCTs available at http://www.sign.ac.uk/methodology/filters.html#random. See web extra Appendix 1 for the complete Medline search strategy. Using the same terms we also searched studies in Clinical Trials.gov and in all published abstracts from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) annual meetings in the last five years. All potentially eligible studies were considered for review, regardless of the language. A manual search was also performed in the reference lists of included articles and in the two previous systematic review studies on this topic.[14,16]

Inclusion and exclusion criteria

We included RCTs that evaluated the effect of dietary fiber (foods or supplements) on the glycemic control of patients with type 2 diabetes, with duration of at least eight weeks. This follow-up period was chosen because changes in HbA1c can be better detected after two to three months of the intervention.[9] Outcomes were changes in HbA1c and fasting plasma glucose from baseline to the end-of-study.

In studies that evaluate the effect of dietary fiber the intervention was defined as the diet with the highest total fiber content and the control diet as the diet with lowest fiber content. In studies that evaluate the effect of fiber supplement, the intervention was defined as the usual diet plus a soluble fiber supplement and the control diet was defined as the usual diet or the usual diet plus a placebo or another type of fiber.

We excluded studies that were not randomized, included children or pregnant women or patients with type 1 diabetes and did not report the chosen outcomes or the means and standard deviations (SD) of them. Crossovers RCTs without a washout period between diets were also excluded.

Study selection and data extraction

Two reviewers (FMS and CKK) independently analyzed the titles and abstract of every paper retrieved from the literature search to identify potentially eligible studies. All articles that did not meet the inclusion criteria were excluded. The full text of the remaining papers was obtained for further examination. Disagreements regarding inclusion were resolved by a third investigator (JCA).

The data of included studies were independently extracted by two reviewers (FMS and TS) using a standardized data extraction form. Disagreements were solved by a third reviewer (JCA). Extracted data included: first author's name, year of publication, number of participants, details of the study design (i.e., crossover or parallel design, duration of the washout period, and randomization method), trial duration, and characteristics of patients (age, body mass index, duration of diabetes, gender, diabetes treatment). Total energy, macronutrients, fiber content, and any evaluation of dietary compliance were extracted from intervention and control diets description. Baseline and end-of-study means and statistical dispersion for HbA1c and fasting plasma glucose were extracted.

Study and body evidence quality assessment

Two reviewers (FMS and TS) independently assessed the sources of bias in included clinical trials as proposed by the Cochrane Collaboration. Biases were classified into six domains: selection, performance, detection, attrition, reporting, and other bias[29,31]. In the domain "other bias" we included the assessment of dietary compliance. The risk of bias in each individual item was classified as high, low, or unclear. Regarding dietary compliance, the risk of bias was classified as "low" if the study described the method of dietary compliance evaluation.

The quality of the body evidence of our systematic review was assessed, according the GRADE approach. This evaluation included factors that may decrease the quality of body evidence (methodological quality, directness of evidence, heterogeneity, precision of effect estimates, risk of publication bias) and factors that may increase it (large magnitude of effect, reduction or spurious effect due to plausible confounding factors, dose-response gradient). Each evaluated factor was rating as high, moderate, low, or very low [29].

Statistical analyses

Changes in fasting plasma glucose and HbA1c were reported as absolute differences between mean values at baseline and end-of-study. HbA1c changes were also expressed as percent of the calculated differences from baseline to the end-of-study. This additional strategy was adopted because the HbA1c method of measurement was not the same in all studies. Changes between baseline and final SD values for fasting plasma glucose and HbA1c were directly extracted from the manuscripts or calculated, assuming a correlation of 0.5 between the baseline and final measures within each group, according to the formula of Follman et al [32] as proposed by Cochrane Handbook[29.] We assumed equal variance among trials and between intervention and controls.

The heterogeneity between the studies was evaluated by Cochran's x test (Q test) and a P for trend ≤0.10 was considered statistically significant. The I^2 test was also performed to evaluate the magnitude of heterogeneity. The pooled estimates of the weight mean differences (WDM) between high fiber diet and control diet groups were calculated using the random effects model (DerSimonian-Laird method) [33] since a significant heterogeneity between studies was identified in preliminary models. Furthermore, this approach has a more conservative assessment of the average effect size.

Potential sources of heterogeneity between trials were investigated by meta-regression analyses. Covariates were chosen based on biological relevance before the meta-analyses were undertaken. The selected covariates were: source of fiber (foods rich in fiber or fiber supplements), difference in dietary fiber content between intervention and control groups, duration and design of the study. Quantitative covariates were categorized as binary variables considering the mean values of these variables in all included studies (≥ mean value and < mean value). Thereafter, we conducted sensitivity analyses (subgroup analyses) including the variables with a positive R-adjusted square on meta-regression analyses, considering that it represents how much the between-study difference could be explained by these variables. [29]

We assessed the possibility of publication bias visually by funnel plot asymmetry and statistically by Begg's and Egger's tests; a significant publication bias was considered if the P value was <0.10. [34-36] The trim-and-fill computation was also used to estimate the effect of publication bias on the interpretation of results if a visual asymmetry in the funnel plot suggested the presence of publication bias.[37]

All statistical analyses were performed using Stata 11.0 software (Stata, College Station, TX, USA). Significance was set at P<0.05 and 95% confidence intervals are quoted throughout.

RESULTS

From the initial search we identified 22,046 studies (Figure 1). Based on title and abstracts, we selected 45 studies for full text examination. In addition 15 studies were identified in the references lists of included studies and in the two previously published systematic reviews on the topic. Studies identified in Clinical Trials.gov (n = 51) and in ADA (n = 325) and EASD (n = 26) meeting abstracts did not fulfilled the inclusion criteria for the current review. Then, we selected 60 studies for full text evaluation.

From the 60 studies initially selected, 11 studies[18-28] fulfilled the inclusion criteria. One study[20] was included as three independent reports because data were described according to the type of diabetes treatment (diet only, insulin, or oral antidiabetic drugs) and, therefore, 13 comparisons were available for analyses (Figure 1). All studies evaluated HbA1c changes and eight studies also reported fasting plasma glucose as an outcome.[19-22, 24,26-28]

Studies characteristics

The essential features of individual studies are summarized in Table 1**.** The total sample size of studies comprises 605 patients with type 2 diabetes, aged 62.0 years, and with diabetes duration from 3.0 to 9.4 years. Eight studies were parallel RCTs. [18,20,21,23,25-28] Three RCTs had a crossover controlled design[19,22,24] with a washout period varying from four to eight weeks. The trial duration ranged from eight to 24 weeks.

In studies in which intervention was foods rich in fiber[18,22,24,27] the difference in dietary fiber content between intervention and control groups ranged from 3.0 to 22.5 grams/day. In studies that evaluate fiber supplements (3.5 to 16.5 grams/day), guar-gum was used in four studies[19-21,25], psyllium in two[23,26], and β-glucan in one.[28] Total energy and dietary macronutrients composition was not described in five [19,20,25,26,28] out of seven studies that evaluated the effect of supplement. All studies [18,22,24,27] that analyzed the effect of high

fiber diets showed differences in the dietary content between intervention and control group. Just one study [27] described the glycemic index (GI) (Table 1).

Diabetes treatments did not differ between intervention and control groups, but in three studies[22,23,25] there was no information about it. Six studies[20,22,23,24,25,28] described the weight of patients at the beginning of the trial (74.0 to 88.4 kg). Regarding the weight change during the follow-up, in six studies[18-20,22,27,28] the weight of patients was not modified) and in three studies[21,24,26] these data were not described. In another two studies[23,25] the weight loss was higher in the intervention group than in the control group[22,24]. In the majority of the manuscripts (78.5%) it was unclear if the participants received recommendations about physical activity. [18-22,25-28]

Study and body evidence quality, publication bias

The risk of bias of included studies is summarized in Table 2**.** The risk of selection bias was low in all trials taken into account the presence of random sequence generation, although the allocation concealment was unclear in the majority studies. In general, the bias of performance was low (83.3% of patients and 58.3% of researches ere blinded). Information about blinding of outcome assessors was described just into two studies (16.7%). Regarding attrition bias, dropouts and/or withdrawals were lower than 20% in seven studies. The dietary compliance was evaluated by the majority of studies.

The assessment of the quality of body evidence of the current systematic review (GRADE approach) is described in Table 3. The within-study risk of bias was classified as moderate, as well as the precision of our effect estimates, especially due to the wide confidence interval for fasting plasma glucose results. Our analyses presented a high heterogeneity that could not be explained and we could not establish a dose-response effect. On the other hand, the risk of publication bias was not identified in our analyses and for our

primary outcome (HbA1c changes) we could demonstrate a clinical relevant effect with large magnitude. So, we classified the quality of body evidence of our systematic review as moderate.

Publication bias was assessed by visually examining a funnel plot, with asymmetry being formally assessed by the Egger regression test. No significant asymmetry was demonstrated both for HbA1c (P = 0.135; Figure 2) and fasting plasma glucose (P = 0.466; Figure 3). Trim-and-fill computation for HbA1c pooled data did not demonstrate any missing study (data not presented).

Analyses of summary estimates

HbA1c change

Data from studies that assessed HbA1c were pooled. HbA1c absolute values decreased 0.55 % (-0.96 to -0.13; I^2 = 94.1%; p<0.001) in patients who consumed high fiber diets as compared to control diets (Figure 4). Twelve comparisons were included in this analysis because one study did not present absolute values of HbA1c, but only the percent of change.[22] The percent of reduction in HbA1c values (13 comparisons) was -4.75% (-9.35 to - 0.15; I^2 = 93.5%; p<0.001). The observed reduction in HbA1c, both in absolute values and in percentage, was observed with a dietary fiber intake from 37.4 to 42.6 g/day (considering a diet with 2000 kcal/day) or with 3.5 to 15g/day of fiber supplements. These results did not change when we conducted the trim-and-fill computation.

The heterogeneity observed in HbA1c analysis (absolute values) was explored by meta-regression (Table 4). The proportion of between-study variance explained by each predefined covariate is shown. Study follow-up was the only variable that individually influenced the heterogeneity (adjusted R-square = 35.62%). A subgroup analysis of HbA1c including the follow-up as a binary variable was not significant: follow-up ≤12 weeks (n = 4;

WMD = -1.488; 95%IC -3.139, 0.164; I square = 95.9%) in comparison with follow-up >12 weeks (n = 8; WMD = - 0.037; 95%IC -0.330, 0.256; I square = 83.9%).

Fasting plasma glucose change

Eight studies (10 comparisons) described data on fasting plasma glucose. Pooled data showed a glucose reduction of -9.97 mg/dl (-18.16 to -1.78); I^2 = 95.5%; p<0.001] in patients who consume high fiber diets compared with control diets (Figure 5).

The observed heterogeneity was explored by univariate meta-regression analyses (Table 4). The patients' age explained 63.56% of the heterogeneity. Study design, period of follow up, quality score of study, type of intervention, and difference in fiber content did not explain the heterogeneity. In the sensitivity analyses we included age as a binary variable according to mean age of studied patients. However, only one study[25] included patients aged <59.4 years and the reduction in fasting plasma glucose in that study was -89.70 (95% confidence interval -105.24, -74.13). In the group that included patients older than 59.4 years, the effect of fiber was not significant [WMD = -0.88 (95% confidence interval -6.78, 5.02); I square = 89.5%, p<0.001)].

DISCUSSION

In this systematic review with meta-analyses the effect of dietary fiber on glycemic control of patients with type 2 diabetes was evaluated through 11 pooled RCT (13 comparisons) lasting at least eight weeks. Diets with foods rich in fiber or fiber supplements caused an absolute reduction of 0.55% in HbA1c - corresponding to an average reduction of 4.75 percent- and 10 mg/dl in fasting plasma glucose values.

In a systematic review published seven years ago diets with low fiber and moderate carbohydrate content were compared with diets with high fiber and carbohydrate contents in

patients with diabetes. Diets rich in fiber and carbohydrate were associated with reduction in HbA1c (6 trials; weighted average percent change: -6%) and fasting, postprandial, and average plasma glucose. The search strategy, the selection criteria for inclusion of studies, and the study quality were not described. [15] Another systematic review, without a meta-analysis, evaluated the effects of psyllium supplementation on glycemic control of patients with type 2 diabetes.[38] Two out of the four included RCTs, also included in the current systematic review, compared the effect of psyllium with placebo in HbA1c. The other two included studies evaluated the acute post-prandial glucose effects only. The authors concluded that psyllium supplementation may be effective to improve glycemic control. Recently another systematic review including 15 clinical trials evaluated the effect of fiber intake on glycemic control of patients with type 2 diabetes. A decrease of 0.26% (absolute value) in HbA1c and 15.3 mg/dl in fasting plasma glucose was demonstrated. [17] Some aspects of that study preclude comparison with our meta-analysis: five out 15 of the included studies lasted less than eight weeks; the method for HbA1c measurement in each trial was not described; and HbA1c values at baseline were not included in the analysis – the authors just compared the final HbA1c values of intervention and control groups. Furthermore, nine RCT that we included in our meta-analysis also fulfilled the selection criteria of their study. Therefore, these trials should have been included by authors in their systematic review.

