UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

EFEITO DA FIBRA ALIMENTAR EM PACIENTES COM DIABETES MELITO: AVALIAÇÃO AGUDA DA RESPOSTA GLICÊMICA E INSULINÊMICA E REVISÃO SISTEMÁTICA DE DESFECHOS RENAIS

TESE DE DOUTORADO

CLÁUDIA MESQUITA DE CARVALHO

Porto Alegre, fevereiro de 2018

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TESE DE DOUTORADO

Cláudia Mesquita de Carvalho

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CONTEÚDO

APRESENTAÇÃO

Esta tese de doutorado segue o proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da UFRGS, sendo apresentada através de uma breve revisão da literatura e dois manuscritos acerca do tema estudado:

CAPÍTULO I: Introdução

CAPÍTULO II: Artigo original referente ao ensaio clínico randomizado acerca do efeito de desjejuns com diferentes fontes de fibra solúvel sobre a glicemia e insulinemia em pacientes com Diabetes Melito tipo 2, publicado no periódico: *American Journal of Clinical Nutrition*: *de Carvalho CM, de Paula TP, Viana LV, Machado VM, de Almeida JC, Azevedo MJ. Plasma glucose and insulin responses after consumption of breakfasts with different sources of soluble fiber in type 2 diabetes patients: a randomized crossover clinical trial. Am J Clin Nutr. 2017 Nov;106(5):1238-1245. doi: 10.3945/ajcn.117.157263*

CAPÍTULO III: Artigo referente à revisão sistemática acerca do consumo de fibras e doença renal do diabetes, a ser submetido para publicação no periódico *Critical Reviews in Food Science and Nutrition.*

CAPÍTULO IV: Considerações finais

LISTA DE ABREVIATURAS E SIGLAS

ADA *American Diabetes Association*

AHA *American Heart Association*

AUC *Area under the curve*

CKD *Chronic kidney disease*

CKD-EPI *Chronic Kidney Disease Epidemiology Collaboration*

CVD *Cardiovascular disease*

DASH *Dietary Approaches to Stop Hypertension*

DKD *Diabetic kidney disease*

DM Diabetes Melito/ Diabetes Mellitus

DRD Doença renal do diabetes

eGFR *Estimated glomerular filtration rate*

HbA1c Hemoglobina glicada/ *Glycated hemoglobina*

HCPA Hospital de Clínicas de Porto Alegre

HFD *High fiber from diet*

HFS *High fiber from supplement*

iAUC *Incremental area under the curve*

PREDIMED *PREvencion con DIeta MEDiterranea*

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

TFG Taxa de filtração glomerular

T2D *Type 2 Diabetes*

UAE *Urinary albumin excretion*

UF *Usual fiber*

WINPEPI *PEPI-for-Windows*

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CAPÍTULO I

INTRODUÇÃO

O Diabetes Melito (DM) é um distúrbio metabólico, na qual ocorre hiperglicemia resultante da diminuição da secreção, da ação da insulina ou de ambos. Pode ser classificado principalmente em duas grandes categorias: DM tipo 1 e tipo 2. O DM tipo 1 tem como causa a deficiência absoluta de secreção de insulina. O DM tipo 2 representa aproximadamente 90 a 95% de todos os tipos de diabetes, sendo a forma mais comum da doença, ocorre geralmente na vida adulta, e tem sua prevalência aumentada conforme a idade, estando associado ao excesso de peso e obesidade na maioria dos casos (1).

Esta doença afeta aproximadamente 425 milhões de pessoas no mundo e acredita-se que em 2035 irá atingir 629 milhões de indivíduos, número que equivale a um aumento de 48% da doença (2). É considerada um problema de saúde pública, alcançando proporções epidêmicas. As implicações de custos do DM são insustentáveis, especialmente nas economias emergentes e em desenvolvimento (2). O DM tipo 2 representa um dos maiores problemas de saúde pública em nosso país em razão da acentuada morbimortalidade e dos altos custos envolvidos no seu tratamento (3). O Brasil está entre os dez países do mundo com maior prevalência de diabetes. Hoje já são 12,5 milhões de brasileiros com a doença, aproximadamente 8,7% de adultos (2). A projeção para 2045 é de que o número de brasileiros com DM aumentará para 20,3 milhões (2).

A hiperglicemia crônica, resultante da resistência à ação da insulina e da incapacidade pancreática em suplantar essa resistência, associada a fatores genéticos e ambientais está associada ao desenvolvimento de complicações microvasculares e macrovasculares (4). Entre elas, a doença cardiovascular é a causa mais frequente de mortalidade em pacientes com DM tipo 2 (5). Outra complicação crônica, a doença renal do diabetes (DRD) também está associada ao aumento da mortalidade, principalmente relacionada com a doença cardiovascular (3), por ser um fator de risco importante para este desfecho (6). A DRD acomete 30 a 50% dos pacientes com DM (7), é diagnosticada pela presença de albuminúria e/ou reduzida taxa de filtração glomerular (TFG) na ausência de sinais e sintomas de outras causas primárias de dano renal (4) **(Tabela 1)**. É a principal causa de doença renal crônica em pacientes que realizam terapia de substituição renal (8).

Modificações no estilo de vida, em especial o manejo da dieta, são recomendadas para um adequado controle glicêmico, que está associado à redução das complicações crônicas (4). Tanto a hiperglicemia de jejum como a pós-prandial são fatores de risco cardiovascular em pacientes com DM, e tem associação com eventos cardiovasculares e mortalidade (9, 10). Ainda, um adequado controle glicêmico demonstra benefício no desenvolvimento de albuminúria em pacientes com DM (11, 12). Tanto os testes de glicemia quanto a hemoglobina glicada (HbA1c) são considerados tradicionais para a avaliação do controle glicêmico (3). A glicemia pós-prandial, dependendo do grau de compensação glicêmica, pode ser responsável por até 70% ou mais dos valores de HbA1c (13, 14). De fato, a HbA1c apresenta uma correlação forte com a glicemia média, sendo que uma glicemia média de 154 mg/dl corresponde a HbA1c igual a 7% (15).

A resposta glicêmica pós-prandial é influenciada especialmente pelos carboidratos, uma vez que são convertidos quase que em sua totalidade em glicose nas primeiras horas após consumidos. Essa influência é dependente da velocidade de liberação deste macronutriente na corrente sanguínea, do seu tempo de depuração consequente à síntese e secreção de insulina e da sensibilidade tecidual periférica à ação desse hormônio (16). Tais efeitos são determinados tanto pela quantidade como pela qualidade do carboidrato consumido. Entre outros fatores, a qualidade do carboidrato presente nos alimentos pode ser avaliada pelo teor de fibras alimentares e pelo índice glicêmico (17).

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. Inclui polissacarídeos, oligossacarídeos, lignina, além de substâncias inerentes às plantas (18). São classificadas em fibras solúveis e insolúveis, sendo que as fibras solúveis se diluem em água formando géis viscosos, e incluem as pectinas, as gomas, a inulina, mucilagens e polissacarídeos de armazenamento. Entre as fibras insolúveis, estão a celulose, as hemiceluloses e a lignina (18, 19).

A maioria das diretrizes recomenda o consumo de pelo menos 25g de fibras totais por dia ou 14 gramas a cada 1000 calorias ingeridas, a fim de auxiliar na prevenção do aparecimento de doenças crônicas (20, 21). A recomendação para pacientes com DM não difere daquela definida para a população geral (4). Esses pacientes devem seguir a recomendação de 14 gramas de fibra a cada 1000 calorias ingeridas ou 25 g/dia para mulheres e 38 g/dia para homens (22). A *American Diabetes Association* (ADA) sugere que a ingestão de carboidratos ocorra através de legumes, frutas, grãos integrais com ênfase em alimentos com mais alto teor de fibras e menor em carga glicêmica, preferível a outras fontes, especialmente aquelas que contêm açúcares adicionados (4).

As fibras da dieta podem ser obtidas através da ingestão de alimentos fonte ou por meio de suplementos de fibras solúveis (ex.: psyllium, inulina, gomas). Não existem suplementos apenas de fibras insolúveis disponíveis comercialmente. A literatura acerca da influência das fibras dietéticas no controle glicêmico de pacientes com DM é vasta e consistente em demonstrar benefícios do consumo aumentado de fibras dietéticas na redução da glicemia e/ou HbA1c (23-25). A literatura também contempla estudos acerca do efeito agudo do consumo de refeições e/ou alimentos ricos em fibras ou com adição de suplementos de fibras na resposta glicêmica pós-prandial em pacientes com DM (26-28). O benefício do consumo de fibras no controle glicêmico parece ser atribuído especialmente às fibras solúveis. Esses efeitos decorrem da viscosidade e da formação de gel no conteúdo intestinal tornando mais lenta a absorção e digestão dos carboidratos, alteração dos níveis de incretinas e ainda tem sido associado ao aumento da sensibilidade à insulina (18).

Não é possível observar na literatura estudos em indivíduos com ou sem DM que tenham comparado o efeito de refeições com mesmo conteúdo de fibras, porém proveniente de diferentes fontes (suplemento ou alimento), na glicemia pós-prandial. Além disso, a fibra alimentar é um dos principais tratamentos não farmacológicos para o DM e suas complicações crônicas (29). Em relação à DRD, estudo transversal com mais de cinco mil pacientes, e apenas um pequeno subgrupo com DM, demonstrou que o risco de albuminúria foi reduzido com a ingestão de fibras alimentares (30). O consumo de fibra tem sido associado à redução de níveis de creatinina (31, 32) e doença renal crônica em pacientes sem DM (33). Em pacientes com DM não está claro o quanto as fibras auxiliam em evitar a progressão da DRD.

Embora a recomendação de uma dieta rica em fibras esteja bem estabelecida para pacientes na população em geral e em pacientes com DM, por auxiliar principalmente no controle glicêmico e proporcionar um efeito protetor no desenvolvimento da doença (34), o papel dos nutrientes isoladamente no desenvolvimento de complicações crônicas do DM ainda não está completamente esclarecido. Nesse contexto, a avaliação da ingestão alimentar a partir de padrões alimentares parece representar um método adequado para estimar essa relação, pois os indivíduos ingerem refeições e não nutrientes de forma isolada (20). Padrões alimentares são definidos como quantidades, proporções, variedade ou combinações de diferentes alimentos e bebidas na alimentação e a frequência com a qual eles são habitualmente consumidos (35). Padrões de dietas ricos em fibras têm sido amplamente recomendados pelas diretrizes com objetivos de promover uma alimentação adequada e saudável e reduzir as doenças crônicas não transmissíveis. São exemplos de padrões de dieta ricos em fibras a dieta Mediterrânea, dieta DASH (*Dietary Approaches to Stop Hypertension*) e dieta vegetariana (20, 36).

Embora as fibras alimentares tenham sido estudadas amplamente no tratamento do DM, e evidenciam inúmeros benefícios, não foi possível observar na literatura se o efeito do suplemento ou alimento fonte de fibra solúvel acarretam os mesmos resultados na resposta glicêmica e insulinêmica de pacientes com DM. Ainda, é necessário elucidar o efeito da fibra alimentar em desfechos de complicações do DM, tais como a DRD. A obtenção destas respostas contribui para que as orientações de práticas alimentares para esta população sejam feitas com maior embasamento científico.

Com base no exposto, a presente tese de doutorado sumariza o resultado de dois projetos, descritos sob a forma de dois artigos científicos, desenvolvida com o objetivo de: (1) comparar o efeito agudo da ingestão de fibras solúveis de alimentos ou suplementos após uma refeição usual na glicose e insulina plasmáticas pós-prandiais em pacientes com DM tipo 2; (2) avaliar o efeito da fibra alimentar na doença renal do diabetes.

Tabela 1 – Doença renal do diabetes | Estágios de classificação da doença renal crônica de acordo com a taxa de filtração glomerular e excreção urinária de albumina

Estágios	Descrição	Taxa de filtração glomerular (ml/min/1,73 m2)
1	TFG normal ou elevada*	≥90
2	TFG levemente reduzida*	60 a 89
3A	Moderada redução da TFG	45 a 59
3B	Redução marcada da TFG	30 a 44
4	Redução grave da TFG	15 a 29
5	Insuficiência renal	<15

* EUA elevada: Concentração de albumina: ≥14 mg/L; Índice albumina:creatinina: ≥30 mg/g; Amostra de urina de 24h: ≥30 mg/24h). TFG: Taxa de filtração glomerular; EUA: Excreção urinária de albumina. Fonte: Diretrizes da Sociedade Brasileira de Diabetes 2015-2016.

