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Dietary Fibre and Cardiovascular Risk in Diabetes Mellitus

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Abstract

Patients with type 1 and 2 diabetes have a higher risk of cardiovascular disease compared to non-diabetic populations. Improved dietary quality is essential to control risk factors and can prevent or delay cardiovascular disease in diabetic patients. Higher dietary fibre intake was inversely associated with cardiovascular disease in several general population studies. However, in diabetes mellitus, and especially type 1 diabetes, little information is available. A literature study was performed to summarize the available evidence for a possible relationship between fibre consumption from natural foods and the risk of developing cardiovascular disease in people with type 2 and type 1 diabetes. In November and December 2014, PubMed was searched for relevant articles. The full texts of 15 articles were reviewed. Prospective cohort studies reported an inverse association between dietary fibre intake and all-cause and cardiovascular disease mortality risk in both diabetes types. Randomized controlled trials were inconsistent. For type 2 diabetes, dietary fibre intake was related to lower plasma glucose and plasma lipid levels. In terms of foods, mainly legume and cereal fibre, vegetables and fruits were found to beneficially influence cardiovascular risk in patients with type 2 diabetes. For type 1 diabetes, no foods were investigated, but dietary fibre had some beneficial effects on cardiovascular risk factors from limited trials. To lower CVD risk in people with type 1 diabetes in the future, the potential of raising fibre in the diet should be further explored.

Keywords: Diabetes mellitus; Cardiovascular disease; Dietary fibre; Risk factors

Abbreviations: T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; CVD: Cardiovascular Disease; DF: Dietary Fibre; RCT: Randomized Controlled Trial; RR: Relative Risk

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Introduction

Diabetes mellitus is the eighth leading cause of death in the world and in 2012 approximately 1.5 million deaths were due to diabetes [1]. Worldwide 387 million people suffer from diabetes mellitus and by 2035 this will rise to 592 million [2]. In 2011, over 830,000 people in the Netherlands were diagnosed with diabetes and each year approximately 50,000 new cases are diagnosed [3].

The two main types of diabetes mellitus are diabetes type 1 (T1D) and diabetes type 2 (T2D) [4]. T2D is the most common form of diabetes mellitus. It accounts for 90% of the cases. The incidence of T2D increases by age. T2D is characterized by increased insulin resistance and decreased insulin sensitivity, as a result of obesity and physical inactivity, amplified by genetic susceptibility and advancing age [5]. T1D accounts for 5-10% of the cases, and is usually diagnosed at a young age [6]. T1D is characterized by complete β-cell destruction and no insulin production, making patients completely depending on life-long insulin treatment [7]. Immunotherapy to protect remaining insulin-producing β-cells can slow disease progression and need for insulin, but is not yet a cure for type 1 diabetes [8].

People with diabetes mellitus have an increased risk of acute or chronic complications. The major chronic complication is cardiovascular disease (CVD), with a 2-3 fold increased risk for T2D and a 4-8 fold increased risk for T1D [6, 9-11]. CVD is caused by atherosclerosis, resulting from chronic inflammation and injury to the arterial wall in the vascular system [12]. Hyperglycaemia and insulin resistance in diabetes mellitus enhance endothelial cell dysfunction and oxidative stress, causing an accelerated development of atherosclerosis [13, 14].

Control of risk factors by dietary therapy along with other lifestyle modifications can prevent or delay complications [15]. A dietary strategy that has been proven to be effective in preventing CVD and mortality in diabetes mellitus patients is modification of carbohydrate quality by substituting refined grain products by low-glycaemic, high fibre products like whole grains, fruits, legumes, vegetables and nuts [16-18]. Dietary fibres (DF) have properties to lower plasma cholesterol and normalize plasma glucose and insulin levels, and thus lower risk of CVD and mortality [12, 17]. However, intake levels of DF as recommended by the American Diabetes Association (14 g/1000 kcal) is often not met, because intake of good sources of DF is low [19-22]. An association between DF and risk of CVD is well established in the general population [23, 24], but in diabetes mellitus, and especially type 1 diabetes, little information is available [19, 24].

This review specifies the relationship between DF consumption from different nutrients and diets and the risk of developing CVD in people with T1D and T2D. Only studies with a prospective cohort design with cardiovascular disease endpoints and randomized controlled trials (RCT) with CVD risk factors (blood pressure, glycaemic control, plasma lipid levels and inflammatory markers) as main outcomes will be discussed, as these are more reliable epidemiological designs.

Materials and Methods

Until June 2016, PubMed was searched for relevant articles.

Randomized controlled trials

To search for RCTs, the following search terms were used: Diabetes or diabetic and fiber or fibre or cereal or legumes or fruit or vegetables in combination with body weight or blood pressure or TG levels or triglyceride or plasma lipid or blood lipid or cholesterol or glycated haemoglobin or insulin sensitivity or insulin resistance or inflammation or glycaemic response or cholesterol or LDL or HDL or plasma glucose or blood glucose. To exclude other research designs, the following terms were added: Trial or experimental or intervention or placebo-controlled or clinical trial or RCT or comparative trial. All terms were included in the title and abstract. Exclusion criteria were articles not written in English, animal studies, children aged <18 y, populations with prior CVD, populations with diagnosed diabetes for less than 6 months, studies with a duration of less than 4 weeks and if a non-natural fibre source was investigated.