A high heterogeneity was detected for HbA1c and fasting plasma glucose meta-analyses. Therefore, we used a random effects model, instead of a fixed model, since random effects model involves an assumption that the effects being estimated in the different studies are not identical. [29] The age of patients was the only identified variable that partially explained the heterogeneity of fasting plasma glucose changes, according to meta-regression and sensitivity analyses. However, just one study included patients younger than 59.4 years and a definitive conclusion about the influence of age on fasting plasma glucose reduction by

increased fiber intake cannot be established. Regarding HbA1c analysis, the age of patients was not associated with heterogeneity.

We could not fully explain the high heterogeneity of our models. Some differences in composition of intervention and control diets (macronutrients - especially carbohydrate content, glycemic index, and energy restriction; and the sources of dietary fiber) between the included studies in our review might have influenced the confidence in final results contributing to the heterogeneity. These aspects could not be investigated as potential sources of heterogeneity because most studies did not report them. Physical activity, weight changes and type of diabetes treatment could also be possible sources of heterogeneity since these variables can influence glycemic control. However, these data were absent or incomplete in most studies and could not be included in our analyses.

The influence of dietary fiber on glucose metabolism has been attributed particularly to soluble rather than to insoluble fiber. Soluble fiber physiologically modulates the postprandial glycaemic response though its effects on the stomach and small bowel. These effects include: delayed gastric emptying; modification of gastrointestinal myoelectrical activity and delayed small bowel transit; reduced glucose diffusion through the unstirred water layer; and reduced accessibility of α-amylase to its substrates due to increased viscosity of gut contents.[16] In addition, both soluble and insoluble fiber intake can improve glycemic control by increasing the insulin sensitivity. [39,40] The mechanisms associated with this last beneficial effect have not yet been completely established.

The results of the current meta-analysis pointed to an average reduction of 0.55% in HbA1c absolute values (relative reduction of 4.75 percent) due to diets containing foods rich in fiber or fiber supplements. A reduction of 5% in HbA1c is clinically relevant and comparable to the decrease achieved through some medications for type 2 diabetes.[41] Lastly, it is meaningful that the improvement of glycemic control achieved with fiber intake occurs

without relevant adverse effects, especially hypoglycemia, that are often associated with anti-diabetic medications.[6] Furthermore, in general population high dietary fiber intake provides many health benefits including enhancement of weight loss and reduction of cardiovascular risk. [42] These effects can be especially relevant in patients with type 2 diabetes.

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook[29] and the PRISMA guidelines.[30] All relevant studies were included, regardless the language. In addition, the inclusion of studies with at lest eight weeks of follow-up allowed the detection the actual HbA1c changes.[9] Considering the GRADE approach, the body evidence of the current review can be classified as moderate.

A possible limitation of our systematic review was the inclusion of studies with a small sample size - most (64%) included less than 50 patients. Also, a high variability of study follow-up (eight to 24 weeks) may be a weakness. Another limitation could be related to HbA1c measurements technique, since the methods were not uniform. For that reason, we decided to describe HbA1c reduction also using percentage of change besides using changes in absolute values. This approach confirmed the beneficial effect of high fiber diets in HbA1c. Another aspect is that we could not demonstrate an independent effect of soluble and insoluble fiber since the majority of studies reported only the total fiber content. In fact, a recent review revealed that studies has been paid insufficient attention to providing detailed description of the characteristics of dietary fibers.[42] Furthermore, in some studies the control group received insoluble fiber as placebo and this can be a confounder since insoluble fibers can influence the post-prandial glucose response.[16] Finally, as expected by the design of our study, the benefit of fiber intake on glucose control cannot be extrapolated to patients with type 1 diabetes.

CONCLUSIONS

Results of our meta-analysis support the recommendation to increase the intake of dietary fiber to decrease HbA1c and fasting plasma glucose in patients with type 2 diabetes. Thus, these patients should be encouraged to include in their daily diet foods rich in fiber, such as whole grain, vegetables, and fruits, or to use fiber supplements. However, considering different types and sources of fibers (soluble and/ or insoluble fibers provided by foods and/ or supplements) RCTs should be performed to explore the best sources and amount of dietary fiber necessary to improve glycemic control in patients with type 2 diabetes.

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No conflict of interest was declared.

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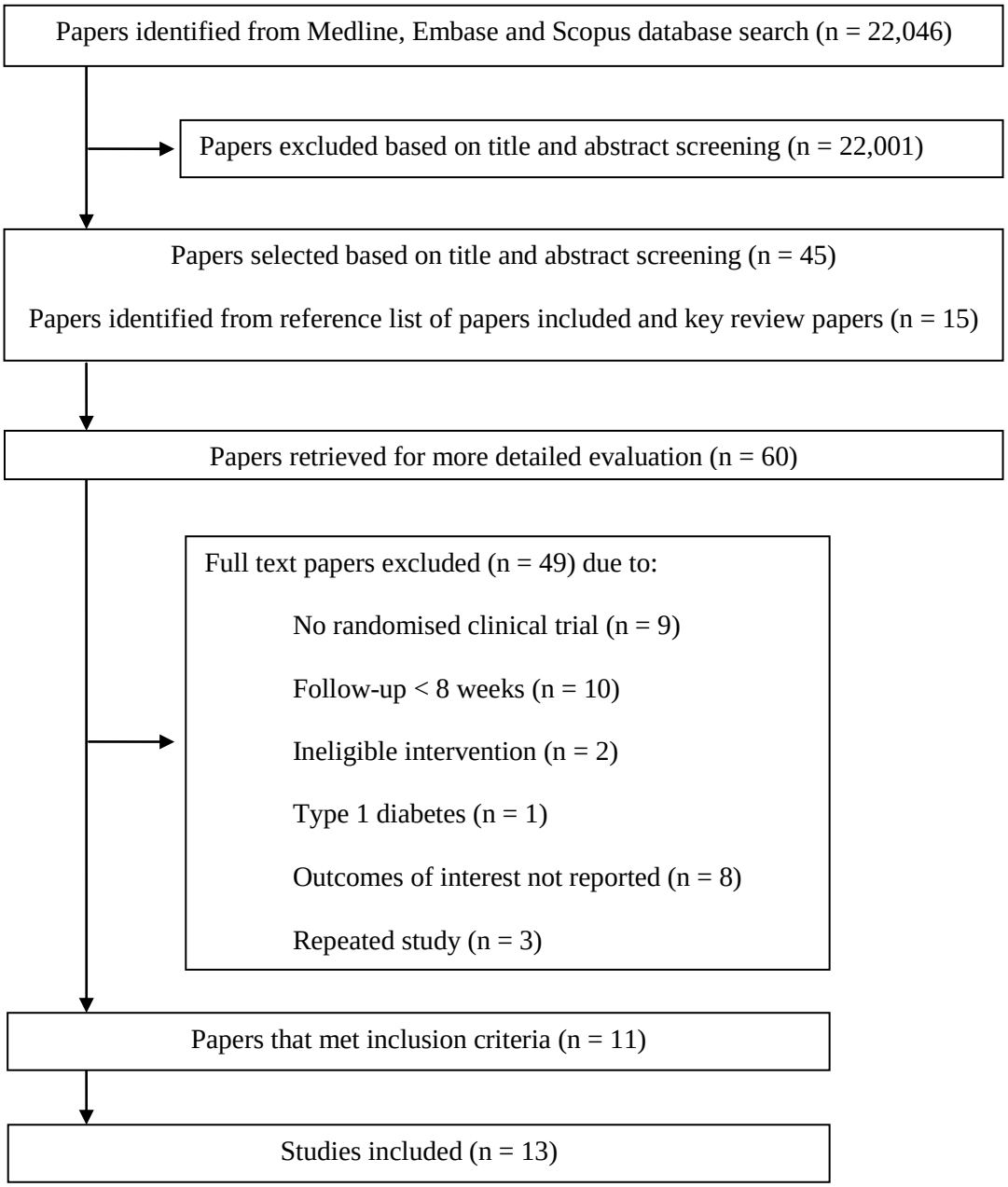