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CAPÍTULO II

Plasma glucose and insulin responses after consumption of breakfasts with different sources of soluble fiber in type 2 diabetes patients: a randomized crossover clinical trial

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Plasma glucose and insulin responses after consumption of breakfasts with different sources of soluble fiber in type 2 diabetes patients: a randomized crossover clinical trial

Plasma glucose response after soluble fiber intake

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Abbreviations list:

AUC: area under the curve; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; HbA1c, glycated hemoglobin; HCPA, Hospital de Clínicas de Porto Alegre; HFD: high fiber from diet; HFS: high fiber from supplement; Type 2 Diabetes (T2D), iAUC: incremental area under the curve; UAE: urinary albumin excretion; UF: usual fiber; WINPEPI: PEPI-for-Windows

Abstract

Background: The amount and quality of carbohydrates are important determinants of plasma glucose after meals. Regarding fiber content, it is unclear whether the intake of soluble fibers from foods or supplements has an equally beneficial effect on lowering the postprandial glucose.

Objective: To compare the acute effect of soluble fiber intake from foods or supplement after a common meal on postprandial plasma glucose and insulin in patients with type 2 diabetes.

Design: A randomized crossover clinical trial was conducted in patients with type 2 diabetes. Patients consumed isocaloric breakfasts (369.8±9.4kcal) with high amounts of fiber from diet food sources (HFD; total fiber 9.7g; soluble fiber 5.4g), high amounts of soluble fiber from guar gum supplement (HFS; total fiber 9.1g; soluble fiber 5.4g), and normal amounts of fiber (UF; total fiber 2.4g; soluble fiber 0.8g). Primary outcomes were postprandial plasma glucose and insulin (0-180min). Data were analyzed by repeated measures analysis of covariance (ANOVA) and post hoc Bonferroni test.

Results: A total of 19 patients [65.8±7.3 years; 10 (5-9) years of diabetes duration; glycated hemoglobin (HbA1c) 7.0±0.8%; body mass index (BMI) 28.2±2.9kg/m^2] completed 57 meal tests. After breakfast, the incremental area under the curve (iAUC) for plasma glucose [mg/dL.min; mean (95%CI)] did not differ between HFD [7861(6257, 9465)] and HFS [7847(5605, 10090)] (*p*=1.00) and were both lower than UF [9527(7549, 11504)] (*p*=0.014 and p=0.037, respectively). Insulin iAUCs [uUI/mL.min; mean (95%CI)] did not differ (*p*=0.877): HFD [3781(2513, 5050)], HFS [4006(2711, 5302), and UF [4315(3027, 5603].

Conclusions: Higher fiber intake was associated with lower postprandial glucose at breakfast, and the intake of soluble fiber from the food and supplement had a similar effect in patients with type 2 diabetes.

Trial registration: Clinicaltrials.gov NCT02204384.

Keywords: plasma glucose, plasma insulin, postprandial period, soluble fiber, dietary fiber, type 2 diabetes

Introduction

An estimated 415 million adults worldwide were living with diabetes and it is expected that the population of patients with type 2 diabetes (T2D) will continue to grow (1). Dietary interventions are essential for blood glucose control and are strongly related to glycated hemoglobin (HbA1c) values (2). Postprandial glucose levels, depending on the degree of glycemic control, can contribute up to 70% on HbA1c values in patients with diabetes (3, 4). In fact, postprandial hyperglycemia has been suggested as a major risk factor for cardiovascular disease and mortality in patients with T2D (5). Postprandial glycemic response is particularly influenced by dietary carbohydrates, given both the amount and quality of carbohydrate consumed. In this sense, the fiber content (6) and glycemic index (7) of foods are important determinants of postprandial glucose responses.

The protective role of diets rich in fiber for all-cause mortality was already demonstrated in patients with diabetes (8) and many studies have demonstrated the benefit of dietary or supplemented fiber consumption on glycemic control in patients with T2D (9-13). In a cross-sectional study we showed that the intake of ≥5 g of soluble fibers from food played a protective role against the metabolic syndrome in patients with T2D (12). We also demonstrated that adding a soluble fiber supplement (10 g/day) to the normal diet for a six-week period resulted in a decrease HbA1c in patients with T2D (13). The beneficial acute effect of soluble fiber intake (psyllium, beta-glucan, and guar) on postprandial plasma glucose response was already observed in patients with diabetes (14-16) after the consumption of a high fiber meal (17) or single beverages or foods (18, 19).

Although there is strong evidence about the benefits of high soluble fiber consumption on glucose control in patients with T2D, it is still unclear whether the effects of fiber intake from dietary sources and supplements are the same. It is known that the fibers have different characteristics and even among the different types of soluble fiber sources from food it is possible to observe different beneficial effects on health (20, 21). A better understanding of the acute effect of soluble fiber intake on glycemic response might allow the adoption of more specific and practical dietary alternatives for patients with T2D. Our hypothesis is that a meal with a high content of soluble fiber from foods determines glycemic and insulinemic responses similar to a meal with a high content of soluble fiber from supplement sources. Thus, the aim of this study was to compare the acute effect of soluble fiber intake from foods or supplements after a common meal on postprandial plasma glucose and insulin in patients with T2D.

Methods

Study design

This was a randomized, open label, crossover clinical trial. Patients were randomized using an online computer-generated sequence (22) to three different test meals. The outcomes of the study were postprandial responses of plasma glucose and insulin.

The study was carried out between September 2014 and December 2015 and was conducted in accordance with the guidelines laid down in the Helsinki Declaration (23). The Hospital Ethics Committee of the Hospital de Clínicas de Porto Alegre (HCPA), Brazil, approved the protocol, and all patients gave written informed consent. This clinical trial was registered at ClinicalTrials.gov (NCT02204384).

Study Protocol

Selected patients were informed about the study, signed the consent form, and were randomized for a sequence of test meals. Baseline laboratory, clinical and nutrition evaluations were performed. Patients received instructions for each morning test meal:

12-h evening fasting, avoiding physical exercise on the day before the experiments, heavy meals and alcohol the night before the test, and abstaining from smoking. Patients were also instructed to maintain their usual medication, diet, and daily physical activities before tests and during washout-periods.

Participants were assigned to each test meal in a random order on three different occasions separated by a one-week washout period. At the start of each test, a 24-h recall from the previous day was performed by the research dietitian. Capillary blood glucose tests were performed with a glucometer before each breakfast test (Accu-Chek Active, Roche Diagnostics, Indianapolis, IN) (24). The capillary blood glucose was used only to rule out high glucose values at the beginning of test meals and values higher than 180 mg/dl preclude the initiation of the test on that day. Bioelectrical impedance analysis was performed and blood pressure was measured. Then, blood samples were drawn via an indwelling cannula for baseline measurements. After this, patients took their usual medications with 150 mL of plain water and received the designed breakfast. They were instructed to consume the meal within 20 min and to remain seated during the test. Blood samples were collected at 0, 30, 60, 120, and, 180 min after the meal and plasma glucose and insulin were measured in all blood samples.

Patients

Consecutive outpatients with T2D attending at the Endocrine Division of our university hospital were selected based on the following inclusion criteria: HbA1c <9%, body mass index (BMI) <35 kg/m², and without current insulin use. Exclusion criteria were: serum creatinine >2.0 mg/dL, digestive diseases (e.g. malabsorption), severe autonomic neuropathy (presence of symptomatic postural hypotension, gastroparesis, and diabetic diarrhea), recent cardiovascular event, cachexia, psychiatric disorder with an impairment of understanding, and participating in other research protocols.

Clinical evaluation

Type 2 diabetes was defined as a diagnosis of diabetes after the age of 35 years with no use of insulin during the first year after diagnosis (25). The diagnosis of diabetes was always confirmed by the attending physician. Hypertension was defined as blood pressure >140/90 mmHg measured on two occasions with digital sphygmomanometer (Omron HEM-705 CP, Omron Healthcare Inc, Lake Forest, IL) or the use of antihypertensive drugs (25). Urinary albumin excretion (UAE) was classified as normal (<14 mg/L) or elevated (≥14 mg/L) according to a random spot urine sample (26, 27). The elevated UAE was confirmed at least twice (25, 28). Cardiovascular evaluation was performed by resting electrocardiogram, and when indicated, exercise electrocardiogram and/or stress myocardial scintigraphy were performed. Cardiovascular events were considered: acute myocardial infarction, stroke, myocardial revascularization, or coronary angioplasty. Diabetic retinopathy was assessed by fundus examination through dilated pupils. Peripheral neuropathy was assessed by monofilament testing in both feet. Physical activity was graded at four levels on the basis of a standardized questionnaire (29) adapted to local habits (30). A sedentary lifestyle was considered if the patient answer was: "I read, watch television, and work in the household at tasks that don't strain me physically", corresponding to the first level of physical activity. Peripheral vascular disease was assessed by asking about the presence of intermittent claudication using the Rose Questionnaire (31) and palpating of peripheral pulses (posterior tibial and dorsalis pedis). Patients were classified as current smokers or non-smokers.

Nutritional evaluation

Body weight, using light clothing without shoes, and height were measured so that BMI could be calculated. Waist circumference was measured midway between the lowest rib margin and the iliac crest, with non-stretch steel measuring tape (Sanny TR4010**,** American Medical do Brasil, São Paulo, BR) (32). Body composition was assessed before each meal test in the fasted state by bioelectrical impedance analysis (InBody230, Biospace Co, Seoul, Korea).

The normal diet was evaluated by a 24-h recall (USDA Automated Multiple-Pass Method) (33) and diet composition was analyzed by the Nutribase 11 Professional Edition software version 11.22 (CyberSoft Inc, Arizona, USA) based on the USDA table (34). Fiber content from both the 24-h recall and the test meals was estimated by using the CRC Handbook of Dietary Fiber in Human Nutrition (35). Glycemic index was estimated as proposed by the FAO (36) by using the international table, with glucose as the standard food (37).

Meal test composition

Table 1 shows the nutritional composition of meal tests. The three breakfasts were isocaloric and had a similar distribution of carbohydrates, proteins, and lipids. Meal tests were defined as follows: a high amount of soluble fiber from dietary food sources (high fiber from diet – HFD), a high amount of soluble fiber from supplement (high fiber from supplement – HFS), and a meal with usual amounts of fiber (usual fiber – UF). HFD and HFS meals had similar amounts of total and soluble fibers and UF had lower fiber than HFD and HFS. The supplement (sachet 5 g Fiber Mais®, Nestlé Brasil, São Paulo, BR) was added using the calculated amount in 150 mL of water. It was composed of 60% partially hydrolyzed guar gum and 40% inulin powder, white in color, tasteless and odorless, and did not modify the appearance and texture of foods.

Breakfasts were prepared by the research dietitian (CMC) in the kitchen of the Clinical Research Center on the day of each test meal. Frequently consumed foods were used to prepare the meals. The composition of meals was determined based on data obtained regarding the nutritional composition of breakfast commonly eaten for 175 patients with T2D who attended the outpatient clinic of the Endocrine Division, in our university hospital. Specifically, the total fiber content of the usual breakfast of these patients ranged from 1.9 to 3.1 g (38). The same commercially available food brands were used for all meal tests.

Laboratory measurements

Measurements were performed at the Clinical Pathology Laboratory of HCPA. Plasma glucose was collected into tubes containing sodium fluoride and EDTA, with a total volume of 4 mL, and measured by the enzymatic hexokinase method (Cobas 8000, Roche Diagnostics, Basel, CH). Plasma insulin was collected into tubes with silica particles activates clotting and separator gel with a total volume of 5 mL and was measured by the chemiluminescence method (Architect plus ci4100, Abbott, Illinois, USA). Blood samples were allowed to clot at room temperature for 30 min and then centrifuged (3100 rpm for 10 min). After isolation, the samples were brought to laboratory. At the beginning of the study, basal biochemical measurements were performed: HbA1c was measured by an automated precision-chromatography technique (Variant II Hemoglobin Testing System, Bio-Rad Laboratories, California, USA), UAE by immunoturbidimetry, serum creatinine by Jaffé’s reaction, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase by UV-Kinetic method, and thyrotropin by electrochemiluminescence (Cobas 8000, Roche Diagnostics, Basel, CH). Total, HDL cholesterol and triglycerides were measured by enzymatic colorimetric method (Cobas 8000, Roche Diagnostics, Basel, CH), and LDL-cholesterol was estimated by Friedewald's formula (39). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate (40).