Prospective cohort studies

To search for prospective cohort studies, the following search terms were used: Diabetes or diabetic and fiber or fibre or diet or nutrition or food or cereal or legumes or fruit or vegetables in combination with cardiovascular or CVD or coronary or stroke or myocardial. To exclude other research designs, the following terms were added: Cohort or longitudinal or follow-up. The terms diabetes or diabetic were included in the title, the other terms in title and abstract. Exclusion criteria were articles not written in English, animal studies, children aged <18 y, populations with prior CVD, populations with diagnosed diabetes for less than 6 months and studies with a duration less than 6 months.

For each selected article the reference list was checked for additional relevant articles which were not identified by the original series, but no new relevant articles were found.

In the end, the full text of 15 articles was reviewed with as exposure dietary fibre and as outcome cardiovascular risk factors. Three articles for T1D (2 RCTs and 1 prospective cohort study) and twelve articles for T2D (9 RCTs and 3 prospective cohort studies) **(Figure 1)**.

Results

Type 2 diabetes

Twelve articles were reviewed for T2D, out of which nine RCTs and three prospective cohort studies.

Randomized controlled trial design: All RCTs reported effects of DF on CVD risk factors in T2D patients. Two of these trials compared diet high in carbohydrates and DF to a diet high in mono unsaturated fatty acid diet [25, 26], two compared a diet high in DF to a diet low in DF [27, 28], three compared a diet high in cereal DF to a diet low in cereal DF [29-31], one compared a diet high in legumes to a diet low in legumes [32, 33], and one compared a diet high in legumes to a diet high in cereal DF [32]. Most trials reported effects of DF on body weight, glycated haemoglobin, total cholesterol and other plasma lipids, plasma glucose and inflammatory markers. Study outcomes varied between trials, but all are related to CVD. The most important results are discussed below. An overview of all study characteristics can be found in **Table 1**.

Carbohydrate/DF diet vs. monounsaturated fatty acid diet: Eighteen T2D patients were enrolled in a randomized crossover design by De Natale et al. [25] After a 4 week wash-out period, they received either first a carbohydrate/DF diet (27 g/1000 kcal DF) or a monounsaturated fatty acid diet (8 g/1000 kcal DF). After 4 weeks the subjects switched diet. At the end of each period, fasting plasma total, LDL, and HDL cholesterol were measured and postprandial values for glucose, insulin, total and HDL cholesterol were measured after a test meal. Participants measured glucose concentrations at home. A significant reduction in total and HDL cholesterol was observed after the carbohydrate/DF diet **(Table 1)**. No significant effects on glucose and insulin levels were found.

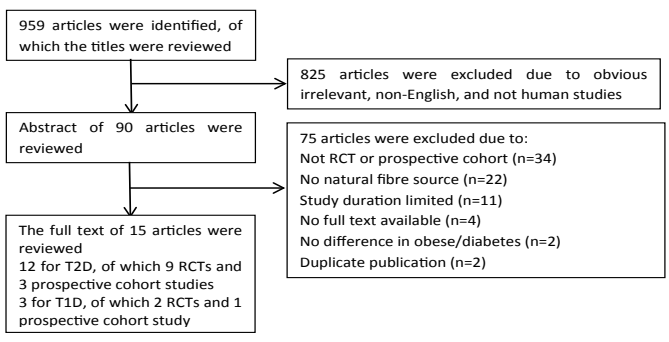

Figure 1 Overview identified articles.

A trial by Tsihlias et al. reported opposite effects compared to the trial by De Natale et al. [26]. In a six months parallel design, 72 T2D patients were allocated to receive either a low-glycaemic index breakfast cereal, high-glycaemic breakfast cereal or monounsaturated fatty acid products supplementary to their normal diet. The high-glycaemic index breakfast group had the highest DF intake (50.3 g/day) compared to the other diets (23 g/day). Nutrient intake was measured by 3-d food records, 2 during the baseline period and 4 during the study. The primary outcome was glycated haemoglobin, measured at baseline, 3 and 6 months, but no significant effects were found **(Table 1)**. Secondary outcomes, plasma glucose and fasting plasma total, LDL and HDL cholesterol, were also not significantly related to the intervention.

High DF diet vs. Low DF diet: In a randomized crossover trial with thirteen T2D subjects by Chandalia et al., a positive effect of a DF diet on glycaemic control and plasma lipid concentrations in T2D patients was reported [27]. The subjects either received the American Diabetes Association diet (24 g/d DF) or a high DF diet (50 g/d DF) for six weeks. After a 7 day wash-out period, the participants switched diet. Plasma lipids, glucose and glycated haemoglobin values were measured at the beginning and end (wk 6) of both study periods. Mean plasma glucose and all plasma lipids, except for HDL cholesterol, were significantly lower in the high DF diet compared to the American Diabetes Association diet **(Table 1)**. Glycated haemoglobin values were slightly lower in the high DF diet, but not significant.