Figure 1 Flow of studies through review

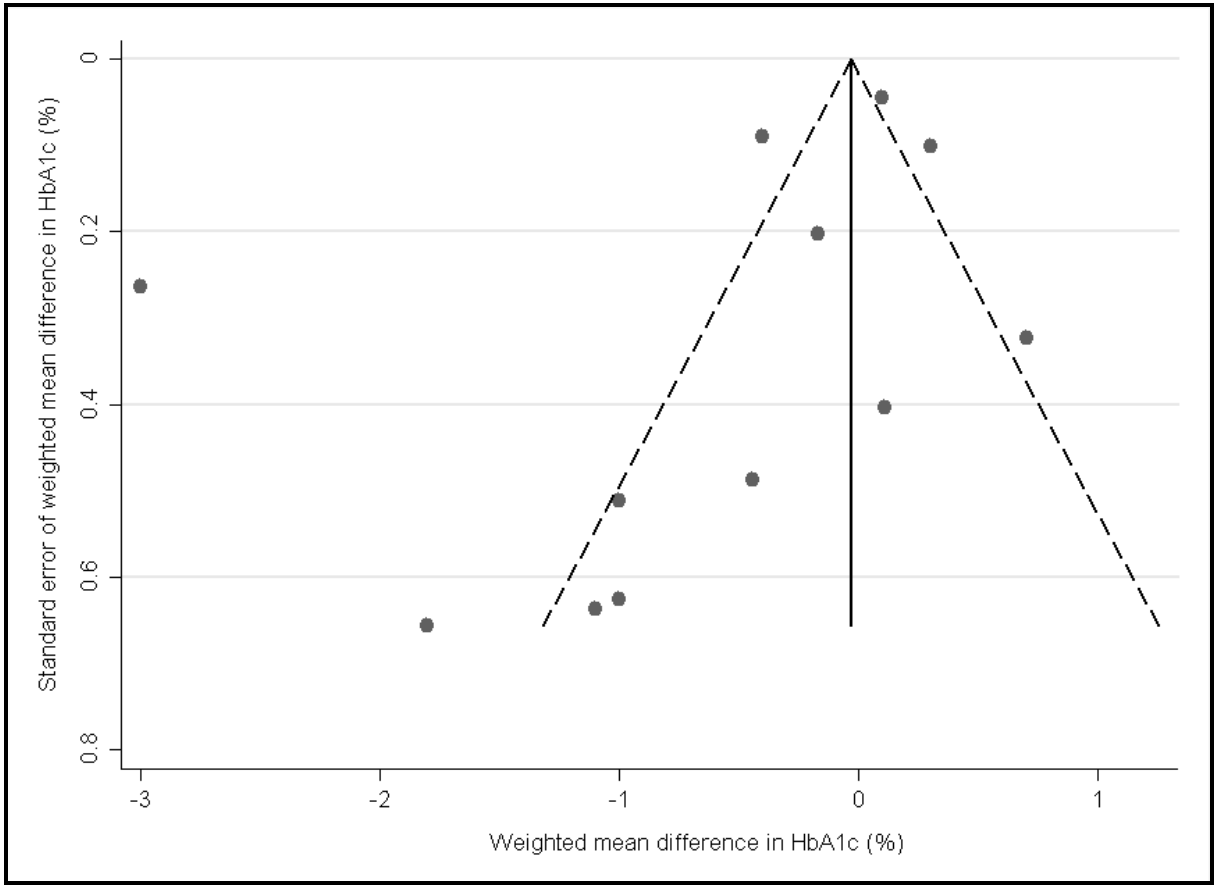

Figure 2 Analysis of publication bias in HbA1c meta-analysis

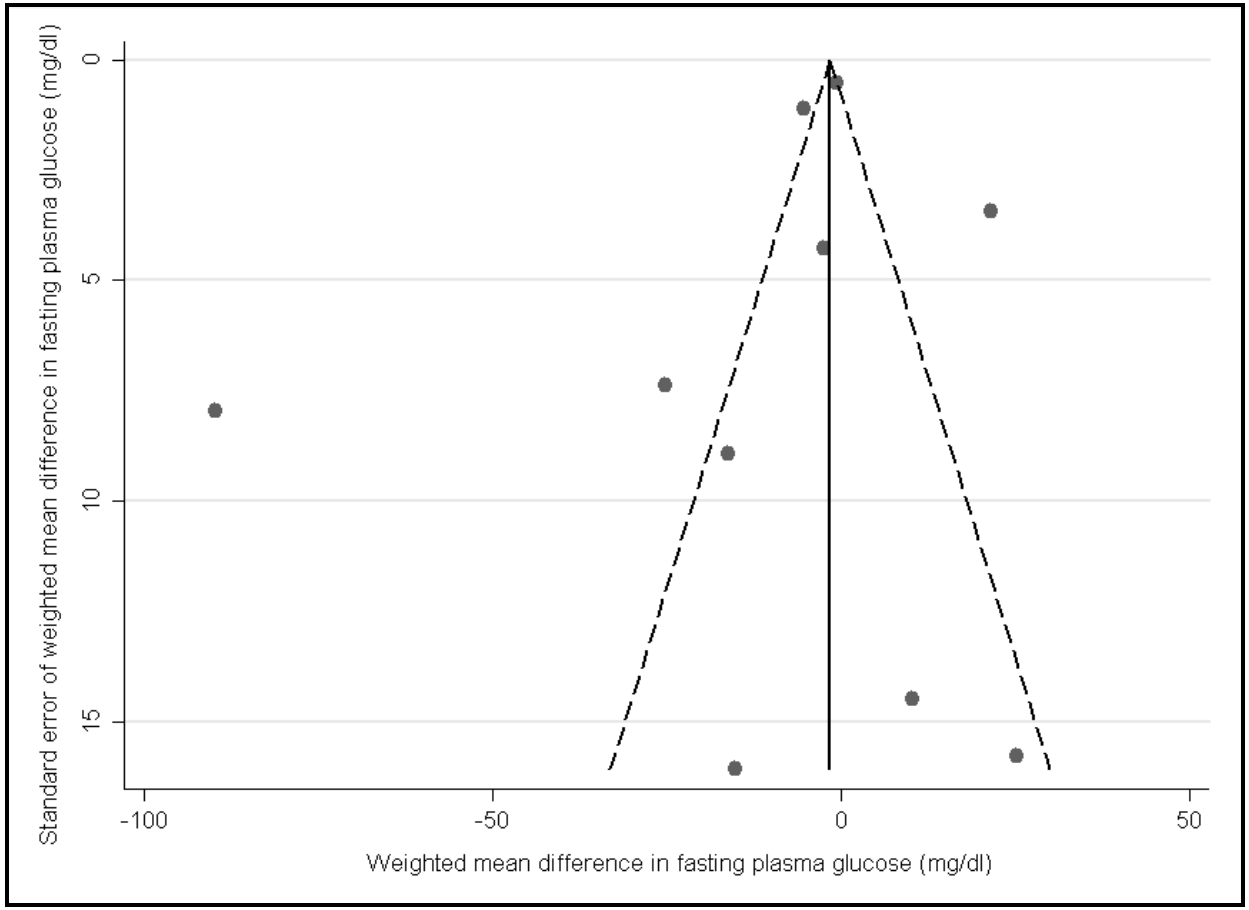

Figure 3 Analysis of publication bias in fasting plasma glucose meta-analysis

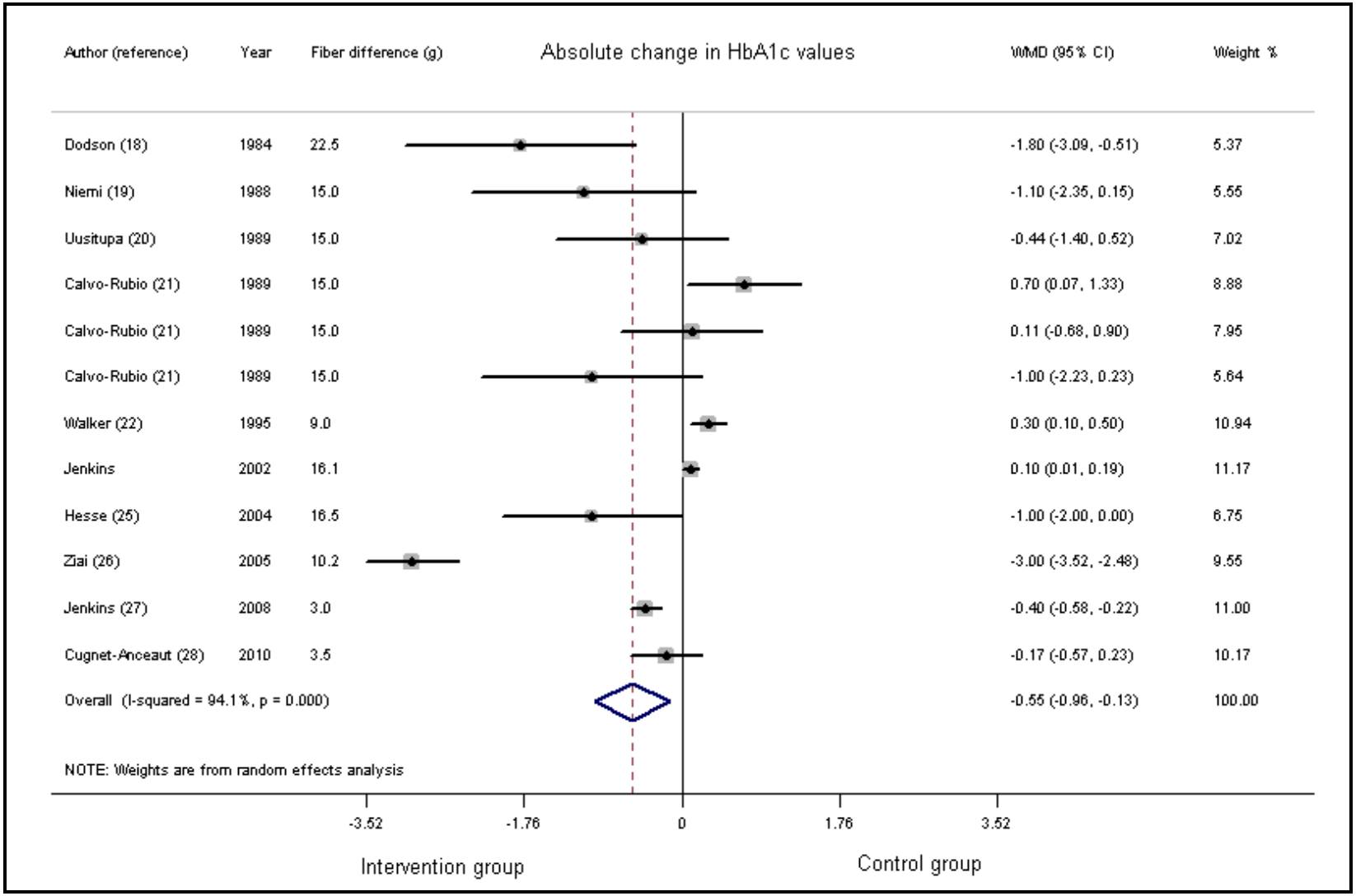

Figure 4 Meta-analysis of the effect of fiber intake in HbA1c

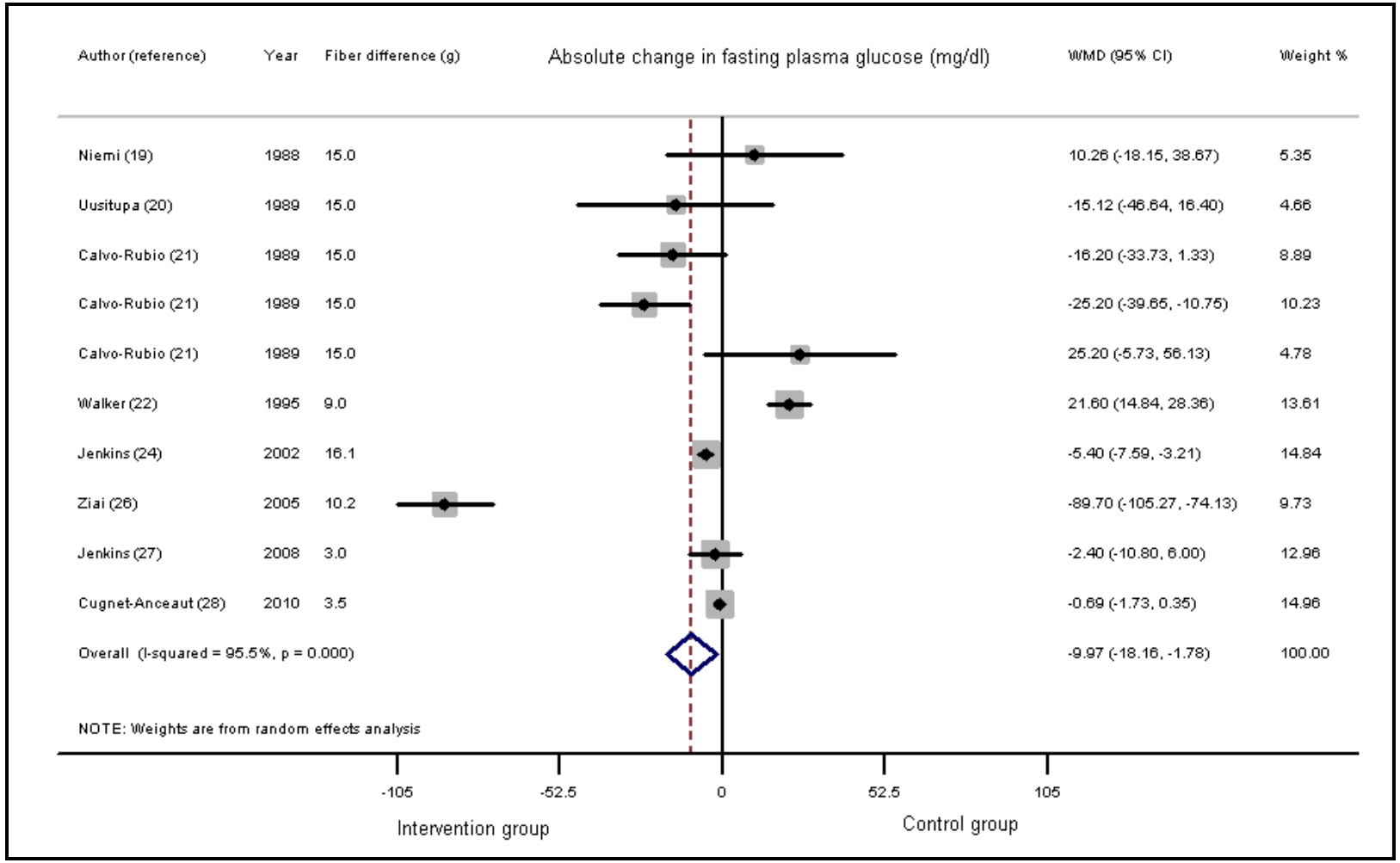

Figure 5 Meta-analysis of the effect of fiber intake in fasting plasma glucose

Table 1 Effect of increased fiber intake in glycemic control of patients with type 2 diabetes: characteristics of the studies