Statistical analyses

Sample size

A sample size of 19 patients (90% power, α: 0.025, considering 10% losses) was estimated based on a non-inferiority hypothesis of glycemic response of HFD and HFS meal tests. This estimate was based on a glucose difference of 5 mmol/L.min (or 90 mg/dL.min) (41). In addition, a sample size of 14 patients (90% power, α: 0.05, considering 10% losses) was estimated based on the assumption that both HFD and HFS meals have a lower postprandial glycemic response (41 mmol/L.min or 738 mg/dL.min) than the UF meal (42). The sample size with the greater n was used; it was calculated using the WINPEPI (PEPI-for-Windows, Jerusalem, IL) version 11.61 software.

Data analysis

Incremental AUC (area under the curve) for plasma glucose and insulin were calculated using the trapezoid rule, ignoring the area beneath the plasma fasting concentration (43). iAUCs as well as the absolute insulin and glucose values at each point (the effect of time and each different meal analyzed separately) were compared by repeated measures ANOVA via a General Linear Model, and a categorical variable entitled "type of meal sequence" was included as a factor in all analyses. A post hoc Bonferroni test was used to identify differences detected by ANOVA.

A per-protocol analysis was performed. Variables with non-normal distribution (Shapiro-Wilk test) were log transformed before analysis (insulin data) and corresponding results are described as absolute values. Data are presented as mean ± SD, mean ± SE (for figures), mean (95% CI), and median and interquartile range (25^{th}-75^{th} percentiles). Significance was defined as $p \leq 0.05$. SPSS Statistics software version 21.0 (IBM Corporation, New York, USA) was used for statistical analyses.

Results

A total of 19 patients with T2D completed the experimental protocol. **Figure 1** shows the flow diagram of patient inclusion. Baseline clinical, laboratory, and anthropometric characteristics of 19 participants are shown in **Table 2**. Regarding anti-hyperglycemic oral agents, eight patients (42.1%) were using metformin only, seven patients (36.8%) were using metformin plus glibenclamide, and three patients (15.8%) were using metformin and glibenclamide, plus other anti-hyperglycemic oral agents: linagliptine (n = 1), dapaglifozin (n = 1), or empaglifozin (n = 1). Diet was the only diabetes treatment in one patient. Most patients were using antihypertensive (n = 16; 84.2%) and lipid-lowering drugs (n = 16; 84.2%).

All test meals were fully consumed within 11.9 ± 3.1 min. Two patients (10.5%) reported changes in their usual bowel function (need to evacuate) after the consumption of HFD meal. Fasting plasma glucose and insulin, BMI, weight, and the previous day's dietary intake of participants before each test were not different between meal tests (**Table 3**).

One meal test was repeated in three patients because blood sample hemolysis precluded insulin measurements and the original test meal randomization was not maintained. There was no interaction between the "type of meal sequence" and iAUCs.

iAUCs for plasma glucose (mg/dL.min) of three consumed test meals were compared (ANOVA; $p = 0.023$): iAUCs of HFD [7861 (6257, 9465)] and HFS [7847

(5605, 10090)] were lower than the iAUC of UF meals [(9527 (7549, 11504)] (p = 0.014 and p = 0.037 respectively); the iAUCs of HFD and HFS meals did not differ (p = 1.00) (**Figure 2A**). No significant group by time interaction was observed (**Figure 2A**).

No differences were demonstrated between insulin iAUCs (uUI/mL.min) of tested breakfasts (ANOVA; p = 0.877): HFD [3781 (2513, 5050)], HFS [4006 (2711, 5302)] and UF [4315 (3027, 5603] (**Figure 2B**). No significant group by time interaction was observed (**Figure 2B**).

We performed the same postprandial comparisons for glucose and insulin iAUCs including an anti-hyperglycemic agent, isolated or combined, as a categorical variable. There was no interaction between the type of anti-hyperglycemic medication and iAUCs for each evaluated test meal and the results did not change for both glucose and insulin responses (data not shown).

Discussion

The present study demonstrated that in patients with T2D, the consumption of breakfast with a high amount of soluble fiber from foods or supplement had the same effect on postprandial glycemic response. Furthermore, the postprandial plasma glucose response was smaller with these high fiber meals when compared with the breakfast containing a usual amount of fiber. We observed 18% difference in plasma glucose iAUCs between the breakfasts that were rich in fiber, irrespective of the source, compared with the one with the usual amount of fiber. In fact, a difference higher than 16% between postprandial glucose iAUCs has been considered to be clinically relevant (43). Postprandial insulin increased after all tested meals, but there was no difference between their iAUCs.

As far as we know, no previous study in patients with T2D was designed to compare the acute glycemic and insulin responses after the intake of soluble fiber from foods or supplements in a common meal. A low postprandial response of plasma glucose after the consumption of soluble fiber was already demonstrated in patients with diabetes (14-18). Most of these studies evaluated the response of insulin and glucose after the consumption of single foods: beverage (14, 18), single cereal bars (16), or single breads (19). Evaluation of the plasma glucose response in a real-life context confers additional clinical applicability to our results. The postprandial responses to meals in the current study evaluated a mixed meal, instead of a single food or beverage. The breakfast's composition was based on the usual morning meals consumed by our outpatients with T2D (38). Meal tests were conducted in well standardized conditions: patients had good chronic glucose control, similar baseline plasma glucose levels, and spent the same time eating the breakfasts. The macronutrient composition of the three breakfasts was very similar, except for the type and amount of fiber, as expected. Finally, the total dietary intake in the previous day in each tested breakfast did not differ.

Different mechanisms have been related to the beneficial effect of soluble fiber on postprandial glucose responses. Among them, the effects of soluble fiber on the stomach and small intestine seems to be involved: increase in the viscosity and gel-forming of gut contents, reduction of glucose diffusion through the unstirred water layer, delay in small bowel transit, reduction of alpha-amylase accessibility to its substrates, and prolonged absorption of carbohydrates in part by increasing incretin levels. In addition, soluble fiber intake has been associated with increased insulin sensitivity (21).

Other studies conducted in patients with type 2 diabetes evaluated the acute insulin response after foods with fiber, but without testing different sources of fibers as we did (15-19). Only one study (17), conducted in a small sample of eight patients with T2D, evaluated glucose and insulin responses after a common meal. Cereal meals with three different amounts of beta-glucan (4.0, 6.0, and 8.4 g) were compared with a standard continental breakfast. Similarly to our study, there is a smaller increment in the glucose AUCs of breakfasts with soluble fiber, but the insulin AUC was not described. In our study, we observed an increase in insulin after all tested meals, but without differences between them. Long-term fiber consumption has been associated with decreased levels of fasting insulin (44), but our study was designed to evaluate the acute postprandial insulin response. Our insulin data were in accordance with a recent meta-analysis on the effects of soluble fiber (psyllium) in postprandial insulin levels in patients with T2D (14) that showed no significant differences in postprandial insulin.

A potential limitation of the current study includes reliance on the manufacturers' label information of food composition instead of laboratory analyses of food nutrients. Moreover, an issue that could not allow the generalization of our data could be the good glycemic, lipid, and blood pressure control of our patients which was already present at baseline. In patients with worse metabolic control metabolic control the effect of soluble fiber may be more important supposing that up to 70% of HbA1c depends on postprandial glucose (3, 4). Finally, our studied sample size was calculated based on the response of glucose after meals, not taking the insulin response into account. We could not discount the absence of differences in insulin responses after breakfasts being related to the sample size calculation.

The current study adds to our understanding of the effect of different sources of soluble fiber on glucose responses after a common meal and provides support for encouraging people with T2D to increase their soluble fiber intake, regardless of the source. The absolute difference (4.6 g) of soluble fiber between both meal tests rich in fiber and the UF meal test is proved to lower on the postprandial glucose of these patients. Fiber intake from dietary foods represents a low-cost option besides providing other important nutrients for health, such as vitamins and minerals.

In conclusion, higher fiber intake was associated with lower postprandial glucose at breakfast, and the intake of soluble fiber from the food and supplement had a similar effect in patients with type 2 diabetes. This may be a useful and practical strategy to improve the postprandial metabolic profile in these patients. These results must be confirmed in long-term clinical trials taking into account total daily intake.

Conflict of Interest: None

Author' Contributions: This manuscript is dedicated to the memory of our dear friend, colleague, mentor, and co-author Mirela Jobim de Azevedo (MJA), MD, PhD who tragically passed away in May 2017. CMC, TPP, JCA, LVV and MJA designed the research; CMC, TPP, VMTM and LVV conducted research; CMC analyzed data; CMC and MJA wrote the paper; LVV had primary responsibility for the final content. All authors read and approved the final manuscript.

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Table 1. Dietary characteristics of breakfast tests: composition and individual foods

	HFD meal	HFS meal	UF meal
Macronutrients and fiber			
Total energy, kcal	379.9	361.3	368.3
Protein, g	15.4	15.6	15.8
% of energy	15.4	16.6	16.8
Fat, g	12.4	12.8	12.9
% of energy	27.9	30.7	30.8
Carbohydrate, g	56.7	50.0	49.6
% of energy	56.7	52.7	52.4
Fiber, g			
Total	9.7	9.1	2.4
Soluble	5.4	5.4[1]	0.8
Insoluble	4.3	3.7	1.6
Glycemic index	44.2	44.9	59.5
Glycemic load	20.0	18.7	25.8

Foods consumed

HFD meal	HFS meal	UF meal
Papaya 180 g	Pear 50 g	Pear 50 g
Orange 150 g	Cream cracker 5 g	Cream cracker 5 g
Semi-skimmed milk 150 mL	Semi-skimmed milk 200 mL	Semi-skimmed milk 200 mL
Rye bread 25 g	Rye bread 50 g	White Bread 50 g
Margarine 10 g	Margarine 5 g	Margarine 5 g
Lean ham 15 g	-	-
Mozzarella cheese 15 g	Mozzarella cheese 15 g	Mozzarella cheese 15 g

Instant coffee 5 g	Instant coffee 5 g	Instant coffee 5 g
Plain water 150 mL	Plain water 150 mL	Plain water 150 mL
-	Fiber Supplement 5 g	-

[1]Including 4.3 g of soluble fiber from each sachet (5g). HFD, high fiber from diet; HFS, high fiber from supplement; UF, usual fiber.

Table 2. Baseline characteristics of 19 patients with type 2 diabetes[1]

	Value
Socio-demographic characteristics	
Women, n(%)	10 (52.6)
White, self-reported ethnicity, n(%)	15 (78.9)
Age, y	65.8 ± 7.3
Years of study, y	9.7 ± 4.7
Current smoking, n(%)	4 (21.0)
Current alcohol beverage intake, n(%)	9 (47.4)
Clinical characteristics	
Diabetes duration, y	10 (5 - 9)
Sedentary lifestyle, n(%)	10 (52.6)
Hypertension, n(%)	16 (84.2)
Systolic blood pressure, mmHg	131 ± 8
Diastolic blood pressure, mmHg	73 ± 7
Diabetic retinopathy, n(%)	7 (36.8)
Peripheral vasculopathy, n(%)	2 (10.5)
Elevated urinary albumin excretion, n(%)	5 (26.3)
Cardiovascular events, n(%)	3 (15.8)
Angioplasty, n(%)	1 (5.3)
Stroke, n(%)	2 (10.5)
Laboratory characteristics	
Fasting plasma glucose, mg/dL	135.8 ± 20.7
Glycated hemoglobin, %	7.0 ± 0.8
Total cholesterol, mg/dL	167.2 ± 43.0

HDL cholesterol	
Men, mg/dL	41.0 ± 10.7
Women, mg/dL	50.3 ± 12.3
LDL cholesterol	92.3 ± 33.2
Triglycerides, mg/dL	130.0 (96.0 - 130.0)
Urinary albumin excretion, mg/L	5.0 (3.0 - 25.8)
Creatinine, mg/dL	0.8 ± 0.2
GFR, mL/min per 1.73 m^2	78.8 ± 15.3
Glutamic oxaloacetic transaminase, U/L	20.3 ± 7.2
Glutamic pyruvic transaminase, U/L	22.4 ± 13.0
Thyrotropin, uUI/mL	2.2 ± 1.0
Anthropometric characteristics	
BMI, kg/m^2	28.2 ± 2.9
Skeletal muscle mass, kg	25.6 ± 4.9
Body fat mass, kg	26.1 ± 6.5
Body fat, %	35.7 ± 6.5
Waist circumference	
Men, cm	102.7 ± 9.9
Women, cm	94.9 ± 8.6
Dietary intake characteristics	
Total energy, kcal	1702 ± 168
Protein, g	61 (47 - 92)
% of energy	18.8 ± 1.5
Fat, g	67 (43 - 77)
% of energy	36.9 ± 2.0