Fourteen T2D patients were enrolled in a randomized crossover study by Karlstrom et al. [28] In two 3 week study periods, a standard diet (18.9 g DF/6.7 MJ) was compared with a diet with an increased amount of cereal DF (42 g DF/6.7 MJ). During both study periods, body weight, plasma glucose and fasting plasma total cholesterol were measured. Fasting plasma glucose concentrations and postprandial glucose concentrations after a standardized breakfast were significantly lower compared to concentrations after a standard diet **(Table 1)**. Furthermore, mean plasma glucose concentrations were significantly lower during treatment with the high-DF diet compared to the standard diet.

Diet high in cereal DF: A randomized crossover study in twenty-three T2D subjects by Jenkins et al. studied the effect of DF from wheat bran in T2D patients [31]. The subjects completed two 3-month phases. In the test phase, bread and breakfast cereals were provided as products high in wheat bran DF (19 g/day additional DF). In the control phase, supplements were low in DF (4 g/day additional cereal DF). During the control phase and the test phase, plasma glucose, plasma lipids, glycated haemoglobin, C-reactive protein and pro-inflammatory cytokines were measured. No significant results were found **(Table 1)**.

Diet high in legumes

In 3 months parallel RCT by Jenkins et al. the effect of legumes was compared with the effects of whole-grain on glycaemic control, serum lipid levels and body weight in 121 T2D patients [32]. These T2D patients consumed a diet high in legumes (25.6 g/1000 kcal DF) versus a diet high in wheat DF (18.5 g/1000 kcal DF). Adherence to the diet was measured by 7-day food records at the beginning and end of the trial. The participants visited the research centre 7 times, at which they were screened. Body weight, glycated haemoglobin, plasma lipids and blood pressure were measured. Both diets decreased body weight and glycated haemoglobin, but the reduction in the legume diet group was bigger **(Table 1)**. Furthermore, fasting plasma total cholesterol decreased significantly more in the legume diet group compared to the high DF wheat group, while HDL cholesterol increased more in the high wheat DF group compared to the legume diet group. This study suggests that the effects of legumes on CVD risk factors seem stronger than whole-grains.

Prospective cohorts design

Three prospective cohort studies reported an association between DF intake and CVD and all-cause mortality in T2D patients. Two of these studies reported results on DF intake [18, 33, 34] and one study reported results for whole-grain, cereal DF and germ intake [12]. The most important results are discussed here, an overview of all studies can be found in **Table 2**.

From the European Prospective Investigation into Cancer and Nutrition, a sub-cohort of 6192 individuals with both T2D and T1D was followed for 9.2 years [18]. Diet was assessed with a food frequency questionnaire. The mean DF intake was 23.5 g/day. During follow-up, 791 deaths were recorded, of which 306 due to CVD. A lower risk of 20% per standard deviation (SD) of DF for both CVD (HR: 0.76; confidence interval (CI), 0.64-0.89) and all-cause mortality (HR: 0.83 (95% CI, 0.75-0.91) was found. A limitation of this study was that no distinguishment was made between T1D and T2D patients. Exclusion of T1D patients based on age at diabetes diagnosis or insulin usage from the study, did not weaken the association.

In 7822 T2D US women from the Nurses' Health study the relationship between whole-grain, cereal DF, bran and germ intake and all-cause and CVD-specific mortality in T2D patients [12]. All participants were followed during 26 years and every four years, participants were asked to fill out food-frequency questionnaires. 852 deaths were confirmed, of which 295 CVD deaths. In the lowest quartile, the median cereal DF intake was 1.9 g/day and in the highest quartile the intake was 6.29 g/day. After adjustment for lifestyle and other covariates, a significant risk reduction of 19% in all-cause mortality was found in the highest quartile (p for trend=0.02). An 8% (95% CI, 4% to 11%) lower risk of all-c mortality was found per 1 g/day of cereal DF. In the age-adjusted model, the highest quintile of cereal DF intake was non-significantly associated with a 31% lower risk of CVD-specific mortality compared with the lowest quintile [relative risk (RR), 0.69; 95% CI, 0.46-1.02]. After further adjustments for confounders these associations were attenuated.

Type 1 diabetes

Randomized controlled trial design: Two RCTs investigated the effect of DF on CVD risk factors in T1D [35-37]. An overview of all study details is provided in **Table 3**.

Table 1 Characteristics and results of 9 randomized controlled trials on DF and cardiovascular risk factors in patients with type 2 diabetes.