Author Year	**Study design Follow-up**	**Sample (diabetes treatment)**	**Diabetes duration (years)**	**Baseline HbA1c ((%) Method**	**Baseline fasting plasma glucose (mg/dl)**	**Intervention and control groups characteristics**	**Fiber difference between groups (g)**	**Possible dietary confounders**
Dodson 1984 [18]	Parallel 8 weeks	50 type 2 DM 50% males 56.8 years old (oral agents)	6.8	**I.** 12.4±3.1 **C.** 10.7±3.3 Chromatography	not reported	**I.** Diet of high fiber (40-45 g/day), high unrefined carbohydrate (50% of energy) and low fat content (25% of energy) **C.** Diet of low carbohydrate (26% of energy), low fiber (20g/day), and high fat content (40% of energy).	22.5	total energy carbohydrate fat protein
Niemi 1988 [19]	Crossover 12 weeks	22 type 2 DM 27.3% males 63.0 years old (diet or oral agents)	not reported	**I.** 12.1±2.3 **C.** 11.4±2.1 Electrophoresis	**I.** 210.6±46.8 **C.** 223.3±48.6	**I**. Usual diet plus 5 grams of guar gum granules 3 times a day **C**. Usual diet plus 5 grams of microcrystalline cellulose 3 times a day	15	Composition of diet not reported
Uusitupa 1989 [20]	Parallel 12 weeks	39 type 2 DM 33.3% males 60.5 years old (oral agents)	9.4	**I.** 8.9 ±1.4 **C.** 9.4±1.5 HPLC	**I.** 220.1±42.7 **C.** 230.4±46.8	**I**. Usual diet plus 5 grams of guar gum granules 3 times a day before the main meals **C**. Usual diet plus 5 grams of	15.0	Composition of diet not reported

					placebo granules (wheat flour) 3 times a day before the main meals			
Calvo-Rubio 1989 [21]	Parallel 12 weeks	9 type 2 DM 62.5% males 62.5 years old (diet only)	2.5	**I.** 8.3±0.6 **C.** 9.3±0.4 Chromatography	**I.** 140.4±10.8 **C.** 124.2±16.2	**I**. Usual diet plus 5 grams of guar gum granules three times a day before the main meals **C**. Usual diet (55% of energy from carbohydrate, 25% from fat and 20% from protein) without supplement	15.0	None
Calvo-Rubio 1989 [21]		15 type 2 DM 60% males 60.8 years old (oral agents)	3.0	**I.** 9.7±0.8 **C.** 10.1±0.9 Chromatography	**I.** 172.8±14.4 **C.** 151.2±9.0			
Calvo-Rubio 1989 [21]		10 type 2 DM 80% males 67.5 years old (insulin)	4.0	**I.** 9.8±1.3 **C.** 9.7±0.7 Chromatography	**I.** 178.2±30.6 **C.** 156.6±12.6			
Walker 1995 [22]	Crossover 12 weeks	24 type 2 DM 37.5% males 69.1 years old (diabetes treatment not reported)	not reported	**I.** 6.4±0.3 **C.** 6.8±0.4 HPLC	**I.** 153±10.8 **C.** 172.8±14.4	**I.** High-carbohydrate and low-fat diet: 21% of energy from fat and 59% of energy from fiber rich-carbohydrate (34 g of fiber/day). **C.** Modified fat diet: 40% of energy from fat and 40% of	9.0	total energy carbohydrate fat

					energy from carbohydrate (25 g of fiber/day)		
Anderson 1999 [23]	Parallel 8 weeks	34 type 2 DM 100% males 62.9 years old (diabetes treatment not reported)	not reported	**I.** 0.073±0.003 **C.** 0.075±0.002 not reported	**I.** 180.4±10.4 **C.** 193.3±10.1	**I.** Psyllium group: traditional weight-maintaining diabetes exchange diet plus an orange-flavored, sugar free product (Metamucil) - two doses (5.1g of psyllium in each of them). **C.** Placebo group: traditional weight-maintaining diabetes exchange diet plus an insoluble fiber, microcrystalline cellulose (two doses of 5.1g).	10.2	total energy fat protein
Jenkins 2002 [24]	Crossover 12 weeks	65 type 2 DM 69.6% males 63.0 years old (diet only or oral agents)	not reported	**I.** 7.0±0.2 **C.** 7.3±0.3 HPLC	**I.** 131.4±5.4 **C.** 133.2±7.2	**I.** Wheat-bran diet (21.3 g/1000 kcal of fiber) providing high wheat bran bread and breakfast cereal. **C.** Control diet (11.7 g/1000 kcal of fiber) providing white bread and low-fiber breakfast cereal.	16.1	total energy protein
Hesse	Parallel	25 type 2 DM				**I**. Fiber group: 5.5 grams of	16.5	Composition

2004 [25]	8 weeks	32% males 58.9 years old (diabetes treatment not reported)	not reported	**I.** 8.7±0.9 **C.** 8.3±0.9 Turbidimetry	**I.** 221.4±41.4 **C.** 230.4±41.4	fiber 3 times a day (16% of guar gum) **C**. Placebo group: 5.5 grams of cellulose 3 times a day		of diet not reported
Ziai 2005 [26]	Parallel 8 weeks	49 type 2 DM gender not reported 56.2 years old (diet only or diet and oral agents)	not reported	**I.** 10.5±0.7 **C.** 9.1±0.5 HPLC	**I.** 208.2±12.7 **C.** 179.1±10.8	**I.** Psyllium group: 5.1 grams of psyllium twice daily **C**. "Placebo group": 5.1 grams of microcrystalline cellulose twice daily	10.2	Composition of diet not reported
Jenkins 2008 [27]	Parallel 24 weeks	210 type 2 DM 61% males 60.5 years old (oral agents)	7.8	**I.** 7.1±0.5 **C.** 7.1±0.6 HPLC	**I.** 141.2±29.3 **C.** 138.8±29.3	**I.** Diet with 18.7 g/1000 kcal of fiber and GI equal to 69.6 defined as low glycemic index diet **C.** Diet with 15.7 g/1000 kcal of fiber and GI equal to 83.5 defined as high fiber diet	3.0	carbohydrate fat protein glycemic index
Cugnet-Anceau 2010 [28]	Parallel 8 weeks	53 type 2 DM gender not reported 61.8 years old (insulin and/ or	not reported	**I.** 7.3±0.9 **C.** 7.5±1.3 HPLC	**I.** 159.1±38.0 **C.** 150.5±41.0	**I.** Diet with one portion/day of ready-to-eat soups enriched with3.5g of β-glucan **C.** Diet with one portion/day	3.5	Composition of diet not reported

	oral agents and/ or diet)	of ready-to-eat soups enriched with 3.5g of maltodextrin

Abbreviatures: DM = diabetes mellitus, I = intervention group, C = control group, kcal = calories, HPLC = high performance liquid column.

Table 2 Assessment of the quality of studies: risk of bias summary

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Dietary compliance assessed**
Dodson, 1984 [18]	low	unclear	Low	unclear	low	low	high
Niemi, 1988 [19]	low	unclear	Low	unclear	low	low	high
Uusitupa, 1989 [20]	low	unclear	Low	unclear	low	low	low
Calvo-Rubio, 1989 [21]	low	unclear	High	unclear	low	low	unclear
Walker, 1995 [22]	low	unclear	Low	unclear	low	low	low
Anderson, 1999 [23]	low	unclear	Low	low	low	low	low
Jenkins, 2002 [24]	low	unclear	Low	unclear	high	low	low
Hesse, 2004 [25]	low	unclear	Low	unclear	low	low	unclear
Ziai, 2005 [26]	low	unclear	Low	unclear	high	low	low
Jenkins, 2008 [27]	low	low	Low	low	high	low	low
Cugnet-Anceau,2010 [28]	low	unclear	Low	unclear	high	low	low

Table 3 Assessment of the quality of body evidence in the current systematic review: GRADE approach

Factor	Quality	Support for judgment
Within-study risk of bias (methodological quality)	Moderate	All trials included a random sequence generation, although allocation bias was unclear in the majority of the studies. The risk of performance bias was low. In general, the blinding of outcomes assessment was unclear and about a third of trials had a high risk of incomplete data outcomes due to dropouts/ withdrawals. Selective reporting bias was low.
Directness of evidence	High	All trials included directly comparisons of an intervention diet with a control diet.
Heterogeneity	Low	A high heterogeneity was observed in the analyses of HbA1c and fasting plasma glucose. This heterogeneity was partially explained by the duration of follow-up and patients' age, respectively.
Precision of effect estimates	Moderate	Confidence interval was wide for fasting plasma glucose, but not for HbA1c changes.
Risk of publication bias	High	No significant asymmetry was demonstrated by the funnel plot, the Egger regression test, and the trim-and-fill computation did not demonstrate any missing study.
Large magnitude effect	High	The magnitude of effect observed for HbA1c reduction, our main clinical relevant outcome, was large.
Effect of confounding factors	Moderate	The good glycemic control of included patients could have underestimated the expected fiber effects in up to half of trials. On the other hand, differences in diet composition between intervention and control diets (besides of dietary fiber content) could have influenced the trials results.
Dose- response gradient	Very low	We could not establish a dose-response effect of fiber intake in glycemic control.

Table 4 Univariate meta-regression of increased fiber intake effect in absolute HbA1c and fasting plasma glucose changes

Covariate	**HbA1c (%)**		**Fasting plasma glucose (mg/dl)**	
	Adjusted R-square (%)	**P > |t|**	**Adjusted R-square (%)**	**P > |t|**
Study design[1]	-1.17	0.860	-335.69	0.235
Study follow- up[2]	35.62	0.034	-6.29	0.787
Patients' age[3]	5.31	0.280	63.56	0.001
Type of intervention[4]	-5.36	0.570	-348.53	0.324
Fiber difference between groups[5]	-7.76	0.480	-287.22	0.657

[1] parallel or crossover; [2] > or ≤ 12-weeks; [3] > or 59.4 years; [4]foods or supplement; [5]> or ≤ 13.0 g/day.

Appendix 1: complete Medline search strategy

((((((((((((((diet therapy[title/abstract])) OR (diet therapy[mesh])) OR (food[mesh])) OR (food[title/abstract])) OR (diet[title/abstract])) OR (diet[mesh])) OR (dietary fiber[title/abstract])) OR (dietary fiber[mesh])) OR (carbohydrates[mesh])) OR (carbohydrates[title/abstract])) OR (dietary carbohydrates[title/abstract])) OR (dietary carbohydrates[mesh]))) AND ((((((((((((((((((((((((Diabetes Mellitus, Type 1[mesh])) OR (Diabetes Mellitus, Insulin-Dependent[title/abstract])) OR (Diabetes Mellitus, Insulin Dependent[title/abstract])) OR (Insulin-Dependent Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Juvenile-Onset[title/abstract])) OR (Diabetes Mellitus, Juvenile Onset[title/abstract])) OR (Juvenile-Onset Diabetes Mellitus[title/abstract])) OR (Type 1 Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Sudden-Onset[title/abstract])) OR (Diabetes Mellitus, Sudden Onset[title/abstract])) OR (Mellitus, Sudden-Onset Diabetes[title/abstract])) OR (Sudden-Onset Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Type I[title/abstract])) OR (IDDM[title/abstract])) OR (Brittle Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Ketosis-Prone[title/abstract])) OR (Diabetes Mellitus, Ketosis Prone[title/abstract])) OR (Ketosis-Prone Diabetes Mellitus[title/abstract])) OR (Diabetes, Autoimmune[title/abstract])) OR (Autoimmune Diabete[title/abstract])) OR (Diabete, Autoimmune[title/abstract])) OR (Autoimmune Diabetes[title/abstract]))) OR ((((((((((((((((((((Diabetes Mellitus, Type 2[mesh])) OR (Diabetes Mellitus, Ketosis-Resistant[title/abstract])) OR (Diabetes Mellitus, Ketosis Resistant[title/abstract])) OR (Ketosis-Resistant Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Non Insulin Dependent[title/abstract])) OR (Diabetes Mellitus, Non-Insulin-Dependent[title/abstract])) OR (Non-Insulin-Dependent Diabetes Mellitus[title/abstract])) OR (Type 2 Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Slow-Onset[title/abstract])) OR (Diabetes Mellitus, Slow Onset[title/abstract])) OR (Slow-Onset Diabetes Mellitus[title/abstract])) OR (Stable Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Type II[title/abstract])) OR (NIDDM[title/abstract])) OR (Diabetes Mellitus, Adult-Onset[title/abstract])) OR (Adult-Onset Diabetes Mellitus[title/abstract])) OR (Diabetes Mellitus, Adult Onset[title/abstract])) OR (Diabetes Mellitus, Noninsulin Dependent[title/abstract]))) NOT (((MODY[title/abstract])) OR (Maturity-Onset Diabetes Mellitus[title/abstract])))))) AND ((((((((((((Randomized controlled trials as Topic/)) OR (Randomized controlled trial/)) OR (Random allocation/)) OR (Double blind method/)) OR (Single blind method/)) OR (Clinical trial/)) OR (exp Clinical Trials as Topic/))) OR (((((((clinic$ adj trial$1) AND .tw.)) OR (((singl$ OR doubl$ OR treb$ OR tripl$) AND adj AND (blind$3 OR mask$3)) AND .tw.)) OR (Placebos/)) OR (Placebo$.tw.)) OR (Randomly allocated.tw.)) OR ((allocated adj2 random) AND .tw.)))) NOT ((((((Case report.tw.)) OR (Letter/)) OR (Historical article/)) OR (Review, multicase.pt.)) OR (Review of reported cases.pt.)))

Capítulo II

Effect of breakfasts with different glycemic index and fiber amounts on plasma glucose, insulin and ghrelin in patients with type 2 diabetes: a randomized clinical trial

(Manuscrito a ser submetido à publicação no periódico American Journal of Clinical Nutrition)

Effect of breakfasts with different glycemic index and fiber content on plasma glucose, insulin and ghrelin in patients with type 2 diabetes: a randomized clinical trial

"Post-prandial effects of carbohydrates in diabetes"

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No conflict of interest was declared.