Carbohydrate, g	192 (143 - 211)
% of energy	44.2 ± 2.2
Fiber, g	
Total	16.9 ± 2.4
Soluble	5.3 ± 0.8
Insoluble	11.5 ± 1.7
Glycemic index	54.2 ± 1.4
Glycemic load	76.6 ± 7.3

[1]Values are mean ± SD, median (25th - 75th percentiles), or number of patients with analyzed characteristic and percentage (%). BMI, body mass index, GFR, glomerular filtration rate

Table 3. Plasma glucose, plasma insulin, and other analyzed variables in each tested breakfast meal in 19 patients with type 2 diabetes[1]

	HFD meal	HFS meal	UF meal	*p**
Fasting plasma glucose, mg/dL	131.7 ± 21.8	131.3 ± 20.8	128.1 ± 23.5	0.741
Fasting plasma insulin, uUI/mL	10.5 ± 6.1	10.2 ± 6.2	9.4 ± 4.8	0.356
BMI, kg/m²	28.1 ± 3.1	28.2 ± 3.1	28.3 ± 3.0	0.815
Body weight, kg	72.3 ± 10.9	72.3 ± 10.5	72.4 ± 10.6	0.638
24-h recall, kcal	1872.6 ± 838.9	1825.2 ± 763.7	1739.5 ± 776.0	0.607
Protein, g	85 (53 - 95)	69 (57 - 92)	78 (47 - 112)	0.941
Fat, g	53 (39 - 75)	54 (40 - 86)	51 (40 - 79)	0.738
Carbohydrate, g	202 (153 - 298)	206 (153 - 249)	211 (158 - 225)	0.728
Fiber, g				
Total	20.1 ± 2.0	20.8 ± 2.3	18.8 ± 1.8	0.768
Soluble	6.8 ± 3.4	6.4 ± 3.3	6.0 ± 2.8	0.690
Insoluble	13.3 ± 6.2	14.4 ± 7.6	12.8 ± 5.5	0.693
Glycemic index	55.8 ± 7.0	54.6 ± 5.2	53.4 ± 4.9	0.309
Glycemic load	78.8 (60.5-116.6)	83.5 (71.8 -103.9)	76.4 (72.9-101.5)	0.588

[1]Values are mean ± SD and median (25^{th} - 75^{th} percentiles). **p* value for ANOVA for repeated measures. BMI, body mass index; HFD, high fiber from diet; HFS, high fiber from supplement; UF, usual fiber.

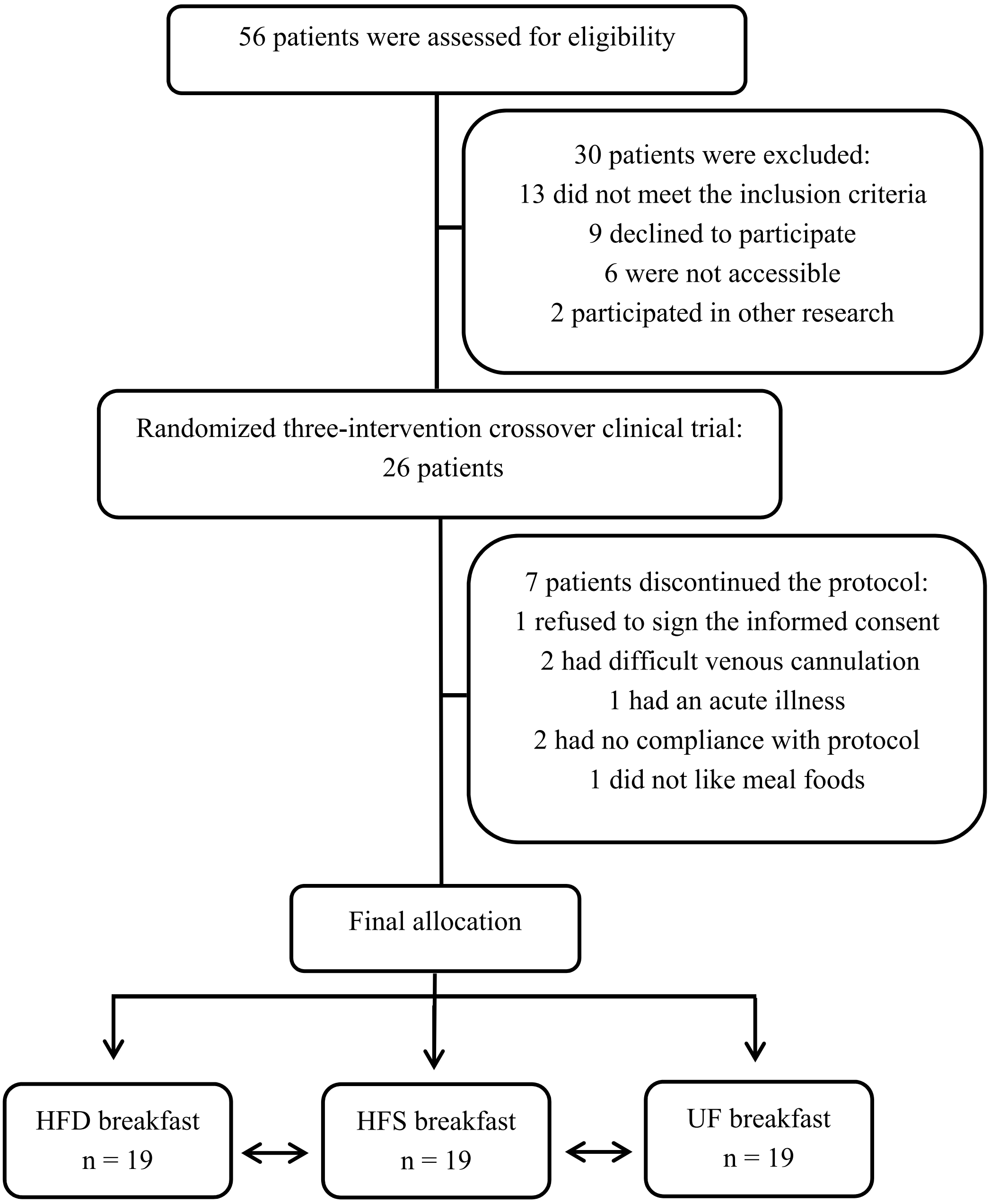

Figure 1. Flow diagram showing the 19 included patients. HFD, high fiber from diet; HFS, high fiber from supplement; UF, usual fiber.

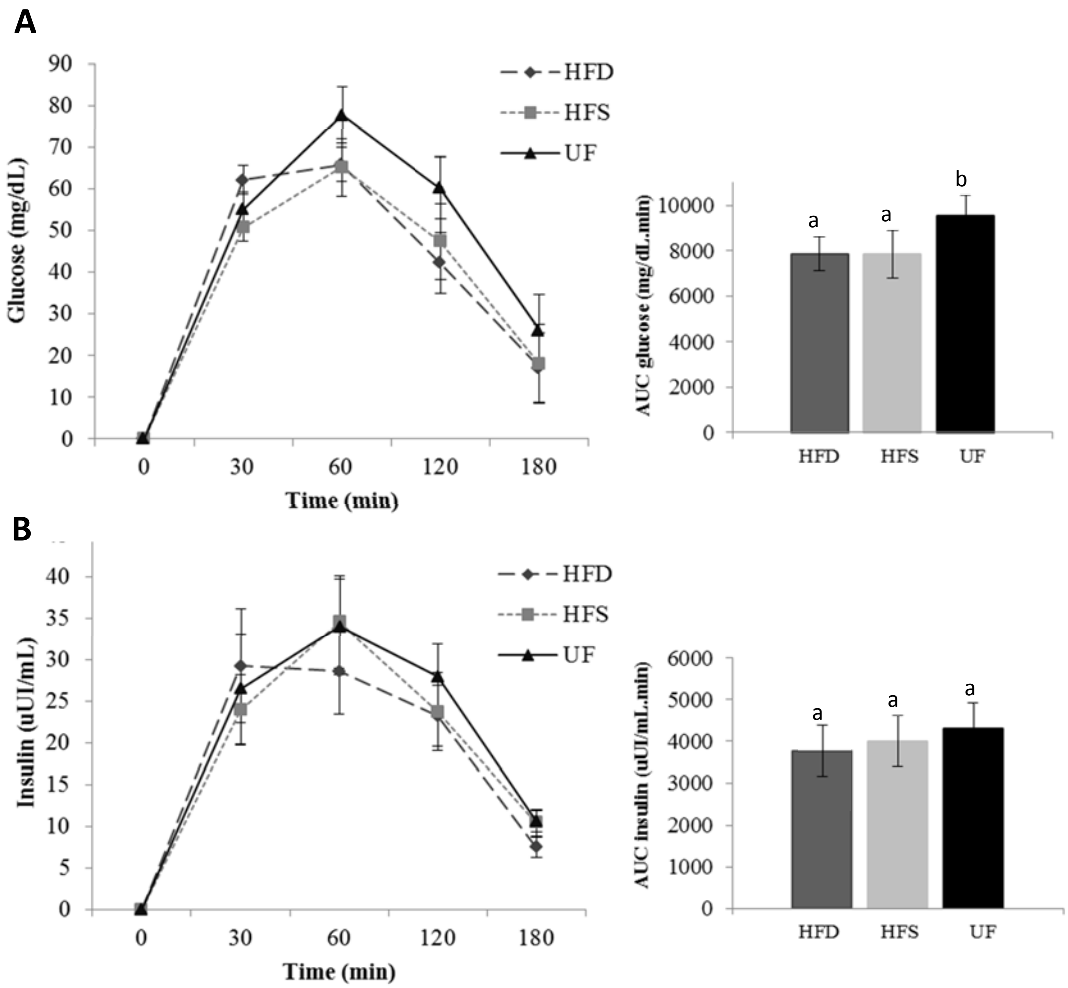

Figure 2. Glucose (A) and insulin (B) responses after tested breakfasts: high fiber from diet (HFD), high fiber from supplement (HFS), and usual fiber (UF) in 19 patients with type 2 diabetes. Values are mean ± SEM. Adjusted for a categorical variable "type of meal sequence". iAUC, incremental area under the curve.

No significant group by time interaction was observed in either panel; A and B: different letters in bars indicate a significant statistical difference (*p* <0.05) between iAUC test meals. ANOVA for repeated measures and post hoc Bonferroni test.

CAPÍTULO III

Dietary fiber intake and diabetic kidney disease: a systematic review

(Manuscrito a ser submetido na publicação no periódico *Critical Reviews in Food Science and Nutrition)*

Dietary fiber intake and diabetic kidney disease: a review of clinical trials

Fiber intake, diabetic kidney disease, and systematic review

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None of the authors have any conflict of interest to declare.

ABSTRACT:

Objective: The aim of this systematic review was to evaluate the effect of dietary fiber on diabetic kidney disease (DKD).

Methods: We searched Medline, Embase, ClinicalTrials.gov, Scopus, Web of Science, and Cochrane databases to identify clinical trials that reported fiber intake (supplemental or dietary pattern rich in fiber) and renal outcomes (albuminuria, proteinuria, estimated glomerular filtration rate [eGFR], dialysis) in patients with diabetes (DM).

Results: From 1,814 studies, 1,766 were excluded leaving 48 papers for full evaluation. Then, seven trials (161 patients, aged 58.3 years, 49% females) were included. The studies were organized in three categories (vegetarian diet, DASH diet and fiber supplement), two evaluated supplements and five dietary patterns. Due to the heterogeneity of the studies, we were not able to perform meta-analyses. Vegetarian diet reduced albuminuria in three trials, two in patients with type 1 DM and one in patients with type 2 DM; and one study demonstrated a change in the eGFR in type 1 DM. The individual quality of the studies was low or uncertain.

Conclusion: The individual effect of the intake of fiber on DKD not was possible to be evaluated, however a vegetarian dietary pattern may have a beneficial effect on these renal outcomes.