Ref.	n	Age (mean or range)	Design	Duration	Control	Measure	Cardiovascular related outcomes	Results	Main conclusions
Karlstrom [29]	14	55-64	Crossover	2 × 3 wk 5d base-line period	Standard diet (18.9 g DF/6.7 MJ)	HF diet (42 g DF/6.7 MJ); fibre from cereal products	BW BG TG TC LDL HDL	NS Sign. differences in FPG at 0700h (fasting) (9.5 (HF diet) vs. 10.1 mmol/L (LF diet) and at 1100 h (postprandial (13.1 (HF diet) vs. 15.1 mmol/L (LF diet) NS NS Fasting LDL-TG sign. lower (0.53 vs. 0.61 mmol/L); P<0.05) Fasting LDL-C sign. lower (3.49 vs. 3.68 mmol/L); P<0.05) NS	Significant lowered blood glucose concentration both post-prandial and after fasting. Differences in LDL too small to make a conclusion. More pronounced effects might be observed with other types of DF
Hollenbec [28]	6	55	Crossover	2 × 4 wk	Total DF 11 g/1000 kcal	Total DF 27 g/1000 kcal	PG, glycated haemoglobin, TC, HDL	NS	DF from natural products has no effect. Drastic increases of DF by supplements or legumes may be necessary to achieve effects
Tsihlias [26]	72	42-79	Parallel	6 mo	Low-GI breakfast cereal (31.1 g/d DF)	High-GI breakfast cereal (50.3 g/d DF) or MUFA products (23.5 g/d DF)	BW, PG, glycated haemoglobin, TC, HDL.	NS	Exchanging 10% of energy from MUFA with carbohydrate from breakfast cereals has no long-term effects. Results from studies lasting 6-12 wk may not reflect long-term effects of high carbohydrate/fibre diets
Chandalia [27]	13	61	Crossover	2 × 6 wk 5 d base-line period 7 d wash-out interval	ADA diet (24 g/d DF) (8 g soluble, 16 g insoluble)	HF diet (50 g/d DF) (25 g soluble, 25 g insoluble)	BW PG Glycated haemoglobin TG TC VLDL LDL HDL	NS Mean PG was lower in the HF diet (0.7 mmol/L; P=0.04). Glycated haemoglobin was lower, but not significant (P=0.09). TG was 10.2% lower in the HF diet (P=0.02). TC was 6.7% lower in the HF diet (P=0.02). VDLD was 12.5% lower in the HF diet (P=0.01). Glycated haemoglobin was lower, but not significant (P=0.11). NS	Intake of DF, especially soluble DF, improves glycaemic control and lowered plasma lipid concentrations. Guidelines should emphasize increase of DF through unfortified foods

Jenkins [30]	23	63	Crossover	2 × 3 mo 2 mo wash-out interval	LF bread and breakfast cereal (additional 4 g/day DF)	HF wheat bran bread and breakfast cereal (additional 19 g/day)	PG, glycated haemoglobin, plasma lipid, SBP, DBP, C-reactive protein, pro-inflammatory cytokines	NS	Addition of wheat bran did not seem to influence glycaemic control or CHD risk factors
De Natale [25]	18	59	Crossover	2 × 4 wk 4 wks base-line period	No control	Carbohydrate/fibre diet (27 g/1000 kcal DF) vs. MUFA diet (8 g/1000 kcal DF)	BW PG TC TG LDL HDL	NS Sign. lower postprandial PG (5.9 vs. 7.3 mmol/l; P<0.05) Lower TC (4.20 vs. 4.40 mmol/L; P<0.05) Fasting levels NS After test meal sign. lower (1.87 vs. 2.70 mmol/l per 6 h) Lower LDL (2.62 vs. 2.82 mmol/l; P<0.05) Lower HDL (0.98 vs. 1.06 mmol/l; P<0.05)	Significant lowered postprandial lipoproteins after carbohydrate/fibre diet. carbohydrate/fibre diet is to be preferred to a diet low in carbohydrates and rich in MUFA
Jenkins [32]	121	60	Parallel	3 mo 1 wk base-line period	No control	Legume diet (25.6 g/1000 kcal DF) vs. high wheat fibre diet (18.5 g/1000 kcal DF)	BW Glycated haemoglobin TC HDL DBP, SBP	Sign. reduction in BW in both groups, with a bigger difference for the legume diet (legume diet -2.7 kg vs. wheat fibre diet -2.0, p=0.001). Sign. reduction in glycated haemoglobin in both groups (legume diet -0.5% vs. wheat fibre diet -0.3%). Sign. reduction in TC for legume diet (-8 mg/dL). NS for wheat fibre diet. NS for legume diet. Sign. increase in HDL level (2 mg/dL) for high wheat fibre diet. Sign. difference in SBP (-4.5 mmHG; p=0.001) and DBP (-3.1 mmHG; P<0.001) for legume diet. NS for high wheat fibre diet	Increased legume consumption as part of a low-GI diet lowered CHD risk factors, even more than wheat intake
Nowotny [31]	36		Parallel	8 wk	No control	Low cereal fibre diet (10 g/day, coffee-free and high red meat (>150 g/day)) vs. high cereal fibre diet (30-50 g/day, coffee (5 cups/day) and free of meat)	BW Insulin sensitivity Pro-inflammatory marker IL-18	NS NS Sign. reduction of pro-inflammatory cytokine IL-18 (0.23 pg/ml; p<0.05), other cytokines remained unchanged.	No evidence of a difference between diets was identified. Effects on insulin sensitivity and subclinical inflammation might be explained by energy restriction and weight loss

Hosseinpour-Niazi [33]	31	58	Crossover	2 × 8 wk 2 wk base-line period	Legume-free TLC based diet (26.9 g/day DF)	Legume-based TLC diet (31.4 g/day DF) (two servings of meat replaced by legumes)	FPG TG LDL TC, DBP, SBP, BMI	Sign. change in FPG (-19.5 vs. -28.7 mg/dL); p<0.001) Sign. change in TG (-19.5 vs. -38.5 mg/dL; p<0.001) Sign. decrease in LDL (-8.7 vs. -15.6; p=0.02). NS	A legume-based TLC diet did significantly improve FPG and some disturbances in lipid profiles, but this may be partly explained by a higher concentration of magnesium and a lower concentration of TC

Note: HF: High Fibre; DF: Dietary Fibre; BW: Body Weight; FPG: Fasting Plasma Glucose; TG: Triglycerides; TC: Fasting Plasma Total Cholesterol; LDL: Low-density Lipoprotein; HDL: High-density Lipoprotein; NS: Non-significant; PG: Plasma Glucose; GI: Glycaemic Index; MUFA: Mono Unsaturated Fatty Acids; ADA: American Diabetes Association; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; IL: Interleukin; TLC: Therapeutic Lifestyle Change; BMI: Body Mass Index

Table 2 Characteristics and results of 3 prospective cohort studies on DF and CVD and all-cause mortality in patients with type 2 diabetes mellitus.