Abbreviations:

GI = glycemic index; HGI-HF = high glycemic index and low fiber; HGI-HF = high glycemic index and high fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber; $HbA1_c$ = glycated hemoglobin; BMI = body mass index; UAE = urinary albumin excretion; HOMA-IR = homeostasis model assessment of insulin resistance index; VAS= visual analogue scale; iAUC = incremental areas under the curves; GEE = generalized estimating equation; LSD = least significance difference.

ClinicalTrials.gov Identifier: NCT01410292

ABSTRACT

Background: Postprandial glucose, an important determinant of glucose control mostly modulated by dietary carbohydrate, has been associated with cardiovascular risk and mortality in patients with diabetes. Meals with low glycemic index (GI) and rich in fiber could be particularly advantageous regarding glucose and insulin response, and appetite regulation.

Objective: To investigate the acute effect of breakfasts with different GI and total fiber content on plasma glucose and insulin, and satiety in patients with type 2 diabetes.

Design: In this crossover randomized clinical trial 14 patients with type 2 diabetes [seven men; 65.8 ± 5.2 years old; 10.0 (2.8 – 16.3) years of diabetes; BMI = 27.16 ± 3.07 kg/m²; $HbA1_C$ = 6.63 ± 0.90%] received four breakfasts: HGI-HF (high GI, high fiber), HGI-LF (high GI, low fiber), LGI-HF (low GI, high fiber), and LGI-LF (low GI, low fiber). The plasma glucose, insulin and total ghrelin were evaluated in the postprandial period (0 to 180 min). Appetite was assessed by a visual analogue scale. Area under the curves (AUC) were calculated and compared by Generalized Estimating Equations (SPSS 18.0 software).

Results: A significant meal X time interaction was observed for glucose, insulin and ghrelin response ($P< 0.001$ for all). The AUC for plasma glucose was higher in HGI-LF breakfast [9.63 mmol/L/min (8.40 – 10.85)] than in LGI-HF [8.95 mmol/L/min (7.72 – 10.19)] and LGI-LF [8.95 mmol/L/min (7.72 – 10.17) meals. The glucose AUC for HGI-HF [9.25 mmol/L/min (8.02 – 10.49)] did not differ from the other meals (P = 0.007). The HGI-LF insulin AUC [65.72 µIU/mL/min (38.24 – 93.19)] was higher than HGI-HF [57.24 µIU/mL/min (32.44 – 82.04)], and the LGI-LF insulin AUC [61.54 µIU/mL/min (36.61 – 86.48)] was higher than LGI-HF [54.16 µIU/mL/min (31.43 – 76.88)] (P = 0.038). Plasma ghrelin decreased significantly only in response to LGI-HF and LGI-LF meals. At 180 min, ghrelin was higher in the HGI-LF [387.92 pg/mL (293.63 – 482.21)] than in the LGI-HF breakfast [447.75 pg/mL (338.73 – 556.77)] without difference with other meals (P = 0.015). Subjective satiety did not differ between breakfasts.

Conclusions: Breakfast with HGI-LF had the less favorable postprandial response for glucose, insulin and ghrelin in patients with type 2 diabetes.

Key-words: glycemic index, dietary fiber, diabetes, blood glucose, ghrelin.

INTRODUCTION

The cardiovascular disease is the major cause of mortality in patients with type 2 diabetes (1). Postprandial hyperglycemia and insulin have been suggested as important risk factors for cardiovascular disease and mortality in these patients (2-4). In fact, the postprandial glucose is an important contributor to HbA1c values (5), a well-known risk factor for the development of chronic diabetic complications (6). Lifestyle interventions, such as dietary modifications (7,8) and physical exercise (9) are essential in the management of glucose control, besides drug therapy (10).

It is well known that the amount and type of carbohydrate are the primary determinants of postprandial glucose and insulin responses to food intake which also varies according to the fiber content (11,12). Moreover, the effect of carbohydrates on postprandial glucose concentration has been also attributed to the glycemic index (GI) of foods. In fact, foods with high GI are associated with a rapid absorption of glucose (13).

The postprandial glucose and insulin excursions have been also linked with appetite markers (14) such as ghrelin. This peptide is predominantly produced by the stomach and its concentrations in plasma rises gradually before and decrease immediately after a meal (15,16). The carbohydrates are probably the most potent dietary postprandial ghrelin suppressor factor (17).

Recent studies point that a low-GI diet improves the glucose control in patients with type 2 diabetes (18,19) and plays a protective role against the development of coronary artery disease (20) and metabolic syndrome (21). Similar beneficial effects have also been observed with diets rich in fiber (22-26). Furthermore, these dietary modifications have been associated with increased satiety (27,28). Therefore, one can assume that low GI diets which are particularly rich in fibers could lead to the most

advantageous postprandial metabolic profile. Thus, the present study was aimed to investigate the acute effect of four breakfasts with different GI and amounts of total fiber on postprandial plasma insulin, glucose, and apettite in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study design

In this 4x4 randomized, within-subject crossover clinical trial, patients with type 2 diabetes were assigned to four breakfasts with different total fiber amount and glycemic index: high glycemic index and high fiber content (HGI-HF), high glycemic index and low fiber content (HGI-LF), low glycemic index and high fiber content (LGI-HF), and low glycemic index and low fiber content (LGI-LF). The sequence of randomization of the four meals was computer-generated in a Web site (www.randomization.com).

The primary outcomes were acute response of plasma glucose and insulin. Total ghrelin and subjective satiety assessment were the secondary outcomes.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, the Ethics Committee of the Hospital approved the protocol and all patients gave written informed consent.

Participants

Patients with type 2 diabetes who consecutively attended the outpatient clinic of the Endocrine Division, Nutrition Unit, at Hospital de Clínicas de Porto Alegre, Brazil, were selected based on the following criteria: $HbA1_C$ <9%, oral antihyperglycemic agents and/or diet as the diabetes treatment, BMI <30 kg/m², serum creatinine <2.0 mg/dL, and random urinary albumin excretion (UAE) <174 mg/L (29). Patients with

postural hypotension or gastrointestinal symptoms suggesting severe autonomic neuropathy were not included.

Clinical evaluation

Sitting blood pressure was measured twice to the nearest 2 mmHg after a 10-min rest, using a standard digital sphygmomanometer (Omron® HEM-705CP). Hypertension was defined as blood pressure higher than 140/90 mmHg measured on two occasions or use of antihypertensive drugs (30). Patients were classified as normal (UAE <14 mg/L) or elevated urinary albumin excretion (UAE ≥14 mg/L) according to a random spot urine sample (29,31). Elevated UAE was always confirmed in a second measurement. Fundus examination was performed (by CKK) through dilated pupils, and patients were classified according to the presence or absence of diabetic retinopathy. Physical activity was graded in four levels based on a standardized questionnaire adapted to local habits (32). Positive alcohol intake was considered in patients who mentioned current intake of any alcoholic beverage. Patients were classified as current smokers or not and their ethnicity was self-identified as white or non-white.

Nutritional evaluation

The body weight and height of patients (without shoes or coats) were obtained with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. BMI was calculated. Waist circumference was measured midway between the lowest rib margin and the iliac crest, near the umbilicus, measured once to the nearest 1 cm, with flexible, non-stretch fiberglass tape.

The usual diet was assessed by a 24-h recall in the run-in period and in the day of each meal test by the research dietitian (FMS). The diet composition was analyzed considering data from USDA table and using the Nutribase 2007 Clinical Nutritional

Manager software v.7.14 (33). The fiber content was estimated according to data provided in the CRC Handbook of Dietary Fiber in Human Nutrition (34). Data intake from macronutrients was expressed as a percentage of total daily energy and the fiber intake was described in crude amounts (g).

The GI of was estimated by the weighted GI value of each consumed food: GI = GIA x gA / g + GIB x gB / g + ..., where GIA is the GI of food A, gA is the amount of available carbohydrate in food A (g), and g is the amount of available carbohydrate in grams of diet. The obtained value was multiplied by 100 and the GI was expressed in % (35). Available carbohydrate was calculated as the total carbohydrate (g) minus total fiber (g) amounts. The values of GI of each food were obtained from the International Table considering the glucose as the standard food (36).

Study protocol

Fifteen patients entered in a run-in period of one to three weeks for two visits. In the first visit laboratory and nutrition evaluation was performed by the research dietitian. In the second visit, patients underwent a clinical evaluation by the endocrinologist and received instructions to the next test days. Visits three, four, five, and six corresponded to the tests' days of the four breakfasts. After that, patients were referred to the outpatient nutrition of the Endocrine Division.

Participants received each breakfast in a randomized order on four different occasions separated by a washout period of seven days when they were advised to maintain their usual diet. On the day prior to each test meal participants were instructed to eat a standard evening meal (until at 20:00 hours) based in the patients usual diet previously prescribed by the researcher dietitian. In addition they were instructed to refrain from consuming any alcohol, caffeine or taking part in any physical activity beyond that of their typical daily activities.

In each test meal upon arrival at the Clinical Research Center of the Hospital, after a 12-h fast, participants were asked by the dietitian to record their 24-h food and beverage consumption to confirm fasting and to ensure that previous instructions had been followed. Patients were weighted and their capillary blood glucose was measured (glucometer, Accu- Check®). The meal test was performed only if fasting plasma glucose in the day of the test was between 70 mg/dL and 150 mg/dL. This procedure was performed in order to ensure that all participants initiate the meal tests with an reasonable glycemic control. Then, blood samples were drawn via an indwelling catheter for the zero time. Participants received the breakfast and were instructed to consume the meal in approximately 20 min under researcher supervision. Patients were blinded to the nutritional characteristics of breakfasts. They remained seated during the test. Blood samples were collected at 15, 30, 60, 90, 120, 150 and 180 min in the postprandial period. Appetite scale was applied on times zero, 60, 120, and 180 min.

The breakfasts were prepared by the research dietitian in the kitchen of the Clinical Research Center on the day of each test meal. At the end of breakfast, participants took their usual medications.

The assessments of the outcomes were blinded: glucose, insulin and ghrelin were measured by blinded technicians.

Breakfasts tests composition

Four breakfasts with different GI and dietary fiber amount were constructed. The macronutrients composition was maintained constant between the meals for each patient. The total energy of meals was estimated to provide 5 kcal/kg. This breakfast composition was based in the usual energy and nutrients consumed during the morning period by 174 patients with type 2 diabetes attended as outpatients in the Hospital

Nutrition Unit (21). **Table 1** provides the nutritional composition of the four test breakfasts. Foods used to prepare each test meal are described in **Box 1**.

Laboratory measurements

Plasma glucose was measured by a glucose oxidase method and $HbA1_C$ by ion exchange HPLC (Merck-Hitachi L-9100 $HbA1_C$ analyzer; reference range 4.8–6.0%; Merck, Darmstadt, Germany). UAE was measured by immunoturbidimetry (Microalb; Ames-Bayer, Tarrytown NY, USA), and serum creatinine by Jaffé's reaction. Plasma insulin was measured by a chemiluminescent method (Elecsys 2010, Basel, Switzerland). Insulin resistance was estimated by homeostasis model assessment of insulin resistance index (HOMA-IR) as follow: fasting serum insulin (μU/ml) x fasting plasma glucose (mmol/l)/22.5 (37).

Serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Darmstadt, Germany; Boehringer Mannheim, Buenos Aires, Argentina) and high-density lipoprotein (HDL) cholesterol by a homogeneous direct method (autoanalyzer, ADVIA 1650). Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula (38).

Total ghrelin was measured using a commercially available ELISA kit according to the manufacturer's protocol. Blood sample were transferred immediately to tubes containing EDTA-2Na (1 mg/mL) and HCl was added to separate the plasma (10% volume of total plasma). According to the manufacturer's protocol the intra-assay and inter-assay coefficient of variation (CV) is 1.32 and 6.62%, respectively. In our sample, the mean intra-assay CV (n=10) was equal to 1.29%.

Visual analogue scale ratings of appetite

Subjective feelings of appetite (hunger, satiety, fullness, prospective food consumption, desire to eat something fatty, salty, sweet or savory) were assessed at time

zero, 60, 120, and 180 min in the postprandial period using a visual analogue scale (VAS). This scale was composed of eight questions and for each one there was a specific word anchored at each end (from zero to 100 mm in length) to express the most positive and the most negative rating (39).