Keywords: dietary fiber; vegetarian diet; diabetic nephropathy; albuminuria; glomerular filtration rate.

INTRODUCTION

Diabetes Mellitus (DM) is a growing worldwide epidemic. Approximately, 425 million adults are affected by this chronic disease (International Diabetes Federation 2017). Most of the financial burden of DM is related to management of its complications, and chronic kidney disease (CKD) is the most expensive and debilitating one (Slabaugh et al. 2015). Cardiovascular disease (CVD) is a frequent cause of mortality in patients with type 2 DM (Lupsa and Inzucchi 2018), and it is well established that CKD is a risk factor for CVD (Sarnak et al. 2003). Among patients with type 2 DM and coronary artery disease, mortality rates were progressively higher in patients with mild and moderate CKD compared with patients with preserved eGFR (Lima et al. 2016).

Fiber intake is associated with better glycemic control (Silva et al. 2013) and cardiovascular risk reduction (McRae 2017). **Table 1** shows an overview of dietary fiber recommendations. The American Diabetes Association (ADA) (Evert et al. 2014) recommends that patients with DM should consume at least 14 grams of fiber for each 1,000 kcals daily and it suggests that carbohydrate intake from vegetables, fruits, legumes, and whole grains, with an emphasis on foods higher in fiber and lower in glycemic load, is preferred over other sources of sugar (American Diabetes 2018a). The American Heart Association (AHA) also endorses healthy dietary patterns rich in fiber to prevent CVD such as Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets (Eckel et al. 2014). In its latest edition, Dietary Guidelines for Americans (Agriculture 2015) reinforces the idea of fiber consumption through specific foods and patterns.

There is no precise recommendation about fiber intake or dietary patterns rich in fiber for patients with CKD (Molitch et al. 2015, KDOQi 2010). Since the effect of dietary fiber on renal outcomes is not well established, and dietary fiber appears to be an important nonpharmacological treatment for DM and CVD, it is necessary to better understand and further investigate its effects on diabetic kidney disease (DKD). Therefore, the aim of this systematic review was to evaluate the effect of dietary fiber (supplemental or dietary pattern rich in fiber) on DKD.

METHODS

This systematic review was carried out using a protocol constructed according to the Cochrane Handbook recommendations (Cochrane Collaboration 2011) and it was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al. 2009) (PROSPERO - CRD42017072535).

Data Sources and Searches

We searched databases from Medline, Embase, ClinicalTrials.gov register, Scopus, Web of Science and Cochrane databases to identify interventional clinical trials that reported dietary fiber intake (supplemental or dietary pattern rich in fiber) and renal outcomes (albuminuria, proteinuria, eGFR, and dialysis) in patients with DM, up to January 2018.

The initial search comprised the terms diabetes, dietary fiber, diabetic nephropathy, albuminuria, proteinuria, diabetic kidney disease, eGFR, renal replacement therapy, kidney failure chronic, and related entry terms. The complete Medline search strategy is presented in **Appendix 1**, available in the Supporting Information for this article online. All potentially eligible studies were reviewed, regardless of the primary outcome or language.

Study Selection

Only interventional clinical trials conducted on patients with diabetes (type 1 or Type 2 DM) with at least one high fiber group were included in the present review. Dietary fiber intake (supplemental or dietary pattern rich in fiber) was compared with conventional or low-fiber diets. Dietary intervention must have lasted at least four weeks. We excluded studies with non-clinical trials design (cohort, cross-sectional, case-control and review studies), with the same dietary intervention in all studied groups, without dietary information, or without data about renal outcomes.

Data Extraction and Quality Assessment

All citations retrieved from electronic databases were imported into the EndNote Program. Two reviewers (CMC, LAG) independently analyzed the titles and abstracts of every paper retrieved from the literature search to identify potentially eligible studies. The full text of the remaining papers was obtained for further examination. Disagreements were solved by a third reviewer (LVV).

Data of included studies were independently extracted by the same two reviewers using a standardized form. Extracted data included: first author's name, year of publication, sample size, study design, trial duration, general characteristics of participants (the type of DM, age, gender, body mass index, HbA1c, hypertension or blood pressure), intervention characteristics and outcomes of interest. A detailed description of type of diet (actual intake or prescribed diet), total energy, macronutrients, fiber content was documented for interventions and comparators.

In this review, we used renal outcomes definitions provided by authors of the included studies. In general, DKD is diagnosed based on the persistence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage (American Diabetes 2018b). End-of-study and baseline means or statistical dispersion for outcomes was extracted.

Methodological quality of studies was measured according to the Cochrane Collaboration’s Handbook (Cochrane Collaboration 2011). Biases were classified into six domains: selection, performance, detection, attrition, reporting, and other (Cochrane Collaboration 2011, Higgins et al. 2011). The "other" chosen domain was the assessment of dietary compliance. The risk of bias was independently analyzed by two reviewers (CMC, LAG) for each domain, and was classified as high, low, or unclear. Regarding dietary compliance, the risk was classified as "low" if the study described the method of a dietary adherence. The performance domain (blinding of participants and personnel) was not possible to evaluate in studies that have dietary intervention (dietary pattern).

RESULTS

Literature search

We identified 1,814 studies in database searches. Of them, 1,766 were excluded based on title and abstract, leaving 48 articles for further full-text evaluation. We excluded 41 studies (**Appendix 2**), mainly due to lack of dietary or renal outcomes information, non-clinical trials design or only abstract available. As a result, seven interventional clinical trials were included in the current systematic review (**Figure 1**).

Study characteristics

The seven interventional clinical trials comprised 161 patients with DM, age from 20 to 74 years (mean 58.3 years) and 49% females. Three trials had renal outcomes as a primary outcome (de Mello et al. 2006, Kontessis et al. 1995, Jibani et al. 1991) and only one study included patients with established renal disease (macroalbuminuria) (de Mello et al. 2006). All trials included few patients (range 8-49), had a small duration of the intervention (four to twelve weeks), and most studies were conducted in Brazil (de Mello et al. 2006, Dall'Alba et al. 2013, Paula et al. 2015). Four trials had a parallel design (Nicholson et al. 1999, Dall'Alba et al. 2013, Farhangi, Javid, and Dehghan 2016, Paula et al. 2015) and three showed a crossover design (de Mello et al. 2006, Jibani et al. 1991, Kontessis et al. 1995). Two studies included patients with type 1 DM (Jibani et al. 1991, Kontessis et al. 1995). Dialysis and proteinuria were not reported in any included studies. Two studies (Nicholson et al. 1999, Paula et al. 2015) did not describe eGFR, one study did not report albuminuria (Farhangi, Javid, and Dehghan 2016), and one study reported fractional albumin clearance (Jibani et al. 1991). **Table 2** shows the complete description of the included trials.

Didactically, the studies were organized into three sections by type of dietary intervention: “vegetarian diet” (n = 4) (Nicholson et al. 1999, de Mello et al. 2006, Jibani et al. 1991, Kontessis et al. 1995), “fiber supplement” (n=2) (Dall'Alba et al. 2013, Farhangi, Javid, and Dehghan 2016), and “DASH diet” (n=1) (Paula et al. 2015). Most interventions were compared to usual diet. Mean fiber intake in the intervention was 24 g/day (range: 20-27 g/day) and 16 g/day (range: 14-20 g/day) in the control group. Given the wide heterogeneity among studies regarding the type and form of dietary interventions, as well as the assessed outcomes, and the small number of studies identified in the literature, we could not perform a meta-analysis of the extracted data. The following sections provide additional detail on the included studies, grouped by type of intervention.

Vegetarian diet

Type 1 DM

Two interventional clinical trials, including 17 adult patients (age 32 to 46 years), 59% females, assessed the vegetarian diets compared to a usual diet in patients with type 1 DM (Kontessis et al. 1995, Jibani et al. 1991). The studies were conducted in Greece (Kontessis et al. 1995) and the United Kingdom (Jibani et al. 1991). The intervention period ranged from four to eight weeks and both had crossover clinical trials. Total fiber intake was 0.2 to 0.4 g/kg/day in the intervention versus 0.1 to 0.3 g/kg/day in the control group.

In the study conducted by Kontessis et al. (Kontessis et al. 1995), diets were isocaloric and with the same quantity of protein, but the intervention group contained exclusively vegetable protein and a mean fiber intake of 0.2 g/kg/day versus 0.1 g/kg/day in the control group. eGRF and albuminuria were significantly lower for the intervention group.

In the study of Jibani et al. (Jibani et al. 1991), the intervention consisted in a predominantly vegetarian diet, with animal protein fraction limited to approximately 30% of the total protein intake. Median actual fiber consumption was 0.4 g/kg/day in the intervention versus 0.3 g/kg/day in the control. There was no change in eGFR, but the fractional albumin clearance was significantly lower in the vegetarian group compared with the conventional diet.

Type 2 DM

We found two randomized clinical trials that assessed the effect of vegetarian diet on patients with type 2 DM (Nicholson et al. 1999, de Mello et al. 2006). The studies were conducted in the United States (Nicholson et al. 1999) and Brazil (de Mello et al. 2006), the sample size ranged from 11 to 17 patients, with a mean age of 57 years, 36% were females, and study duration ranged from four to twelve weeks. In the interventions, patients ingested 26.5 g of total fiber versus 20g in the control groups (conventional diets).

In the pilot trial of Nicholson et al. (Nicholson et al. 1999), the intervention consisted in a low-fat vegan diet compared to conventional diet, and there was no difference in the albuminuria between groups. The study performed by Mello et al. (de Mello et al. 2006) was a crossover trial that evaluated the effects of a lactovegetarian compared with a chicken based or usual diet. No difference was observed in the eGFR between the vegetarian and usual or chicken diet. However, lactovegetarian and chicken-based diets reduced albuminuria by the same amount compared with usual diet. The quantity of fiber was greater in the lactovegetarian group, but the protein intake was smaller in the lactovegetarian group compared with chicken and usual diets.

Fiber supplement

Two randomized clinical trials conducted in patients with type 2 DM used 10g of a soluble fiber supplement (guar gum or inulin) (Dall'Alba et al. 2013, Farhangi, Javid, and Dehghan 2016). The studies were conducted in Brazil (Dall'Alba et al. 2013) and Iran (Farhangi, Javid, and Dehghan 2016) and the sample size ranged from 40 to 49 patients with a mean age of 54.5 years, 71% females, and mostly obese patients (BMI: 30.3 kg/m^2). The intervention period ranged from six weeks to two months.

In the study of Dall'Alba et al. (Dall'Alba et al. 2013), total fiber intake was 24 g/day (10 g/day of guar gum supplement) compared with 16 g/day in the control taken for six weeks. There was no difference in the eGFR and albuminuria between groups.

The study of Farhangi et al. (Farhangi, Javid, and Dehghan 2016) included only women and the intervention group received a 10 g/day chicory inulin as supplemental fiber and the control group received 10 g/day maltodextrin for two months. No information was available about total fiber intake. No changes in eGFR values had been observed.

DASH diet

Only one study evaluated the benefit of DASH diet and physical activity for four weeks compared with a diet based on ADA recommendations in patients with type 2 DM (Paula et al. 2015). The study was conducted in Brazil and included 40 patients with DM and hypertension, mean age 62 years old, 55% females. The total fiber consumed in the intervention group was 20 versus 14 g/day in the control group. There were no differences in albuminuria between groups at the end-of-the study.

Methodological Quality Assessment of Studies

None of the included studies satisfied all areas established by the Cochrane Handbook (Cochrane Collaboration 2011). In general, the quality of the studies was low or uncertain. The selection bias domain was not possible to be evaluated in one study, because it was a non-randomized clinical trial (Jibani et al. 1991). Three studies provided a detailed description about random sequence generation (Farhangi, Javid, and Dehghan 2016, Paula et al. 2015, Dall'Alba et al. 2013), while only one study described the method used for allocation concealment (Farhangi, Javid, and Dehghan 2016). The blinding of participants was described in two studies (dietary fiber supplement) (Dall'Alba et al. 2013, Farhangi, Javid, and Dehghan 2016). The intervention providers were blinded to the group assignment in only one study (Farhangi, Javid, and Dehghan 2016). One study had a loss of follow-up greater than 20% in the run-in period (~57%). On reporting bias, one study presented the outcome eGFR without having previously described it in the registry (de Mello et al. 2006). All studies properly presented the item “diet or supplement adherence". **Table 3** shows the complete assessment of the methodological quality of the included studies.