Ref.	Study (subjects)	n	Age (mean or range)	Duration of follow-up	Dietary assessment method	Fibre intake	Outcome measure	Results	Adjustment for potential confounders
He [12]	Nurses' Health Study	7822 women	30-55	26 y	FFQ	Median: Q1 1.9 g/day cereal F vs. Q5 6.29 g/day cereal F	CVD mortality All-cause mortality	No sign. results for CVD-specific mortality after adjustment for confounders RR=0.81 for all-specific mortality in highest quintile (P for trend=0.02), 8% risk reduction for every 1g/d DF (95% CI, 4% to 11%).	Age, smoking status, BMI, alcohol intake, physical activity, parental history of MI, menopausal status, hormone therapy usage, duration DM
Burger [18]	Sub-cohort of European Prospective Investigation into Cancer and Nutrition (EPIC) (combined T1D and T2D)	6192	57.4	9.2 y	FFQ	Mean DF intake: 23.5 g/day	CVD mortality All-cause mortality	CVD mortality risk: RR: 0.76 (95% CI, 0.64-0.89) All-cause mortality: RR per SD increase in DF: 0.83 (95% CI, 0.75-0.91)	Model 1: No adjustments Model 2: Adjustments for CVD-related risk factors Model 3: Adjustments for factors associated with severity of diabetes Model 4: Adjustments for dietary factors
Tanaka [34]	Japan Diabetes Complications Study (JDCS)	1414	40-70	8.1 y	FFQ	Mean DF in quartiles ranged from 8.7 to 21.8	Times to stroke, CHD	NS	Age, sex, BMI, glycated haemoglobin, diabetes duration, diabetic retinopathy, treatment by insulin, treatment by oral hypoglycaemic agents, SBP, LDL, HDL, TG, current smoking, physical activity, alcohol intake, proportions of total fat, SFA, n-6 FA, n-3 FA, C intake, Na intake

Note: FFQ: Food Frequency Questionnaire; RR: Relative Risk; SD: Standard Deviation; SFA: Saturated Fatty Acids; FA: Fatty Acid

The effect of high DF intake from natural products and glycaemic control in T1D patients was investigated in a parallel trial by Giacco et al. [35]. In a 24 week randomized parallel study 54 T1D subjects from the Neopolitan cohort of a large multicentre study either received a low DF diet (15 g/day) versus a high DF diet (50 g/day), with emphasis on soluble DF. Subjects in the high DF diet were advised to consume one serving of legumes, three servings of high DF fruit and two servings of high DF vegetables a day, whereas subjects in the low DF diet had to limit legume consumption to less than a week and to consume preferentially low DF fruit and low DF vegetables. At the beginning of the 24 wk period and at the end, fasting plasma samples were taken

Table 3 Characteristics and results of 2 randomized controlled trials on DF and cardiovascular risk factors in type 1 diabetes mellitus.

Ref.	n	Age (mean or range)	Design	Duration	Measure	Cardiovascular related outcomes	Results	Main conclusions
Anderson [36]	10	35-65	Crossover	2 × 4 wk, 6 wk wash-out period	LCLF diet (39 en% CH, 5 g/d DF) vs. HCHF diet (70 en% CH, 35 g/d DF)	BW FG, glycated haemoglobin TG, LDL TC HDL	NS NS NS Sign. differences in TC (5.12 in LCLF vs. 4.67 mmol/L in HCHF; p<0.0004) HDL-C (1.40 in LCLF vs. 1.27 mmol/L in HCHF, P<0.0013)	HCHF diets lower cholesterol without altering plasma glucose levels and triglycerides. HCHF diets should be standard for diabetes management
Giacco [35]	46	28	Parallel	24 wk, 4 wk base-line period	LF diet (15 g/day) vs. HF diet (50 g/day) (vegetable, legume and fruit)	BW MDPG Glycated haemoglobin TG, TC, HDL	NS Sign. difference in MDPG (11.2 vs. 14.7 mmol/L; p<0.001). Sign. reduction of glycated haemoglobin (8.6 vs. 9.1%; p<0.05). NS	HF diets are feasible and improves glycaemic control

Note: LCLF: Low Carbohydrate, Low Fibre; HCHF: High Carbohydrate, High Fibre; MDPG: Mean Daily Plasma Glucose

for measurement of fasting plasma total, HDL cholesterol and glycated haemoglobin concentrations. Plasma glucose was significantly lower in the HF group, and this result was even stronger in the subgroup of patients compliant to the intervention diet (per-protocol analyses) (n=46) (11.2 vs. 14.7 mmol/L; p<0.001). Also, glycated haemoglobin was significantly lower in the subgroup (8.6 vs. 9.1%; p<0.05). No significant effects were found on body weight and plasma lipids.