The adopted VAS was previously back-translated to Portuguese since the original scale was constructed in English language (40). Briefly, in the first stage the forward translation was made by two researchers (FMS and CKK). Then, together with these researchers, a recording observer (MJA) synthesized the results. After this, two certified translators translated the questionnaire back into the original language and a committee reviewed all the translations. In the final stage of the process the VAS was applied in a sample of 34 consecutively attended outpatients with type 2 diabetes [55.8% females, aged 60.2 (44-78) years old, and with 8 years (0-15) of education] from the same Diabetes Division of patients from the current study.

STATISTICAL PROCEDURES

Sample size

A sample size of 14 patients (80% power, 0.05 alpha, considering 20% losses) was estimated considering the difference of 238 ± 65 mg/mL/min between two areas under curves (AUC) of the glucose response after the consumption of foods with different GI and fiber amount (oat bran breakfast cereal versus β-glucan breakfast cereal) in patients with type 2 diabetes (41). Regarding the ghrelin postprandial response, the estimated sample size was nine patients based on a AUC difference of 10 ± 5 ng/L/h between two breakfasts with different quality of carbohydrates (42).

Data analyses

Time point differences between fasting and postprandial glucose, insulin, ghrelin, and VAS questions were calculated. The AUC were calculated using the trapezoidal rule. The maximum increases from the baseline concentrations were calculated by subtracting the fasting value from the highest value during the test meal. We tested for time x treatment interactions and the effect of time and meals separately using Generalized Estimating Equation (GEE) followed by multiple comparison post-hoc tests (the least significant difference, LSD). Spearman coefficient was calculated to evaluate the correlation between ghrelin with insulin, HOMA-IR, and glucose.

Data are presented as mean ± standard deviation, median (P_{25}-P_{75}), absolute and relative frequencies, or mean (CI 95%). Statistical significance was defined as P-value <0.05 and SPSS Statistical software version 18.0 was used for statistical analyses.

RESULTS

Participants

A total of 14 patients with type 2 diabetes completed the experimental protocol. Baseline clinical and laboratory characteristics, as well as anthropometric features, of the study participants are shown in **Table 2**.

Regarding antihyperglycemic oral agents, eight patients (57.1%) were using only metformin and four patients (28.6%) were using metformin plus glibenclamide. In two patients (14.3%) diet was the only diabetes therapy. Most patients (n = 11; 78.6%) were using antihypertensive drugs, including diuretics (81.8%), angiotensin converting enzyme inhibitors (63.6%), β-blockers (63.6%), calcium channel blockers (45.5%), and angiotensin II receptors antagonists (9.1%). More than 70% of patients were using lipid-lowering drugs (n = 10).

The daily dietary intake of participants before each meal test did not change (data not shown). In the previous day of meal tests patients reported intake equal to 1456.3 ± 206.2 kcal/day, 18.6 ± 3.4% of energy from protein, 29.0 ± 4.4% from fat, and 52.2 ± 3.3% from carbohydrates. Their dietary fiber intake was 19.3 ± 5.4 grams/day and 24-h GI was equal to 52.5 ± 4.6%.

During the test meals, all breakfasts were fully eaten during 12.5 ± 2.4 min. No complaints or digestive disturbances were observed. The body weight of patients did not change during the four meal tests protocol: 1st test = 70.9 ± 13.7 kg, 2nd test = 70.8 ± 13.5 kg, 3rd test = 70.7 ±13.6 kg, and 4th meal = 70.9 ± 13.7 kg; *P* = 0.239).

Plasma glucose response

The plasma glucose response showed a significant time x meal interaction (P < 0.001). Plasma glucose concentration increased after the four breakfasts and all values were different from baseline at 120 min in LGI-HF and 150 min in the other test meals. Plasma glucose significantly increased at 30 min in HGI-HF, LGI-HF, and LGI-HF and at 60 min for the HGI-LF breakfasts. These times corresponded to the highest glucose values for each meal. When the meals were compared, glucose concentration did not differ at 30 min. At 60 min, plasma glucose concentration was higher in HGI-LF as compared to HGI-HF, LGI-HF, and LGI-LF meals (P <0.001). The highest glucose concentration (worst glycemic response) was maintained at 180 min in the HGI-LF breakfast (**Figure 1A and Supplementary Table 1**).

The AUC for plasma glucose was higher in the HGI-LF breakfast [9.63 mmol/L/min (8.40 – 10.85)] than in LGI-HF [8.95 mmol/L/min (7.72 – 10.19)] and LGI-LF [8.95 mmol/L/min (7.72 – 10.17) meals. The glucose AUC for HGI-HF [9.25 mmol/L/min (8.02 – 10.49)] did not differ from the other meals (**Figure 2A**).

Plasma insulin response

A significant time x meal interaction (P < 0.001) was demonstrated in the plasma insulin response. Significant increase in plasma insulin concentration was observed after the consumption of all meals and it occurred at the first 30 min for HGI-HF, LGI-HF and LGI-HF, and at the first 60 min for the HGI-LF breakfast, when were identified the highest insulin values. The plasma insulin concentration increased from baseline to 120 min (LGI-HF), 150 min (LGI-LF), and 180 min (HGI-HF, HGI-LF). The plasma insulin concentration was different between meals at 150 min: the LGI-HF breakfast presented lower insulin concentration as compared to LGI-LF, HGI-HF, and HGI-LF breakfasts (**Figure 1B and Supplementary Table 2**).

The insulin AUC of HGI-LF breakfast [65.72 µIU/mL/min (38.24 – 93.19)] was higher than HGI-HF [57.24 µIU/mL/min (32.44 – 82.04)] without difference in comparison with the others two meals. The LGI-LF [61.54 µIU/mL/min (36.61 – 86.48)] had higher insulin AUC than LGI-HF breakfast [54.16 µIU/mL/min (31.43 – 76.88)] without difference with the other two breakfasts (**Figure 2B**). A difference between insulin AUC of HGI-LF and LGI-HF was observed, but it did not reach the statistical significance ($P = 0.06$).

The insulin resistance response to test meals followed the same pattern as described for insulin and glucose concentration with difference in AUC of HOMA-IR indexes between the four breakfasts ($P = 0.030$ for GEE). The AUC of HOMA-IR index for HGI-LF (26.5; 95%IC 13.4-32.5) was higher than HGI-HF [(22.9; 95%IC 16.3-36.6), $P = 0.019$] and LGI-HF [(20.2; 95%IC 13.6-26.9), $P = 0.032$] but did not differ from the LGI-LF breakfast [(23.4; 95%IC 14.9-31.8), $P = 0.910$]. There was no difference between the other meals.

Plasma ghrelin response

Postprandial total plasma ghrelin response to the breakfasts was evaluated in the ten firstly enrolled patients. Gender proportion, age, diabetes duration, glycemic control, body weight, BMI, and waist circumference did not differ from the other included patients (data not shown).

The plasma ghrelin response showed a significant time x meal interaction ($P < 0.001$). Total plasma ghrelin decreased after LGI-HF and LGI-LF breakfasts and did not change after HGI-HF and HGI-LF meals. The AUC for each meal was not calculated because baseline ghrelin concentrations were different between the four meals. Then, the ghrelin baseline values were included as covariates in the GEE model for the comparison of plasma ghrelin concentration between the four breakfasts. No one difference in total ghrelin was observed up to 150 min. At 180 min ghrelin concentration in the HGI-LF breakfast was higher than in the LGI-HF without difference with the HGI-HF and LGI-LF meals (**Table 3**).

Subjective appetite assessment

In the postprandial period of all breakfasts the VAS questions (hungry, satiety, fullness and desire of prospective food consumption) significantly changed from baseline ($P < 0.001$ for all analyses) but these changes did not differ between the meals ($P > 0.05$ for all analyses; data not shown). The subjective appetite assessment was also performed by the calculation of mean AUC for each question of the VAS and no difference was observed between breakfasts (**Table 4**). No correlation was observed between VAS-AUC scale questions and ghrelin-AUC (data not shown).

Correlations between plasma glucose, insulin, and ghrelin

Inverse correlations of insulin-AUC, HOMA-IR-AUC and for glucose-AUC with ghrelin-AUC were observed: insulin with ghrelin, r = -0.759 (P < 0.001); HOMA-IR with ghrelin, r = -0.875 (P < 0.001); and glucose with ghrelin, r = -0.399 (P = 0.011).

DISCUSSION

In this study, we demonstrate that, in patients with type 2 diabetes, a breakfast with HGI-LF had the less favorable postprandial response as evidenced by (i) increased plasma glucose response, (ii) increased insulin response, and (iii) lower satiety response assessed by plasma total ghrelin as compared to the other breakfast composition (HGI-HF, LGI-HF and LGI-LF). Thus, our study supports the concept that a diet with decreased GI and rich in fiber content should be encouraged in patients with diabetes.

The HGI-LF meal had higher glucose AUC as compared with meals with LGI regardless the fiber amount since it did not differ from HGI-HF breakfast. However, the lowest insulin response was observed in response to the breakfasts with highest fiber amounts (HGI-HF and LGI-HF), independent of their respective GI. Taking these together, these results suggest that to obtain the most favorable glucose and insulin postprandial profile it would be need to reduce the GI and/or increase the fiber amount of a meal. Of note, our data did not allow us to identify what was the most beneficial dietary strategy: increase the fiber content or decrease the GI.

Several studies have evaluated the effect of meals with different GI, or fiber, or carbohydrate amount in postprandial glucose and insulin in patients without diabetes (43-45). A randomized clinical trial including 12 healthy subjects showed that glucose tolerance at subsequent meals can be notably improved by consumption of cereal products with low GI and high content indigestible carbohydrates such as barley or rye kernel breakfasts (43). Another trial evaluated the postprandial glucose and insulin

response to three bread-based test meals differing in available carbohydrate and total fiber amount. The authors demonstrated a higher glucose and insulin response with white bread test meal in comparison to meals with whole grain breads (44). These studies in general demonstrated a beneficial effect of increasing fiber and/or reducing GI of meals on postprandial glucose and insulin concentration. The reduction of carbohydrate amount, besides the GI, can also reduce the postprandial glycemia and insulinemia. This aspect was demonstrated by a study performed in 26 overweight or obese adults who received four diets with different GI and total carbohydrate amount over the course of a 12-h day (45). We identified in the literature only one study that evaluated the effect of foods with different GI and fiber in glucose control in patients with diabetes. That study was designed to determine whether the addition of β-glucan reduced the GI of oat products. A lower glucose response was observed after the consumption of products with low GI and high fiber amount (oat bran breakfast cereal and β-glucan breakfast cereal) than with white bread (41).

Glucose and specially insulin response have been associated with appetite, hunger, and/or satiety (46). After a meal, the highest post-prandial glucose increment and its earliest and sharpest decline seemed to be a key for the appearance of hunger (47). In our study, despite changes in postprandial glucose and insulin after meals, no effect on subjective measures of hunger (VAS scale) was observed. Conversely, we demonstrated a reduction in total ghrelin concentration in breakfasts with low GI. Furthermore, at the end of the meal challenge (180 min) the lowest ghrelin concentration occurred with the LGI-HF meal. Therefore, we are able to observe an agreement in the objective appetite response with glucose and insulin concentrations. This aspect was reinforced by the demonstration of a strong inverse correlation between plasma insulin and glucose with ghrelin. Other authors have previously described these

same correlations in subjects without diabetes (42,48). Probably, also in patients with diabetes the plasma ghrelin has a greater sensitivity to measure satiety than subjective scales (48).

Our study has the strength of evaluating metabolic responses to breakfasts that correspond to a commonplace meal such as a sandwich plus coffee and fruit, instead a dietary formula. This aspect confers an additional practical clinical relevance to our results. In addition we were able to control for any effects of previous diet by having participants consumed a standard dinner in the previous day of the meal tests. Furthermore, all breakfasts were isocaloric and had the same distribution of macronutrients, differing only in their GI and total fiber amount.

One possible limitation of the present study could be related to the use of GI calculated from tables instead of GI determined from each included meal food. Even though, this is still a controversy subject (49,50) and we calculated the GI of meals as recommended by FAO. We used the glucose as the standard food and an average GI value if more than one GI was available. Another possible shortcoming of our study could be the measurement of total ghrelin instead of the acylated-ghrelin, which has been considered the active form involved in the regulation of appetite (51). However, recently data has shown that the des-acylated form, which accounts for more than 90% of total circulating ghrelin, has also an appetite suppressing role (52).