DISCUSSION

Diet is the cornerstone treatment for patients with DM and as far as we know this is the first systematic review that attempts to shows benefits of a consumption of dietary fiber on renal outcomes in patients with DM. Among the seven included studies, only the vegetarian dietary pattern was associated with beneficial kidney outcomes: three studies showed a reduction of albuminuria (two conducted in patients with type 1 DM and one in patients with type 2 DM) and one study demonstrated a change in the eGFR in patients with type 1 DM.

As we already know, the pathogenesis of diabetic nephropathy has complex mechanisms including the effect of high glucose, endothelial dysfunction inflammation, renin-angiotensin system activation, reactive oxygen species, increase of advanced glycation end-product and glomerular hyperfiltration (Maezawa, Takemoto, and Yokote 2015). Dietary fiber plays an important role in glycemic control (Fujii et al. 2013, Silva et al. 2013) and regardless of the source (food or supplements) fiber exhibits hypoglycemic actions in patients with type 2 DM (Post et al. 2012, de Carvalho et al. 2017). Some studies have shown that good glycemic control reduces albuminuria (Showail and Ghoraba 2016, DCCT Edic research group 2014, Chen et al. 2014) in patients with DM and dietary fiber intake was found to be associated with a reduced risk of albuminuria in a cross-sectional study (Metcalf et al. 1993). Recently, a Japanese randomized clinical trial showed that a diet higher in fiber was able to improve endothelial function, possibly by a reduction of glucose excursions, in patients with type 2 DM (Kondo et al. 2017).

In the general population, consumption of fiber-rich foods can reduce serum creatinine levels (Chiavaroli et al. 2015, Salmean et al. 2013) and may increase eGFR in CKD patients without DM (Salmean et al. 2013). A prospective study showed that high fiber intake, mainly from legumes and vegetables, was related to lower incidence of CKD after six years of follow-up. For every additional 5 g/day of fiber intake, there was an 11% reduction in risk of CKD (Mirmiran et al. 2018). In fact, the precise effects of dietary fiber consumption on renal function are not well known, but healthy dietary patterns with high fiber are associated with lower mortality in people with kidney disease (Kelly et al. 2017).

In our systematic review, a dietary pattern rich in fiber: vegetarian diet was the only category associated with a reduction in albuminuria in both type 1 and type 2 DM patients and reduction in eGFR in a group of patients with type 1 DM and possible hyperfiltration. It is worth noting that protein intake was lower in two out of three of these studies. It has been suggested that plant-based proteins may exert beneficial effects on blood pressure, protein loss in urine, and GFR, and reduce renal tissue damage preventing the progression of CKD when compared to animal proteins (Gluba-Brzozka, Franczyk, and Rysz 2017). It is difficult to isolate the effect of a single nutrient, in this case, dietary fiber from protein. A vegetarian dietary pattern is usually richer in fibers, but it is lower in animal protein, which may be more suitable for these patients and exert beneficial glomerular effects (Melina, Craig, and Levin 2016). Carbohydrates can be nutrients usually high in this dietary pattern, but this happened in two of them, and in only one study that demonstrated albuminuria reduction in patients with type 2 diabetes. But, in this study the protein was lower too. Higher eGFR has been demonstrated in patients with a normal renal function on an animal protein diet in comparison with a person on a vegetable-based diet (Lohsiriwat 2013, Barai et al. 2008).

In our review, no other dietary pattern had favorable effects on renal outcomes. DASH diet was not able to reduce eGFR or albuminuria in patients with type 2 DM similar to the results of Jacobs et al. in patients without DM (Jacobs et al. 2009). However, in two large, prospective, long-term studies, adherence to DASH diet was associated with protection against eGFR decline (Lin et al. 2011, Rebholz et al. 2016). No clinical trial specifically designed to evaluate the effects of Mediterranean diet in patients with DM was identified in our database search. In a recent cohort study, a Mediterranean dietary pattern was associated with a decreased risk of CKD in patients with and without DM (Asghari et al. 2017). A Mediterranean diet was too evaluated in a randomized clinical trial, PREDIMED (*PREvencion con DIeta MEDiterranea*) study. However, two subgroup analyses that evaluated only patients with type 2 DM, showed no difference in nephropathy between Mediterranean groups compared to a low-fat diet (Diaz-Lopez et al. 2015, Diaz-Lopez et al. 2012). This studies were not included in this systematic review due not present the amount of dietary fiber intake.

Limitations of our systematic review are the small number of studies, with a small sample size, few ethnic groups represented among the participants, and short follow-up time (no more than twelve weeks). This may limit the effect of any dietary intervention in renal outcomes, particularly because CKD is a slowly progressive disease. Many years may be necessary for the development of kidney damage. In fact, DKD was present in only one study in our systematic review (de Mello et al. 2006). Regarding the quality of the included studies, lack of description of trial characteristics made the quality analysis unclear in several domains. Fiber dietary intake in included studies was lower than recommended by most dietary guidelines (38 g/day for men and 25 g/day women) (Dahl and Stewart 2015, Evert et al. 2014, Efsa Panel on Dietetic Products and Allergies 2010). Also, we could not establish an independent fiber effect on renal outcomes since most included studies evaluated eating patterns. On the other hand, dietary patterns seem to be more important than a single nutrient and offer a more practical application in public health promotion since it is easier for people to adopt dietary patterns instead of specific nutrients from their diets (Medina-Remon et al. 2018).

Evidence of benefits of dietary fiber on renal outcomes in patients with DM is still limited, and more precise indications of the amount, duration, and the type of fiber intake to achieve these goals are needed. Regrettably, we could not evaluate the individual effect of different fiber sources (legumes, vegetables, or fruits) on the outcomes. We know that all fibers are not the same and sources of fibers carry other nutrients (i.e. vitamins and minerals) that on their own already have positive effects on health. Available data extrapolated from the general population, show that fiber intake is likely protective against CKD progression and mortality (Krishnamurthy et al. 2012, Fujii et al. 2013, Mirmiran et al. 2018), and every effort should be made to encourage higher fiber intake in the CKD population. Unfortunately, we could not reach a definitive conclusion regarding the beneficial effect of fiber in DKD in our systematic review. Still, larger, longer, better design trials are needed to evaluate the effect of fiber on DKD.

In conclusion, the individual effect of the intake of fiber on DKD not was possible to be evaluated on our systematic review, however a vegetarian dietary pattern may have a beneficial effect on these renal outcomes. However, new randomized trials are needed to reach a definitive conclusion.

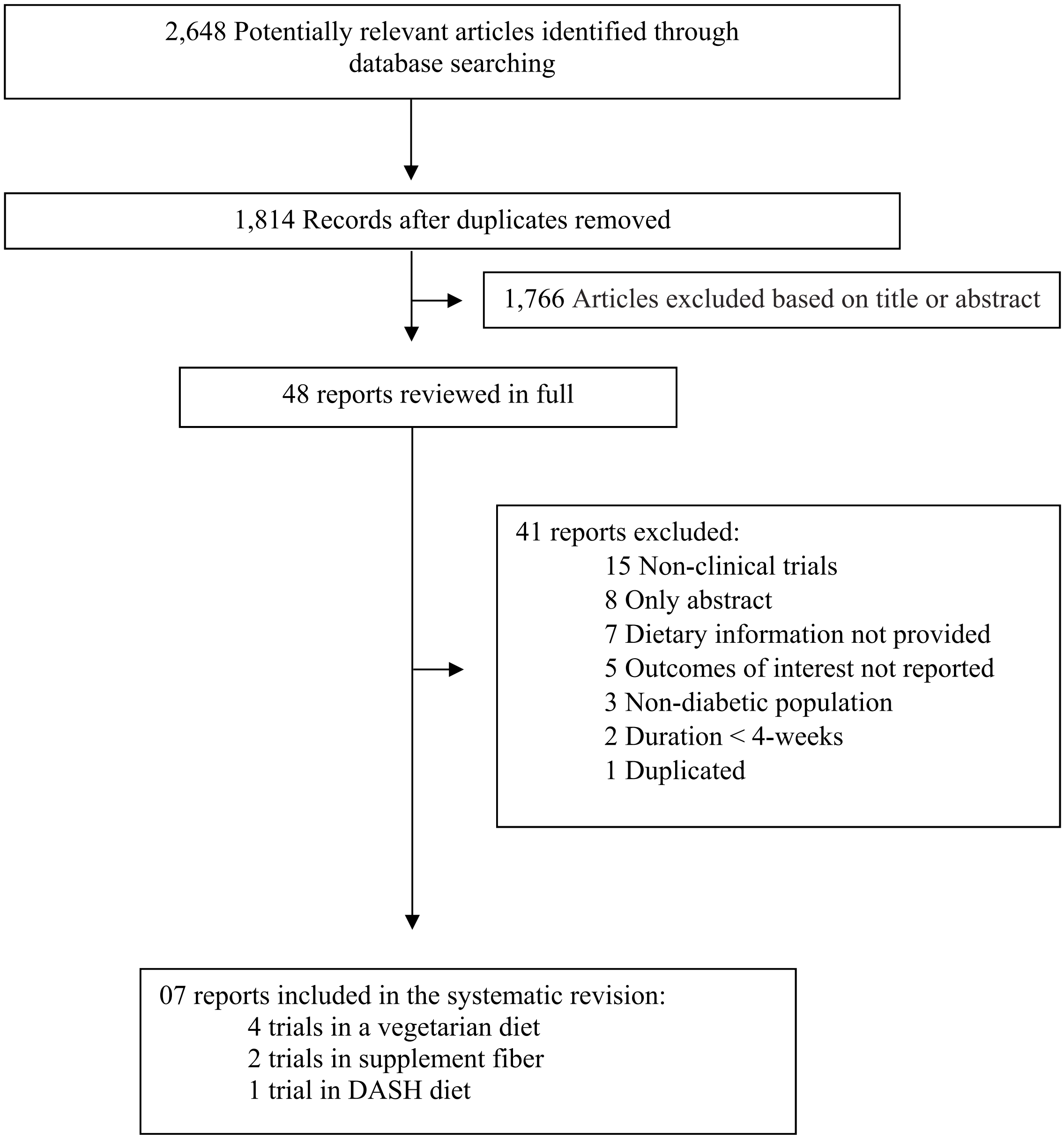

Figure 1. Flow diagram of the literature search to identify clinical trials evaluating the effect of dietary fiber on renal outcomes (albuminuria, eGFR) of patients with diabetes.

Table 1: Characteristics of dietary patterns and fiber recommendation

Dietary patterns/ Guidelines recommendations	Main foods	Nutrients characteristics
DASH diet[1, 2, 4]	Includes vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils; <25% dietary intake from fat; low in sweets, sugar-sweetened beverages, and tropical oils.	Low in saturated fats and cholesterol Rich in fiber Rich in protein
Vegetarian diet[2,3, 4]	Includes whole grains, vegetables, fruits, legumes, nuts, seeds, soy and, if desired, dairy products, and eggs. Does not include meat, fowl or seafood, or products containing those foods.	Rich in fiber Rich in n-6 fatty acids Rich in vegetable protein
Mediterranean diet[1, 2, 4]	Includes fruits, vegetables, whole grains, beans, nuts, seeds, seafood, olive oil; low to moderate amounts of poultry, and dairy products, with little red meat; low to moderate wine consumption (optional).	Rich in fiber Rich in monounsaturated and polyunsaturated fat
Guidelines recommendations	[1]AHA: Rich in fiber [2]American Guideline: 14g/1000kcal [5]European Guideline: 25 g/day [4]ADA: 14g/1000 kcal or 25 g/day women – 38 g/day men [6]KDOQI/[7]KDIGO: no specific recommendation	

ADA = American Diabetes Association; AHA = American Heart Association; KDOQI = Kidney Disease Outcomes Quality Initiative; KDIGO = Kidney Disease Outcomes Quality Initiative

[1]American Heart Association - Guideline on Lifestyle Management to Reduce Cardiovascular Risk, 2013; [2]Dietary Guidelines for Americans, 2015; [3]Position of the American Dietetic Association: Vegetarian Diets, 2015; [4]American Diabetes Association, 2014/2018; [5]Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre, 2010; [6]KDOQI - Chronic Kidney Disease Evidence-Based Nutrition Practice Guideline, 2010; [7]Diabetic Kidney Disease– A clinical update from Kidney Disease: KDIGO

Table 2. Characteristics of the studies evaluating the effect of fiber intake on renal outcomes (albuminuria and eGFR) in patients with diabetes.