A randomized crossover trial from Anderson et al. found an effect of a diet high in carbohydrates and DF on plasma lipids [37]. Ten T1D patients were randomly allocated to a high-carbohydrate (70%), high DF (70 g) or low carbohydrate (39%), low DF (10 g) diet for a 4 week period, with a 6 week wash-out period. The high carbohydrate, high DF diet did produce greater significant reductions from baseline in fasting plasma total cholesterol compared to the low carbohydrate, low DF group (-26.3% vs. -14.3%; P<0.0004), but, HDL cholesterol was also reduced (-29.3% vs. -8.3%, P<0.0013).

Prospective cohorts design

A study by Schoenaker et al. **(Table 4)** is the first large prospective cohort study with a sufficient number of CVD cases and deaths in young T1D patients to report the associations between SFA and DF and risk of CVD and all-cause mortality in this population [19]. This study examines the relationship between dietary saturated fatty acids (SFA) and total, soluble and insoluble DF and incident CVD and all-cause mortality in 3250 T1D patients from the EURODIAB Prospective Complications Study during a follow-up of 7.4 years. The median total DF intake was 8.2 g/1000 kcal. In the 2108 participants available for analysis, 148 fatal and non-fatal CVD incident cases and 46 all-cause death occurred. After adjustment for confounders, total DF, per 5 g/day, was associated with lower CVD incidence and mortality (RR 0.84; 95% CI 0.72, 0.98). This association was stronger for soluble DF (RR 0.61; 95% CI 0.38, 0.97) compared to insoluble DF (RR 0.76; 5% CI 0.61, 0.94).

Discussion

This review is the first to provide a clear overview of the current evidence of DF from natural foods on CVD risk in T2D and T1D. The main findings were that DF intake is important for T2D and T1D and is effective in reducing CVD risk. Prospective cohort studies in T2D patients indicated lower all-cause and CVD mortality risk, but DF intake was low, even in the highest quartiles. Encouraging patients to achieve the recommended daily intake for DF (14 g/1000 kcal) should be a priority. Several RCTs reported positive effects of high DF intake, but sources of DF and study outcomes differed. Therefore, studies are inconsistent and the exact mechanism of DF on CVD risk factors remains unclear. In T1D patients, DF had beneficial effects on glycaemic control, fasting plasma total and HDL cholesterol, however, only few studies were available.

Although RCTs and prospective cohort studies were included to assure only high quality designs, studies discussed in this review had several limitations. Most RCTs had limited intervention periods (<6 mo), a small sample size (n=6-121) and evaluated the combination of high DF and other foods, making it difficult to discern the independent effect of DF. DF intakes to reduce CVD risk factors are sometimes unrealistic, requiring DF intakes of >50 g/day. A problem in prospective cohort studies with overweight individuals and diabetes patients is energy misreporting. Foods that largely contribute to glycaemic index are underreported, and fruit and vegetables tend to be over reported. Furthermore, prospective cohort studies report that over the quartiles of

Table 4 Characteristics and results of 2 prospective cohort studies on DF and CVD and all-cause mortality in type 1 diabetes mellitus.

Ref.	Subjects	n	Age (mean or range)	Duration of follow-up	Dietary assessment method	Fibre intake	Outcome measure	Results	Adjustment for potential confounders
Schoenaker [19]	EURODIAB	3250	35-65	7.4 y	3 day dietary record	Median fibre intake: 8.2 g/1000 kcal	Fatal and non-fatal CVD incident cases All-cause mortality	Per 5 g/day: TDF: RR 0.84 (95% CI 0.72,0.98) SDF: RR 0.61 (95% CI 0.38,0.97) IDF: RR 0.76 (95% CI 0.61,0.94) Per 5 g/day: TDF: RR 0.72 (95% CI 0.55, 0.95) SDF: RR 0.34 (95% CI 0.14,0.80) IDF: RR 0.66 (95% CI 0.45,0.97)	Age, sex, energy (kJ/day), diabetes duration (years), glycated haemoglobin (%), smoking status, physical activity, alcohol, total DF, SFA intake
Burger [18]	European Prospective Investigation into Cancer and Nutrition (EPIC) (combined T1D and T2D)	6192	57.4	9.2 y	FFQ	Mean DF intake: 23.5 g/day	CVD mortality All-cause mortality	CVD mortality risk: RR: 0.82 All-cause mortality: RR per SD increase in DF: 0.83	Model 1: No adjustments Model 2: Adjustments for CVD-related risk factors Model 3: Adjustments for factors associated with severity of diabetes Model 4: Adjustments for dietary factors

Note: TDF: Total Dietary Fibre; SDF: Soluble Dietary Fibre; IDF: Insoluble Dietary Fibre

DF intake, individuals use less insulin, smoke less and have a healthier diet, thus suggesting that DF intake might be associated with health-seeking behaviour [18, 19]. If no adjustment is made for these confounders, the association may be partly explained by residual confounding.

This current review is unique, as it only discussed studies that achieved an increased DF content by using naturally occurring high DF foods. Previous studies investigating the effect of DF used added substances like guar gum, psyllium and pectin to the daily food intake. These supplements have shown to improve glycaemic control [37-39], and plasma lipid levels [40, 41] in T2D patients, but could cause side-effects such as gas or stomach cramping.