The current study provides relevant information about the advantageous acute postprandial effects of mixed meals rich in fiber and/or with a low GI. Probably these effects can be reproducible in during the day taken into account all meals. Actually, the increase of fiber intake and/or reduction of GI of foods are important dietary features in some valuable diets useful for the management of type 2 diabetes such as the Mediterranean diet (53). Replacement of foods with high GI and/or low fiber content

for foods with low GI and/or high fiber amount seems to be a practical alternative to dietary management of patients with diabetes. Examples of foods with low/ intermediate GI and rich in fiber are: oat bran (4 tablespoon – 60g: GI = 59% and total fiber = 8.7 g), black beans (5 tablespoon – 100g: GI = 20% and total fiber = 6.2 g), fruits as papaya (1 small slice – 100g: GI = 56% and total fiber = 2.5 g), orange (1 small unit – 100g: GI = 37% and total fiber = 2.4 g), or pear (1 medium unit – 150g; GI = 38% and total fiber = 3.9 g), and rye bread (2 slices – 50g: GI = 50% and total fiber = 3.3 g) (34,36). These approaches can reduce HbA1c values and have beneficial effects on cardiovascular disease and mortality in patients with type 2 diabetes. However this assumptions needs to be confirmed in long term clinical trials.

CONCLUSION

In patients with type 2 diabetes the worst postprandial profile for plasma glucose and insulin was observed with HGI-LF breakfast. In addition, the lowest satiety, as evaluated by total plasma ghrelin, also occurred with this meal. Reducing GI and/or increasing the fiber content of meals seem to be a relevant strategy to improve the postprandial metabolic profile of these patients.

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Table 1. Energy, macronutrientes, fiber content, and glycemic index of the breakfasts.

	HGI-HF	HGI-LF	LGI-HF	LGI-LF
Total energy (kcal)	356.98 ± 17.75	369.84 ± 18.03	360.85 ± 17.68	358.50 ± 17.75
kcal/kg	5.01 ± 1.31	5.19 ± 1.34	5.07 ± 1.31	5.04 ± 1.31
Protein (% of energy)	16.80 ± 0.03	17.20 ± 0.02	17.35 ± 0.05	17.41 ± 0.02
Fat (% of energy)	25.25 ± 0.08	25.00 ± 0.07	25.38 ± 0.123	24.78 ± 0.02
Carbohydrates (% of energy)	57.95 ± 0.07	57.73 ± 0.08	57.27 ± 0.09	57.81 ± 0.04
Total fiber (g)	5.95 ± 0.30	2.48 ± 0.43	6.21 ± 0.30	1.95 ± 0.01
Glycemic index (%)	60.36 ± 0.02	60.94 ± 1.73	37.69 ± 0.04	39.84 ± 1.33

Data are mean ± standard deviation.

Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber.

Box 1. Foods consumed according each breakfast *.

HGI-HF	HGI-LF
White Bread (50 g)	White Bread (50 g)
Margarine Becel® (7 g)	Margarine Becel® (7 g)
Mozzarella cheese (15 g)	Mozzarella cheese (10 g)
Lean ham (15 g)	Lean ham (15 g)
Semi-skimmed milk (150 mL)	Skimmed milk (175 mL)
Decaffeinated coffee (50 mL)	Decaffeinated coffee (50 mL)
Breakfast cereal All-Bran® (10 g)	Cream cracker (15 g)
Papaya (75 g)	Banana (30 g)
LGI-HF	**LGI-LF**
Orange cake (45 g)	Orange cake (60 g)
Whole milk (130 mL)	Mozzarella cheese (10g)
Decaffeinated coffee (40 mL)	Skimmed milk (275 mL)
Skim yogurt (130 g)	Decaffeinated coffee (25 mL)
Breakfast cereal All-Bran® (15 g)	Apple without peel (50 g)
Papaya (35 g)	

* Amounts of foods considering a meal test for a patient with body weight equal to 70 kg. Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber

Table 2. Baseline characteristics of patients with type 2 diabetes (n=14)

Clinical Characteristics	
Gender (male)	7 (50.0%)
Ethnicity (white)	11 (78.6%)
Age (years)	65.8 ± 5.2
Diabetes duration (years)	10.0 (2.8 – 16.3)
Current smoking	0 (0.0%)
Current alcohol beverage intake	8 (57.1%)
Sedentary lifestyle	10 (71.4%)
Hypertension	11 (78.6%)
Systolic blood pressure (mm Hg)	143.00 ± 9.71
Diastolic blood pressure (mm Hg)	79.07 ± 6.03
Diabetic retinopathy	1 (7.1%)
Vasculopathy	1 (7.1%)
Microalbuminuria	1 (7.1%)
Cardiovascular events	3 (21.4%)
Acute myocardial infarction	2 (14.3%)
Stroke	1 (7.1%)
Laboratory Characteristics	
Fasting plasma glucose (mg/dL)	120.21 ± 17.29
$HbA1_C$ (%)	6.63 ± 0.90
Total cholesterol (mg/dL)	164.43 ± 36.50
HDL cholesterol (mg/dL)	
Males	43.00 ± 16.85
Females	48.43 ± 1 6.20
LDL cholesterol (mg/dL)	100.35 ± 24.04
Triglycerides (mg/dL)	130.92 ± 63.12
Urinary albumin excretion (mg/L)	4.85 (3.00 – 9.53)
Serum creatinine (mg/dL)	0.89 ± 0.19
Anthropometric Characteristics	
Weight (kg)	71.19 ± 13.49
BMI (kg/m^2)	27.16 ± 3.07
Waist circumference (cm)	
Males	102.14 ± 4.32

Females	85.70 ± 9.88

Data are mean ± standard deviation, median (P_{25}-P_{75}), or number (%) of patients with the analyzed characteristic.

Table 3. Plasma ghrelin postprandial response of breakfasts with different GI and fiber content: comparison within each meal and between meals

Time	HGI-HF	HGI-LF	LGI-HF	LGI-LF	*P*-value**
0 min	486.87 (452.23 – 521.52) [a]	489.01 (456.79 – 521.52) [a]	502.33 (466.09 – 538.58) [a]	493.67 (460.07 – 527.27) [a]	**0.001**
30 min	442.55 (378.97 – 506.12) [a]	426.77 (381.64 – 471.89) [a]	440.23 (414.72 – 465.74) [b]	440.51 (414.30 – 466.73) [b]	0.876
60 min	416.29 (350.89 – 481.71) [a]	408.96 (353.24 – 464.68) [a]	440.23 (414.72 – 465.74) [c]	440.51 (414.30 – 466.73) [c]	0.308
120 min	419.87 (379.64 – 460.10) [a]	408.03 (336.45 – 479.60) [a]	375.51 (311.29 – 439.73) [d]	391.21 (341.61 – 440.82) [d]	0.240
180 min	403.08 (302.87 – 503.30) [a,1,2,3]	447.75 (338.73 – 556.77) [a,1,2]	387.92 (293.63 – 482.21) [e,1,3]	418.81 (352.50 – 485.13) [e,1,2,3]	**0.038**
P*-value	0.137	0.388	**0.002**	**0.007**	-

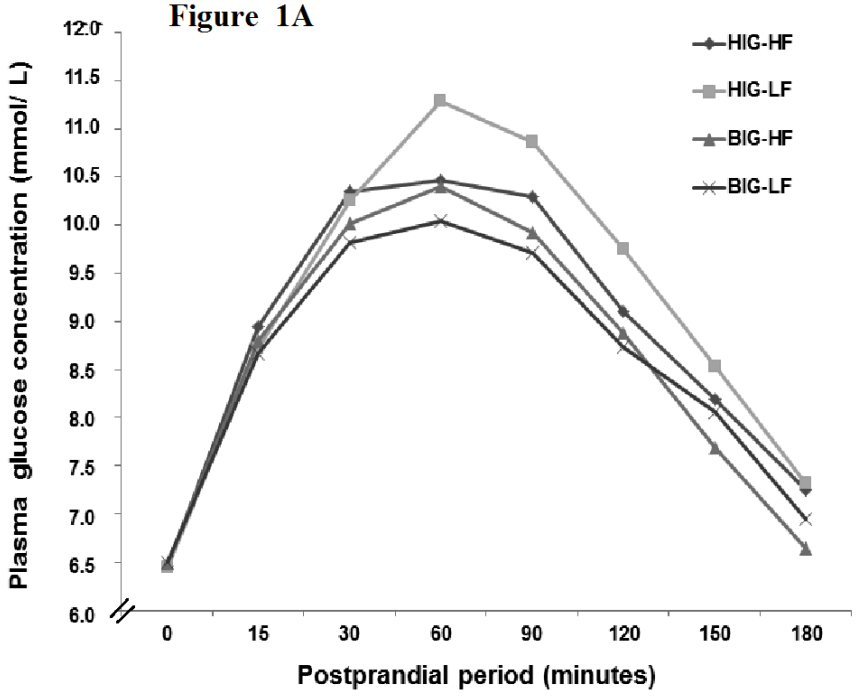
GEE analysis with LSD post-hoc comparisons, adjusted for baseline ghrelin values (mean value = 492.97 pg/mL). Data are mean (95% CI). P* indicates the significance for the comparison between the times at each meal: different superscript letters indicate significant difference in comparison between each time and the 0' time. P** indicates the significance for the comparison between the meals at each time: different superscript numbers indicate significant difference between meals. Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber

Table 4. Visual analogue scale of satiety: area under the curve response of breakfasts with different GI and fiber content for each question

	HGI-HF	HGI-LF	LGI-HF	LGI-LF	P- value
1. Are you hungry?	25.20	23.35	25.75	29.29	0.509
(0 = Not hungry / 100 = Have never been more hungry)	(17.14 – 33.27)	(12.41 – 34.28)	(15.57 – 35.94)	(17.80 – 40.77)	
2. Have you had enough to eat?	70.51	62.86	66.85	61.58	0.089
(0 = Completely empty / 100 = Cannot eat another bite)	(61.41 – 79.61)	(48.96 – 76.76)	(53.36 – 80.34)	(50.13 – 73.04)	
3. Are you full? How full?	61.36	60.82	63.49	62.45	0.921
(0 = Not at all full / 100 = Totally full)	(49.43 – 73.29)	(48.91 – 72.73)	(49.42 – 77.55)	(52.19 – 72.72)	
4. How much more do you think you can eat?	28.49	31.30	29.16	31.22	0.576
(0 = Nothing at all / 100 = A lot)	(18.86 – 38.12)	(21.59 – 41.01)	(17.88 – 40.43)	(20.07 – 42.36)	
5. Would you like to eat something sweet?	83.34	80.08	79.48	81.07	0.321
(0 = Yes, very much / 100 = Not at all)	(76.92 – 89.76)	(72.58 – 87.59)	(70.69 – 88.26)	(73.87 – 88.27)	
6. Would you like to eat something salty?	55.71	58.51	52.37	54.70	0.391
(0 = Yes, very much / 100 = Not at all)	(41.88 – 69.54)	(46.95 – 70.08)	(38.02 – 66.72)	(41.95 – 57.46)	
7. Would you like to eat something flavorful?	61.69	60.23	59.49	54.38	0.607
(0 = Yes, very much / 100 = Not at all)	(48.36 – 75.02)	(49.11 – 71.36)	(44.78 – 74.19)	(44.36 – 64.39)	
8. Would you like to eat something fatty?	74.56	80.04	76.26	82.91	0.396

(0 = Yes, very much / 100 = Not at all)	(60.84 – 88.28)	(70.99 – 89.09)	(66.00 – 86.52)	(75.80 – 90.02)

GEE analysis with LSD post-hoc comparisons. Data are mean AUC for 180 minutes post-prandial (95% CI). **Abbreviations**: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber.