Author Year Country	Sample characteristics	Study design	Diet characteristics	Renal Outcomes
			Type 1 diabetes	
			Vegetarian diet	
Jibani **1991** n = 8 United Kingdom	Females: 37.5% Hypertension: 25% Age: 46 (22-70) years HbA1c: NA BMI: NA Withdrawals: 20% Duration: 8-weeks	Crossover clinical trial Washout: 8-weeks	**Intervention (n = 10):** vegetarian diet * Energy: 32 (23-34) kcal/kg/day CHO: 3.4 (2.3-4.2) g/kg/day; Prot: 1.0 g/kg/day; Lip: 1.2 g/kg/day Total fiber: 0.4 g/kg/day Soluble fiber: NA Insoluble fiber: NA **Control (n = 10):** conventional diet * Energy: 29 (15-35) kcal/kg /day CHO: 3.7 (2.6-4.6) g/kg/day; Prot: 1.4 g/kg/day; Lip: 1.4 g/kg/day Total fiber: 0.3 g/kg/day Soluble fiber: NA Insoluble fiber: NA	**Intervention** eGFR (ml/min/1.73 m^2) § Final: 109 (48-163) Fractional albumin clearance ($x10^{-4}$) ** Final: 87 (23-829) **Control** eGFR (ml/min/1.73 m^2) Final: 109 (45-134) Fractional albumin clearance ($x10^{-4}$) Final: 188 (58-810)
Kontessis **1995** n=9 Greece	Females: 77.8% Hypertension: 0% Age: 32 (20-48) years HbA1c: 6.7 (5.1-8.4) BMI: 23.8 (20.6-27.8) Withdrawals: 0% Duration: 4-weeks	Randomized crossover clinical trial Washout: ≥1-week	**Intervention (n = 9):** vegetal protein diet * Energy: 22.8±3.8 kcal/kg/day CHO: 2.8±0.7 g/kg/day; Prot: 0.95±0.3 g/kg/day; Lip: 0.9±0.1 g/kg/day Total fiber: 0.2±0.03 g/kg/day Soluble fiber: NA Insoluble fiber: NA **Control (n = 9):** animal protein diet * Energy: 23.3±3.7 kcal/kg /day CHO: 2.4±0.65 g/kg/day; Prot: 1.1±0.3 g/kg/day; Lip: 0.95±0.1 g/kg/day Total fiber: 0.1±0.1 g/kg/day	**Intervention** eGFR (ml/min/1.73 m^2) ** Basal: 110 (88-129) Final: 89.9±4.1 Albuminuria (mg/24h) ** Final: 10.4 (1.3-22.5) **Control** eGFR (ml/min/1.73 m^2) Basal: 110 (88-129) Final: 105.6±5.1

			Soluble fiber: NA Insoluble fiber: NA	Albuminuria (mg/24h) Final: 17.1 (4.1-44.5)
		Type 2 diabetes		
		Vegetarian diet		
Nicholson 1999 n = 11 USA	Females: 45.5% Hypertension: 81.8% Age: 54.3 (34-74) years HbA1c: 8.2±1.5% BMI: NA Withdrawals: 15.4% Duration: 12-weeks	Randomized clinical trial	**Intervention (n = 7):** low fat vegan diet * Energy: 1409±549 kcal/day CHO: 75±4.4%; Prot: 14±1.6%; Lip: 11±4.7% Total fiber: 26±8.2 g/day Soluble fiber: NA Insoluble fiber: NA **Control (n = 4):** conventional diet * Energy: 1526±314 kcal/day CHO: 51±3.5%; Prot: 18±1.4%; Lip: 31±2.4% Total fiber: 20±2.7 g/day Soluble fiber: NA Insoluble fiber: NA	**Intervention** Albuminuria (mg/24h) § Basal: 434.8±565.5 Final: 155.2±182.6 **Control** Albuminuria (mg/24h) Basal: 82.9±114.6 Final: 169.2±298
Mello 2006 n = 17 Brazil	Females: 17.6% Hypertension: 47% Age: 59±11 years HbA1c: 7.6±2.6% BMI: 26.2±2.6 kg/m^2 Withdrawals: 57.5% Duration: 4-weeks	Randomized crossover clinical trial Washout: 4-weeks	**Intervention (n = 17):** lactovegetarian diet * Energy: 1634±451 kcal/day CHO: 58.7±6.8%; Prot: 11.6±1.5%; Lip: 29.5±6.8% Total fiber: 27±8.1 g/day Soluble fiber: NA Insoluble fiber: NA **Control (n = 17):** usual diet * Energy: 1901±480 kcal/day CHO: 46.9±6.7%; Prot: 21.9±3.4%; Lip: 30.8±6.3% Total fiber: 20±7.5 g/day Soluble fiber: NA Insoluble fiber: NA	**Intervention** eGFR (ml/min/1.73 m^2) **§** Final: 81.9±25.3 Albuminuria (mg/24h) ** Final: 332.5 (111.1-1449) **Control** eGFR (ml/min/1.73 m^2) Final: 81.8±22.2 Albuminuria (mg/24h) Final: 453.6 (324.4-1774.4)
		Fiber supplement		

Dall'Alba 2013 n = 44 Brazil	Females: 38.6% Hypertension: 93.2% Age: 62±9.7 years HbA1c: 6.9±0.8% BMI: 29.8±3.7 kg/m^2 Withdrawals: 4.3% Duration: 6-weeks	Randomized clinical trial	**Intervention (n = 23):** 10 g guar gum supplement* Energy: 1700±439 kcal/day CHO: 184.2±28.1 g/day; Prot: 81.5±15.4 g/day; Lip: 61.5±10.2 g/day Total fiber: 24.3±5.4 g/day Soluble fiber: 14.8±1.9 g/day Insoluble fiber: 9.5±3.6 g/day **Control (n = 21):** control group * Energy: 1553±371 kcal/day CHO: 191.9±27.3 g/day; Prot: 86.3±12 g/day; Lip: 58.3±12.8 g/day Total fiber: 15.7±6.3 g/day Soluble fiber: 5.2±1.9 g/day Insoluble fiber: 10.5±4.7 g/day	**Intervention** eGFR (ml/min/1.73 m^2) § Basal: 84.8±16.6 Final: 85±16.2 Albuminuria (mg/24h) ‡ Basal: 6.8 (3-17.5) Final: 6.2 (3-9.5) **Control** eGFR (ml/min/1.73 m^2) § Basal: 89.2±16.7 Final: 89±17.4 Albuminuria (mg/24h) § Basal: 6.7 (3-19.3) Final: 7.6 (3-15.8)
Farhangi 2016 n = 49 Iran	Females: 100% Hypertension: NA Age: 48.3 ±8.8 years HbA1c: 8.3±0.9% BMI: 30.8±3.9 kg/m^2 Withdrawals: 9.3% Duration: 2-months	Randomized clinical trial	**Intervention (n = 27):** 10g chicory inulin supplement Energy: NA CHO: NA; Prot: NA; Lip: NA Total fiber: NA Soluble fiber: 10 g/day Insoluble fiber: NA **Control (n = 22):** placebo Energy: NA CHO: NA; Prot: NA; Lip: NA Total fiber: NA Soluble fiber: NA Insoluble fiber: NA	**Intervention** eGFR (ml/min/1.73 m^2) § Basal: 86.3±14 Final: 84.3±13.6 **Control** eGFR (ml/min/1.73 m^2) Basal: 85.3±13.5 Final: 82.1±16.1
		DASH diet		

Paula 2015 n = 40 Brazil	Females: 55% Hypertension: 100% Age: 62.2±8.4 years HbA1c: 8.7±1.8% BMI: 29.4±3.4 kg/m2 Withdrawals: 0% Duration: 4-weeks	Randomized clinical trial	**Intervention (n = 20):** DASH diet* Energy: 1585±321 kcal/day CHO: 47.1±7.3%; Prot: 23.5±6.7%; Lip: 29.4±5.8% Total fiber: 20.1±4.3 g/day Soluble fiber: 6.1±2.1 g/day Insoluble fiber: 12.9±2.9 g/day **Control (n = 20):** ADA recommendations * Energy: 1752±299 kcal/day CHO: 39.3±9.9%; Prot: 23±3.8%; Lip: 36.8±8% Total fiber: 14.1±4.8 g/day Soluble fiber: 4.7±2.1 g/day Insoluble fiber: 11±5.3 g/day	**Intervention** Albuminuria (mg/24h) § Basal: 41.6 (22.1-185.8) Final: 31.8 (10.2-132.7) ‡ **Control** Albuminuria (mg/24h) Basal: 43.5 (18.5-194.4) Final: 33.4 (11.2-119.6)

Abbreviators: ADA = American Diabetic Association; BMI = body mass index; kcal = kilocalories; CHO = carbohydrates; DASH = Dietary Approaches to Stop Hypertension; eGFR: estimated glomerular filtration rate; Lip = Lipids; NA = Not available; NS = Not significant; Prot = Protein.

* actual intake ** p <0.05 for the effect of diet between groups; ‡ p <0.05 for the effect of diet within group; § Not significant

Table 3. Assessment of methodological quality or risk of bias item for each included study.

	Selection Bias		**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Other Bias**
	Random sequence generation	Allocation Concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Diet/supplement adherence
Jibani, 1991	NA*	NA*	NA*	Uncertain	Low	Uncertain	Low
Kontessis, 1995	Uncertain	Uncertain	NA*	Uncertain	Uncertain	Uncertain	Low
Nicholson, 1999	Uncertain	Uncertain	NA*	Uncertain	Low	Uncertain	Low
Mello, 2006	Uncertain	Uncertain	NA*	Uncertain	High	Uncertain	Low
Dall'Alba, 2013	Low	Uncertain	High	Uncertain	Low	Low	Low
Paula, 2015	Low	Uncertain	NA*	Uncertain	Low	Low	Low
Farhangi, 2016	Low	Low	Low	Low	Low	High	Low

Abbreviators: *NA = not applicable for this type of study. Adapted from Cochrane Collaboration's tool.

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Appendix 1. MEDLINE search strategy for the systematic review

(((("Diabetes Mellitus" [Mesh] OR (Diabetes Mellitus) OR “Diet, Diabetic" [Mesh] OR (Diet, Diabetic) OR (Diabetic Diets) OR (Diets, Diabetic) OR (Diabetic Diet) OR "Diabetes Mellitus, Type 2" [Mesh] OR (Diabetes Mellitus, Type 2) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Type 2 Diabetes Mellitus) OR (Diabetes Mellitus, Type II) OR Stable Diabetes Mellitus OR (Stable Diabetes Mellitus) OR (Diabetes Mellitus, Stable) OR (Slow-Onset Diabetes Mellitus) OR (Diabetes Mellitus, Slow Onset) OR (Diabetes Mellitus, Slow-Onset) OR (Diabetes Mellitus, Noninsulin Dependent) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Non-Insulin-Dependent) OR (Diabetes Mellitus, Non Insulin Dependent) OR (Maturity-Onset Diabetes) OR (Diabetes Mellitus, Adult-Onset) OR (Diabetes Mellitus, Noninsulin-Dependent) OR (Adult-Onset Diabetes Mellitus) OR (Diabetes Mellitus, Adult Onset) OR (NIDDM) OR (Diabetes Mellitus, Maturity Onset) OR (Diabetes Mellitus, Maturity-Onset) OR (Diabetes Mellitus, Ketosis-Resistant) OR (Diabetes Mellitus, Ketosis Resistant) OR (Ketosis-Resistant Diabetes Mellitus) OR (Type II DM) OR (Type 2 DM) OR "Diabetes Mellitus, Type 1" [Mesh] OR (Diabetes Mellitus, Type 1) OR (Diabetes Mellitus, Brittle) OR (Brittle Diabetes Mellitus) OR (Diabetes Mellitus, Insulin-Dependent) OR (Diabetes Mellitus, Insulin Dependent) OR (Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Juvenile-Onset) OR (Diabetes Mellitus, Juvenile Onset) OR (Juvenile-Onset Diabetes Mellitus) OR (Diabetes Mellitus, Ketosis-Prone) OR (Diabetes Mellitus, Ketosis Prone) OR (Ketosis-Prone Diabetes Mellitus) OR (Juvenile-Onset Diabetes) OR (Diabetes, Juvenile-Onset) OR (Juvenile Onset Diabetes) OR (Diabetes Mellitus, Type I) OR (Diabetes Mellitus, Sudden-Onset) OR (Diabetes Mellitus, Sudden Onset) OR (Diabetes Mellitus, Sudden Onset) OR (Sudden-Onset Diabetes Mellitus) OR (Type 1 Diabetes Mellitus) OR (Diabetes Mellitus, Insulin-Dependent, 1) OR (Insulin-Dependent Diabetes Mellitus 1) OR (Insulin Dependent Diabetes Mellitus 1) OR (Type 1 Diabetes) OR (Diabetes, Type 1) OR (IDDM) OR (Diabetes, Autoimmune) OR (Autoimmune Diabetes)))) AND (("Dietary Fiber" [Mesh] OR (Dietary Fiber) OR (Fiber, Dietary) OR (Dietary Fibers) OR (Fibers, Dietary) OR (Roughage) OR (Roughages) OR (Wheat Bran) OR (Bran, Wheat) OR (Brans, Wheat) OR (Wheat Brans) OR "Whole Grains" [Mesh] OR (Whole Grains) OR (Grain, Whole) OR (Grains, Whole) OR (Whole Grain) OR (Whole Grain Cereals) OR (Cereal, Whole Grain) OR (Cereals, Whole Grain) OR (Grain Cereal, Whole) OR (Grain Cereals, Whole) OR (Whole Grain Cereal) OR (Cereal fiber) OR "Plants, Edible" [Mesh] OR (Plants, Edible) OR (Edible Plant) OR (Edible Plants) OR (Plant, Edible) OR (Food Plants)