CVD risk factors

Several mechanisms have been suggested on how DF works on CVD risk factors. Mechanisms depend on the solubility of the DF. Certain fruits, vegetables and legumes are rich in soluble DF, which can slow digesting by formation of gels in the small intestine that attenuate postprandial plasma glucose and lipid rises [24]. Insoluble DF is found in foods such as whole-grains, wheat bran and vegetables, and works by decreasing absorption of dietary carbohydrate, thus lessening the postprandial rise in plasma glucose and insulin concentration [28]. It is also believed that DF could reduce fasting plasma cholesterol by increasing bile-acid excretion [27]. Furthermore, both soluble and insoluble DF appear to alter secretion of gut hormones which promotes satiety and thus reduce body weight [42]. Several studies in diabetic patients suggest that soluble DF has greater effects on CVD risk [19, 27, 35, 43], but, in the healthy population, insoluble DF was more effective [22]. A mixture of both soluble DF and insoluble DF is thus recommended. Below, epidemiological evidence of the effect of DF on different CVD risk factors in T2D and T1D patients is discussed and compared to the general population.

Blood pressure: One of the major risk factors for CVD in diabetes patients is hypertension (defined as ≥ 140/90 mmHg), as part of glycaemic abnormalities [5]. Treatment aims to reduce blood pressure to <135/85 mm Hg, often by administering antihypertensive drugs. Weight loss and increased exercise, combined with improved diet quality can reduce the dependency

on antihypertensive drugs. In the general population, a positive association between high DF intake and blood pressure reduction is well established [44, 45]. In T2D, only three RCTs measured the effect of DF on blood pressure [30, 32, 33]. Jenkins et al. found a significant reduction of both systolic blood pressure and diastolic blood pressure in the low-glycaemic index legume diet group compared to a high wheat fibre diet group. However, this difference was small because of the use as wheat fibre as a positive control. Hosseinpour-Niazi et al. found no significant effect of legumes on blood pressure. Only a small difference in DF intake between the intervention group and the control group was observed, which may explain the non-significant results. No studies reported the effect of DF on blood pressure in T1D patients.

Glycaemic control: Another important risk factor for CVD is chronic hyperglycaemia. In a T2D cohort, plasma glucose was independently related to CVD death [46]. A pooled analysis from prospective cohort studies on CVD showed a RR of 1.18 (95% CI, 1.10 to 1.26) in T2D patients and a RR of 1.15 (95% CI, 0.92 to 1.43) in T1D for incident CVD with every 1% increase in glycated haemoglobin levels [47]. Several trials showed that glycaemic control improved after high intakes of DF in T2D patients [24, 26, 28, 31, 32]. A carbohydrate/DF diet was more effective in lowering plasma glucose compared to a monounsaturated fatty acid diet, and legume DF was more beneficial than wheat DF. For T1D, only two RCTs reported effects of high-DF diet, which both had different results. High DF foods, particularly those rich in soluble DF (fruits, vegetables, and legumes) improved plasma glucose and glycated haemoglobin levels in a trial by Giacco et al. [33] Anderson et al. reported a slight reduction in glycated haemoglobin and fasting plasma glucose levels, but this was not significant [36]. A high intake of both carbohydrate and DF might have obscured the individual effects of DF only. Furthermore, study sample was small, and three of the subjects in this study received drugs known to affect glycaemic control. More research is needed to report a clear association of DF on glycaemic control in T1D.

Plasma lipids: Fasting plasma cholesterol and triglyceride (TG) levels are of great importance in the prediction of CVD mortality in the general population, T1D and T2D patients [46]. DF has been associated with improved plasma lipid profiles in healthy people [48], but studies in the diabetic population were inconsistent. In general, T2D patients appear to have increased concentrations of serum triglycerides and VLDL and decreased level of HDL cholesterol compared to people without diabetes. In several trials, high DF diets could lower triglycerides, fasting plasma total, LDL and VLDL cholesterol, but a high DF intake was required for these effects [27, 29]. In T1D, trials reported small or no effects on plasma lipids, which, however, where very low, as T1D have plasma lipid concentrations similar to the general population [33, 35].

Body weight: Weight management is an important nutritional strategy for overweight and obese T2D patients [49]. Weight reduction is effective in improving glycaemic control and CVD risk factors [49, 50]. Epidemiologic evidence that DF intake is associated with body weight in the general and T1D and T2D population is strong [51, 52]. However, most RCTs report no significant differences in body weight, as they were designed to provide a diet for the patients with individually calculated energy content to keep a stable body weight throughout the study [25, 28, 30]. A crossover RCT suggested that an increase in DF (50 g/d vs. 24 g/d) did not have an effect on body weight [27]. Another crossover RCT reported that both a legume-rich diet and a whole-grain rich diet reduced body weight by -2.7 kg and -2.0 kg respectively, but as the intervention period was 3 months, this difference was not clinically relevant [32]. T1D studies are not focussed on body weight; therefore, no conclusion can be drawn. In general, maintenance of a normal body weight is recommended [53].