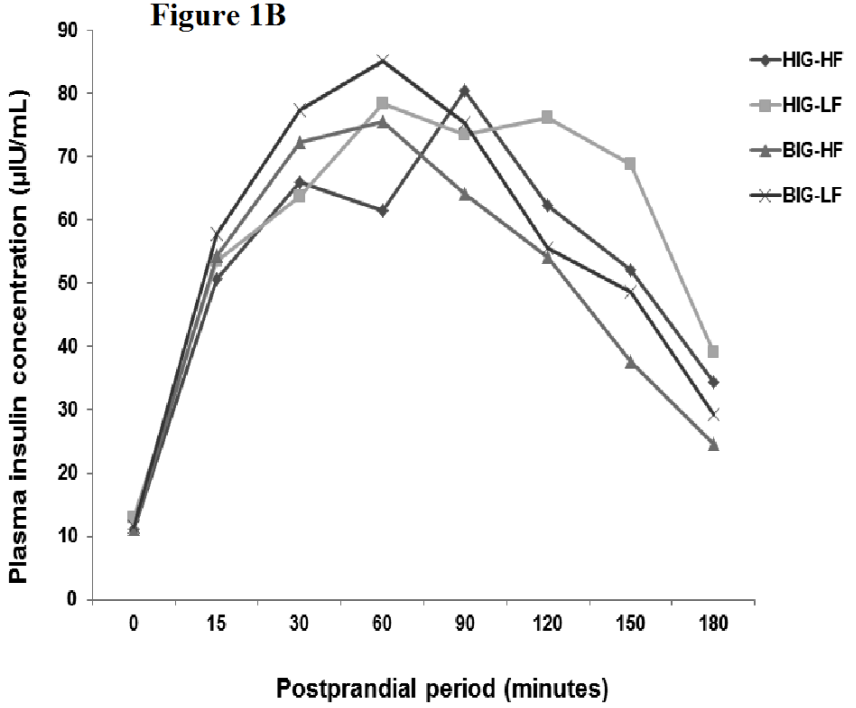


Figure 1: Plasma glucose and insulin postprandial response to breakfasts in test.

(A): plasma glucose concentration in postprandial period. GEE analysis showed a significant time x meal interaction for glucose response ($P < 0.001$) and a significant time effect for all meals ($P < 0.001$). (B): plasma insulin concentration in postprandial period. GEE analysis showed a significant time x meal

interaction for insulin response ($P < 0.001$)) and a significant time effect for all meals ($P < 0.001$). Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber.

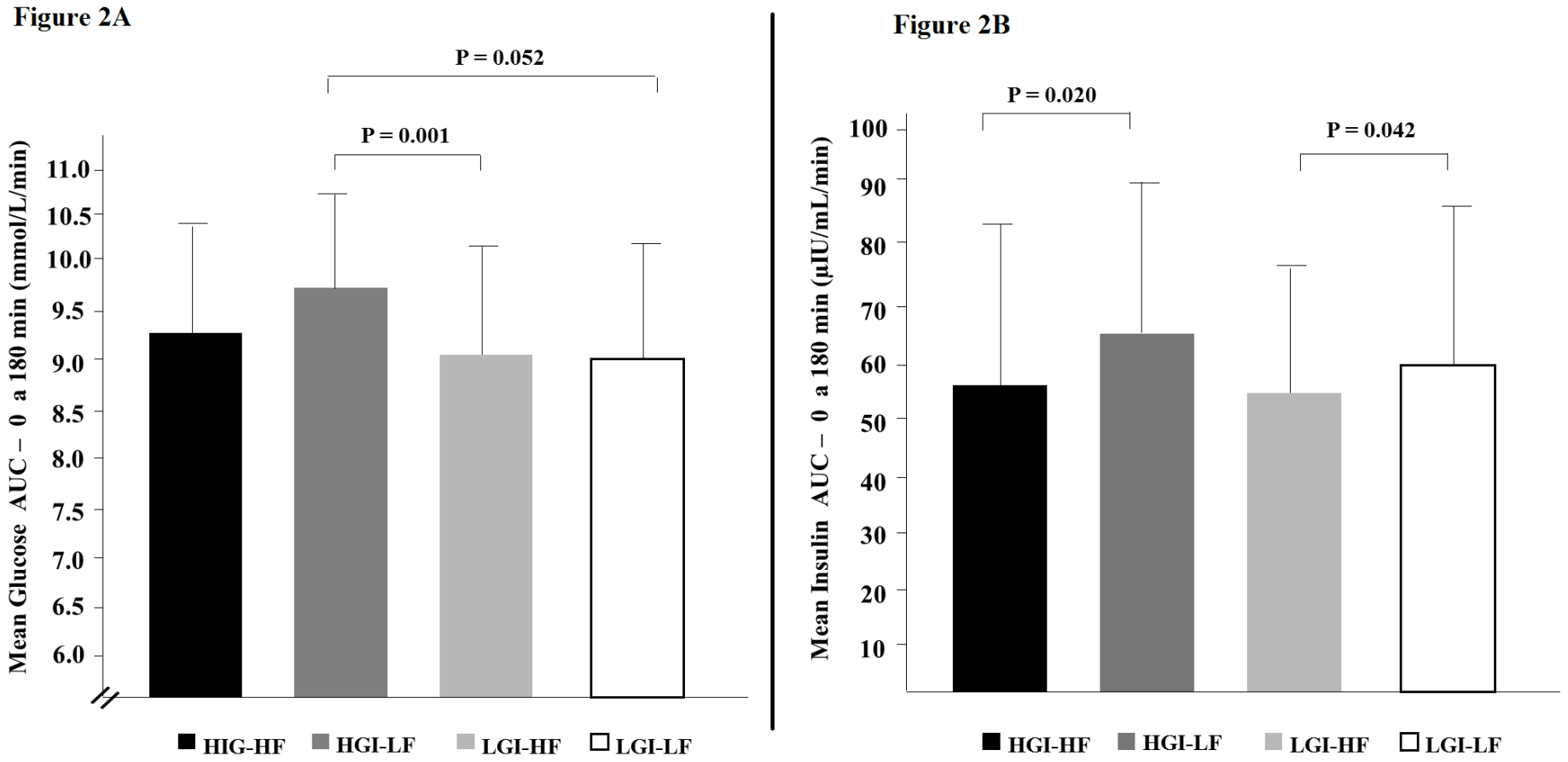


Figure 2: Plasma glucose and insulin area under the curve response of breakfasts with different GI and fiber content.

(A) a significant difference between mean glucose AUC for breakfasts in test was observed (P= 0.007). (B) a significant difference between mean glucose AUC for breakfasts in test was observed (P= 0.038). GEE analysis followed by LSD post-hoc tests, with P values presented in the Figures. Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber.

Supplementary Table 1. Plasma glucose postprandial response (mmol/L) of breakfasts with different GI and fiber content: comparison within each meal and between meals

Time	HGI-HF	HGI-LF	LGI-HF	LGI-LF	*P*-value**
0 min	6.46 (5.83 – 7.09) [a]	6.44 (5.89 – 6.98) [a]	6.49 (5.95 – 7.03) [a]	6.49 (5.88 – 7.10) [a]	0.992
15 min	8.94 (8.08 – 9.81) [b]	8.71 (7.87 – 9.56) [b]	8.80 (8.00 – 9.59) [b]	8.67 (7.79 – 9.55) [b]	0.918
30 min	10.35 (9.31 – 11.39) [c]	10.25 (9.12 – 11.39) [c]	10.02 (9.06 – 10.98) [c]	9.82 (8.70 – 10.93) [c]	0.724
60 min	10.46 (8.95 – 11.97) [d, 1]	11.29 (9.96 – 12.62) [d,2]	10.40 (9.01 – 11.79) [d,1]	10.04 (8.74 – 11.35) [d,1]	**<0.001**
90 min	10.29 (8.81 – 11.77) [e,1]	10.87 (9.51 – 12.23) [e, 1]	9.92 (8.38 – 11.46) [e,1,2]	9.72 (8.19 – 11.24) [e,1,2,3]	**0.005**
120 min	9.09 (7.61 – 10.59) [f, 1]	9.74 (8.23 – 11.25) [f, 2]	8.89 (7.29 – 10.48) [f,1]	8.73 (7.13 – 10.33) [f,1]	**0.001**
150 min	8.19 (6.71 – 9.67) [g,1]	8.54 (6.92 – 10.15) [g,1]	7.69 (6.11 – 9.26) [a,1,2]	8.06 (6.59 – 9.52) [g,1,2]	**0.045**
180 min	7.25 (5.78 – 8.72) [a,1]	7.32 (5.82 – 8.82) [a,1,2]	6.64 (5.23 – 8.06) [a,1]	6.94 (5.56 – 8.33) [a,1]	**0.004**
P*-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	-

GEE analysis with LSD post-hoc comparisons: *P*-value* indicates comparison within each meal and different superscript letters indicate a significant difference between each time and baseline (LSD <0.05); *P*-value** indicates comparison between meals and different superscript numbers indicate significant differences (LSD <0.05). Data are mean (95% CI). Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber.

Supplementary Table 2. Plasma insulin postprandial response (µIU/mL) of breakfasts with different GI and fiber content: comparison within each meal and between meals

Time	HGI-HF	HGI-LF	LGI-HF	LGI-LF	*P*-value**
0 min	11.06 (7.69 – 14.42) [a]	12.89 (8.88 – 16.90) [a]	11.22 (8.39 – 14.06) [a]	11.55 (7.79 – 15.31) [a]	0.236
15 min	50.64 (19.92 – 81.36) [b]	53.44 (21.22 – 85.67) [b]	54.41 (13.20 – 95.62) [b]	57.76 (20.30 – 95.22) [b]	0.724
30 min	66.01 (29.53 – 102.50) [c]	63.75 (30.64 – 96.86) [c]	72.21 (20.02 – 124.40) [c]	77.47 (25.52 – 129.42) [c]	0.503
60 min	61.46 (32.86 – 90.06) [d]	78.42(45.68 – 111.17) [d]	75.60 (37.39 – 113.80) [d]	85.22 (43.61 – 126.85) [d]	0.072
90 min	80.37 (37,.57 – 123.17) [e]	73.50 (46.34 – 100.65) [e]	64.06 (40.28 – 87.85) [e]	75.25 (48.59– 101.91) [e]	0.191
120 min	62.29 (35.75 – 88.83) [f]	76.26 (43.78 – 108.74) [f]	54.14 (35.73– 72.54) [f]	55.52 (36.88 – 74.17) [f]	0.111
150 min	52.13 (27.65 – 76.61) [g,1]	68.85 (29.80 – 107.89) [g,2]	37.62 (23.05 – 52.19) [a,3]	48.72 (30.36 – 67.09) [g,1]	**0.020**
180 min	34.34 (21.41 – 47.28) [h,1]	39.00 (20.04 – 57.95) [h,1]	24.60 (16.57 – 32.63) [a,2]	29.35 (19.92 – 38.77) [a,1,2]	**0.015**
P*-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**-**

GEE analysis with LSD post-hoc comparisons. Data are mean (95% CI). P* indicates the significance for the comparison between the times at each meal: different superscript letters indicate significant difference in comparison between each time and the 0' time. P** indicates the significance for the comparison

between the meals at each time: different superscript numbers indicate significant difference between meals. Abbreviations: HGI-HF = high glycemic index and high fiber; HGI-LF = high glycemic index and low fiber; LGI-HF = low glycemic index and high fiber; LGI-LF = low glycemic index and low fiber

CONSIDERAÇÕES FINAIS

Através de revisão sistemática com metanálise de 11 ECR com pelo menos oito semanas de duração demonstrou-se que dietas ricas em fibras (~ 20g/ 1000 calorias) promovem uma redução absoluta de 0,50% na HbA1c e de cerca de 10 mg/dl na glicemia plasmática de jejum em pacientes com DM tipo 2. A importância das fibras dietéticas e do IG no controle glicêmico e na saciedade de pacientes com DM tipo 2 foi reforçada pelos resultados do ensaio clínico randomizado cruzado conduzido com quatro refeições em teste. Nesse ensaio, que representa uma prova de conceito, o consumo de desjejum com elevado IG e baixo conteúdo de fibras apresentou um perfil metabólico pós-prandial menos favorável (maior resposta da glicemia e da insulina), além de ter tido menor efeito na saciedade.

Os dados originais apresentados na presente tese de doutorado indicam que a orientação nutricional de pacientes com DM tipo 2, voltada à melhora do controle glicêmico e à promoção de saciedade prolongada, deve priorizar o consumo de alimentos com baixo IG e/ou com maior conteúdo de fibras. Para que a dieta desses pacientes apresente nas 24 horas um baixo IG e um conteúdo elevado de fibras é necessário que seja estimulado o consumo diário de alimentos integrais como aveia, granola e/ou pão de centeio no desjejum; de leguminosas como feijão e lentilha e de vegetais no almoço e no jantar; bem como de frutas como mamão, laranja, bergamota e pera junto às refeições principais e/ou nos lanches intermediários.

Como perspectiva futura, novos ensaios clínicos randomizados que incluam manipulação dietéticas do conteúdo de fibras e do IG, no contexto de 24 horas, realizados durante períodos mais prolongados, deverão confirmar os dados observados no experimento agudo realizado. Provavelmente, dentro de um contexto de refeição/ dieta usual, ambas as manipulações dietéticas (reduzir IG e aumentar conteúdo de fibras) sejam importantes e possam representar duas opções de conduta dietoterápica a ser adotada na dependência do perfil de cada paciente com diabetes.