OR (Food Plant) OR (Plant, Food) OR (Plants, Food) OR "Vegetables" [Mesh] OR (Vegetables) OR (Vegetable) OR "Fruit" [Mesh] OR (Fruit) OR (Fruits) OR (Plant Aril) OR (Arils, Plant) OR (Aril, Plant) OR (Plant Arils) OR (Fiber) OR (Soluble fiber) OR (Total fiber) OR (Insoluble fiber) OR "Diet, Vegetarian"[Mesh] OR (Diet, Vegetarian) OR (Diets, Vegetarian) OR (Vegetarian Diets) OR (Vegetarian Diet) OR (Vegetarianism) OR "Diet, Vegan" [Mesh] OR (Diet, Vegan) OR (Diets, Vegan) OR (Vegan Diets) OR (Vegan Diet) OR (Veganism) OR (Diet, Dash) OR (Diets, Dash) OR (Dash Diet) OR (Dash Diets) OR (Dash) OR (Dietary Approaches to Stop Hypertension) OR "Diet, Mediterranean"[Mesh] OR (Diet, Mediterranean) OR (Mediterranean Diet) OR (Diets, Mediterranean) OR "Inulin"[Mesh] OR (Inulin) OR "Psyllium"[Mesh] OR (Psyllium) OR (Gum, Ispaghule) OR (Ispaghula) OR (Guar gum) OR (Gum guar)))) AND (("Diabetic Nephropathies" [Mesh] OR (Diabetic Nephropathies) OR (Nephropathies, Diabetic) OR (Nephropathy, Diabetic) OR (Diabetic Nephropathy) OR (Diabetic Kidney Disease) OR (Diabetic Kidney Diseases) OR (Kidney Disease, Diabetic) OR (Kidney Diseases, Diabetic) OR (Diabetic Glomerulosclerosis) OR (Kimmelstiel-Wilson Syndrome) OR (Kimmelstiel Wilson Syndrome) OR (Syndrome, Kimmelstiel-Wilson) OR (Kimmelstiel-Wilson Disease) OR (Kimmelstiel Wilson Disease) OR (Nodular Glomerulosclerosis) OR (Glomerulosclerosis, Nodular) OR (Glomerulosclerosis, Diabetic) OR "Albuminuria"[Mesh] OR (Albuminuria) OR (Albuminurias) OR "Proteinuria"[Mesh] OR (Proteinuria) OR (Proteinurias) OR (Microalbuminuria) OR (Macroalbuminuria) OR (Diabetic Renal Disease) OR (Increased urinary albumin excretion) OR "Glomerular Filtration Rate"[Mesh] OR (Glomerular Filtration Rate) OR (Filtration Rate, Glomerular) OR (Filtration Rates, Glomerular) OR (Glomerular Filtration Rates) OR (Rate, Glomerular Filtration) OR (Rates, Glomerular Filtration) OR (Chronic Kidney Disease) OR ("Renal Replacement Therapy"[Mesh]) OR (Renal Replacement Therapy) OR "Dialysis"[Mesh] OR (Dialysis) OR (Dialyses) OR "Renal Dialysis"[Mesh] OR (Renal Dialysis) OR (Hemodialysis) OR (Hemodialyses) OR "Kidney Failure, Chronic"[Mesh] OR (Kidney Failure, Chronic) OR (End-Stage Kidney Disease) OR (Disease, End-Stage Kidney) OR (End Stage Kidney Disease) OR (Kidney Disease, End-Stage) OR (Chronic Kidney Failure) OR (End-Stage Renal Disease) OR (Disease, End-Stage Renal) OR (End Stage Renal Disease) OR (Renal Disease, End-Stage) OR (Renal Disease, End Stage) OR (Renal Failure, End-Stage) OR (End-Stage Renal Failure) OR (Renal Failure, End Stage) OR (Renal Failure, Chronic) OR (Chronic Renal Failure) OR (ESRD) OR (ESKD) OR "Renal Insufficiency, Chronic"[Mesh] OR (Renal Insufficiency, Chronic) OR (Chronic Renal Insufficiencies) OR (Chronic Renal Insufficiencies) OR (Renal

Insufficiencies, Chronic) OR (Chronic Renal Insufficiency) OR (Kidney Insufficiency, Chronic) OR (Chronic Kidney Insufficiency) OR (Chronic Kidney Insufficiencies) OR (Kidney Insufficiencies, Chronic) OR (Chronic Kidney Diseases) OR (Chronic Kidney Disease) OR (Disease, Chronic Kidney) OR (Diseases, Chronic Kidney) OR (Kidney Disease, Chronic) OR (Kidney Diseases, Chronic) OR (Chronic Renal Diseases) OR (Chronic Renal Disease) OR (Disease, Chronic Renal) OR (Diseases, Chronic Renal) OR (Renal Disease, Chronic) OR (Renal Diseases, Chronic)))

Appendix 2. Excluded studies of the systematic review (n=41)

Author	Year	Periodic	Reasons to exclusion
Paisey	1984	Diabetes Care	Non-clinical trials
Parillo	1984	Minerva Endocrinologica	Duration < 4-weeks
Barsotti	1987	Infusionstherapie und Klinische Ernährung	Only abstract
Parillo	1988	American Journal of Clinical Nutrition	Duration < 4-weeks
Barsotti	1988	Contribuitions of Nephrology	Only abstract
Naumova	1990	Vŭtreshni Bolesti	Only abstract
Barsotti	1991	American Journal of Nephrology	Non-diabetic population
Metcalf	1993	Clinical Chemistry	Outcomes of interest not reported
Hadfield	1993	Practical Diabetes	Non-clinical trials
Oldrizzi	1994	Journal of the American Society of Neprhology	Dietary information not provided
Citro	1998	Minerva Endocrinologica	Outcomes of interest not reported
GSEDNu	2006	Journal of Diabetes and Complications	Non-clinical trials
Brunori	2007	American Journal of Kidney Diseases	Non-diabetic population
Cámara	2008	Revista Espanhola de Salud Publica	Outcomes of interest not reported
Glover	2009	Food Hydrocolloids	Outcomes of interest not reported
Teixeira	2010	Diabetes	Outcomes of interest not reported
Gong	2011	Diabetologia	Dietary information not provided

Lin	2011	American Journal of Kidney Diseases	Dietary information not provided
Sun	2011	Journal of Chinese Clinical Medicine	Only abstract
Reddy	2012	Kidney Research Clinical Practice	Non-clinical trials
Dunkler	2013	JAMA Internal Medicine	Non-clinical trials
Chang	2013	American Journal of Kidney Diseases	Non-clinical trials
Tirosh	2013	Diabetes Care	Only abstract
Dans	2013	Phillipine Journal of Internal med	Only abstract
Khatri	2014	Clinical Journal of the American Society of Nephrology	Non-clinical trials
Hsu	2014	Clinical Nutrition	Non-clinical trials
Xu	2014	Clinical Journal of the American Society of Nephrology	Non-clinical trials
Díaz-López	2015	Diabetes Care	Dietary information not provided
Villarini	2015	Annali di Igiene	Non-diabetic population
Lee	2015	Nephrology Dialysis Transplantation	Non-clinical trials
Nazha	2015	Nephrology Dialysis Transplantation	Only abstract
Rebholz	2016	American Journal of Kidney Diseases	Duplicated
Dunkler	2016	American Journal of Kidney Diseases	Non-clinical trials
Piccoli	2016	BMC Nephrology	Dietary information not provided
Ashgari	2016	Hypertension Research	Non-clinical trials
Hirahatake	2016	Circulation	Dietary information not provided
Rebhold	2016	American Journal of Nephrology	Non-clinical trials

Mejia	2016	The FASEB Journal	Only abstract
Ashgari	2017	Nephrology, Dialysis, Transplantation	Non-clinical trials
Horikawa	2017	Nutrients	Non-clinical trials
Duncan	2017	Diabetology & Metabolic Syndrome	Dietary information not provided

CAPÍTULO IV

CONSIDERAÇÕES FINAIS

De uma maneira geral as complicações crônicas do DM estão associadas, entre outros fatores, a hiperglicemia de jejum e pós-prandial. Tais complicações podem ser prevenidas e conjuntamente tratadas com a modificação no estilo de vida, além do tratamento farmacológico, sendo a alimentação uma peça fundamental para este objetivo. Embora o tratamento do DM, no aspecto de controle glicêmico seja um desafio na prática diária já que na maioria das vezes o indivíduo não apresenta qualquer tipo de sintomas.

Os dados do ensaio clínico randomizado exposto na presente tese de doutorado indicam que o desjejum de pacientes com DM tipo 2 deve apresentar um maior teor de fibras, visando uma menor glicose pós-prandial. O consumo de fibras solúveis pode ser obtido através de alimentos ou suplemento, independente da fonte, pois ambos apresentaram um efeito semelhante na resposta glicêmica destes indivíduos. Esta intervenção, de forma aguda, é uma estratégia útil e prática para um adequado controle metabólico de pacientes com DM. O consumo de fibra através de suplemento pode ser favorável, por fornecer uma quantidade maior de fibras por porção, embora generalizar os benefícios de todas as fibras solúveis só seria possível a partir da avaliação do uso de outros suplementos comparados aos alimentos fonte. Entretanto, a ingestão de fibras de origem alimentar, encontrada *in natura* nos alimentos, além de menor custo, fornece benefício semelhante sobre a glicemia pós-prandial e, possui nutrientes adicionais importantes para a saúde da população.

Através da revisão sistemática de sete ensaios clínicos com pelo menos quatro semanas de duração não conseguimos chegar a uma conclusão definitiva do efeito benéfico da fibra sobre a DRD. Embora existam menos evidências acerca dos benefícios sobre a DRD, é provável que a dieta vegetariana, um padrão alimentar rico em fibras, porém com baixo teor de proteína animal, possa ter um efeito benéfico sobre esta complicação do DM. Dessa forma, conclusões inequívocas a respeito deste único nutriente (fibra) não podem ser aceitas.

Como perspectivas futuras, novos ensaios clínicos randomizados que incluam manipulação dietéticas do conteúdo de fibras a longo prazo e levando em consideração a ingestão diária total deverão ser realizados para confirmar os dados observados no experimento agudo realizado. Tais observações são fortes indicadores que o consumo de fibras por pacientes com DM deva ser estimulado, seja por meio de alimentos fonte ou suplementos, mas sempre dentro de um plano alimentar saudável. Provavelmente, dentro de um contexto de 24 horas, ambas as manipulações dietéticas (fibra do alimento ou suplemento) sejam importantes e representam duas opções de condutas dietoterápicas para pacientes com DM. Em relação ao consumo de dietas ricas em fibras e DRD, ensaios clínicos maiores, e realizados com maior duração são necessários para avaliar o efeito da alimentação rica em fibra em desfechos renais nos pacientes com DM.