Other risk factors

Inflammation, as a response to oxidized LDL cholesterol injury, or infection, causes atherosclerosis and thus plays a role in CVD [54]. Inflammation triggers the production of pro-inflammatory cytokines. Diabetic patients have elevated levels of acute-phase proteins (such as C-reactive protein), interleukin-1β and interleukin-6 [55]. In a cross-over RCT in T2D patients, cereal DF did tend to improve subclinical inflammation by reducing pro-inflammatory cytokine interleukin-18 [31]. However, diets differed not only in amount of cereal DF, but also in coffee consumption and red meat intake, thus independent effects of DF were not measured. Another study reported no effect of cereal DF on inflammatory markers [32]. In both T2D and T1D, there is a lack of evidence on the association between DF and inflammatory markers. Another risk factor for CVD is carotid intima media thickness (IMT) [56]. Both T1D and T2D patients have greater carotid IMT compared to healthy people, which is associated with higher risk for CVD. A recent study by Petersen et al. is the first to report the effects of diet on carotid IMT in T1D and T2D patients. Increased fruit and vegetable intake showed greater carotid IMT regression in the treatment group compared to the control group (mean ± SD: -0.02 ± 0.04 mm vs. -0.004 ± 0.04 mm; P=0.009). Together with other risk factors such as clotting factors and homocysteine, inflammatory markers and carotid IMT could be a useful tool to predict CVD risk in diabetic patients, but more research is needed.

Recommendations for further research

This review clarifies what kind of studies are lacking. For cereal and legume DF evidence is convincing in the general and T2D population [12, 24, 32, 43, 57]. For vegetables and fruit, some evidence is available. A pooled analysis of 10 prospective cohort studies showed that fruit DF, but not vegetable DF, reduced risk of coronary heart disease in the general population (RRs corresponding to 10 g/d increments were 0.84 (95% CI, 0.70-0.99) and 1.00 (95% CI, 0.88-1.13), respectively) [24]. An explanation for the lack of support for an association with vegetables is because studies included heavily processed, nutrient-poor and high-glycaemic index vegetables, such as corn and peas. In T2D patients, vegetables and fruits did improve CVD related outcomes [27], and have shown to reduce stroke [34] and CVD and all-cause

mortality [58]. Overall, DF intake levels of approximately 25 g/day for at least six weeks were sufficient to obtain significant outcomes in T2D patients [32, 33].

Oat β-glucan, an important cereal fibre, is known for its LDL and total cholesterol lowering effects in the general population [59]. In T2D patients, some evidence is available on the beneficial effects of oat β-glucan, but evidence is scarce [43, 60]. A recent meta-analysis showed a significantly greater effect of intakes of ≥ 3 g/day of oat β-glucan in T2D patients compared to the general population, which suggest that subjects with evaluated CVD risk due to T2D obtain more benefit from the cholesterol lowering effects of oats [43]. However, this is based on only three short-term studies and more data is needed upon the effects of long-term intake of oat β-glucan in T1D patients.

The evidence for T2D is convincing, but for T1D, additional research is needed. The absolute and relative risk of CVD morbidity and mortality is much higher in T1D compared to the general and T2D population, stressing the importance of new research [11]. Long exposure to poor glycaemic control might explain the evaluated CVD risk [46], but to what extend remains unclear. Other risk factors, as hypertension and inflammation, are also important, but do not completely explain the higher CVD risk for T1D patients. Schoenaker et al. showed that an increase of 5 g/day in total DF was associated with a lower all-cause mortality and CVD risk in T1D patients [19]. The association for soluble DF was stronger than for insoluble DF. With increased intakes of only 2g/day, CVD risk was lowered by 18% (95% CI 0.67, 0.97).

A suggestion is a crossover RCT comparing a diet with high amounts of soluble DF-rich fruits and vegetables compared to a diet with moderate amounts of fruit and vegetables. Primary outcome should be glycated haemoglobin as this is a useful measurement to determine average plasma glucose levels over 8-12 weeks. Taken this in consideration, the study duration should be at least two twelve-week periods separated by an eight-week washout period. Furthermore, most previous studies measured glycated haemoglobin, making it easier to compare data. Secondary outcome measures should include body weight, BMI, fasting plasma glucose, lipid profile, inflammation markers and systolic and diastolic blood pressure. Patients (>18 y) of both genders with T1D should be included and sample size based on power calculations. Combining this new trial with existing data will help to establish a clear association in the future.

Conclusion

Evidence from prospective cohort studies suggests an association between dietary fibre and cardiovascular disease risk in diabetic patients. However, this is based on only a few studies and research in more populations is needed. Results from trials on the effects of DF on CVD risk factors are inconsistent, and different CVD risk factors are affected in each study. Plasma glucose, glycated haemoglobin and plasma lipid levels are important predictors for CVD, and showed to be improved with high DF intake. Other risk factors, blood pressure, body weight and inflammation, tend to improve, but additional trials are needed to provide a reliable association.

This review shows that it is feasible in the long-term to increase dietary fibre intake with natural food products to levels beneficial for diabetic patients. In T2D, certain types of cereal fibre had a plasma lipid and glucose level lowering effect. Legumes might even have stronger effects, presumably because of high soluble fibre content. More research is needed on the potential effects of low glycaemic index, fibre rich vegetables and fruits, especially in T1D patients. An association between DF and CVD risk was reported in one cohort study, and combining this study with data of new trials might support a statement about DF and CVD risk in T1D patients in the future.

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