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SYSTEMATIC REVIEWS AND META-ANALYSES

Dietary patterns and management of type 2 diabetes: A systematic review of randomised clinical trials

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Abstract *Background and aim:* The aim of the present review is to examine evidence from published studies on the effectiveness of six or more months of low carbohydrate, macrobiotic, vegan, vegetarian, Mediterranean and intermittent fasting (IF) diets compared to low fat diets on diabetes control and management.
Methods and results: In accordance with PRISMA guidelines, Cochrane CENTRAL, PubMed and Scopus databases were systematically searched for relevant studies. Twenty randomised controlled trials (RCTs) > 6 months that investigated the effectiveness of various dietary patterns on type 2 diabetes mellitus (T2DM) were included. Risk of bias was assessed using the Cochrane tool.

There were no significant differences in glycemic control, weight and lipids for the majority of low carbohydrate diets (LCDs) compared to low fat diets (LFDs). Four out of fifteen LCD interventions showed better glycemic control while weight loss was greater in one study. The Mediterranean dietary pattern demonstrated greater reduction in body weight and HbA1c levels and delayed requirement for diabetes medications. The vegan and macrobiotic diet demonstrated improved glycemic control, while the vegetarian diet showed greater body weight reduction and insulin sensitivity.
Conclusions: Although more long-term intervention trials are required, mounting evidence supports the view that vegan, vegetarian and Mediterranean dietary patterns should be implemented in public health strategies, in order to better control glycemic markers in individuals with T2DM.

Introduction

An estimated 425 million adults (20–79 years) living with diabetes mellitus (both Type 1 and 2) worldwide, and this estimate is projected to rise to 628.6 million by 2045. T2DM accounts for roughly 90% of all diabetes cases worldwide [1]. T2DM is considered one of the fastest growing diseases globally, representing a serious public health concern. Up to 90% of T2DM cases are potentially preventable if individuals follow a healthy diet and

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lifestyle [2]. An estimated 80%–90% of persons with T2DM are overweight or obese. A modest weight loss of 5%–10% of initial body weight can substantially improve glycemic control and cardiovascular disease risk factors. Attaining and maintaining a healthy body weight and preventing weight regain are the short- and long-term goals in overweight or/and obese people with diabetes [3]. What is particularly critical in diabetes management is long-term improvement in clinical measures, particularly glycaemia which in turn reduces the risk of micro and macro vascular complications of diabetes [4].

Medical nutrition therapy aims to attain individualised glycemic, blood pressure, and lipid goals and delay or prevent complications of diabetes. Therefore, dietary advice is one of the cornerstones in the management of T2DM. There is now a call for the integration of food and dietary pattern-based approaches into prevention and management of T2DM. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have begun to integrate this approach into their dietary guidelines [5]. The main argument has been that an approach that focuses on nutrients alone misses important nutrient interactions as food and dietary patterns represent more than just a combination of nutrients [6,7]. A variety of eating patterns (combinations of different foods or food groups) have been effective for the management of diabetes [7]. However, there is limited evidence on the optimal dietary approach to improve glycemic control and manage complications in T2DM.

This review provides new insights into the adherence, safety and sustainability of dietary patterns in the long-term management of T2DM along with their effectiveness on glycemic control and cardiovascular risk factors in T2DM patients. It focusses on dietary pattern approaches rather than a traditional carbohydrate-centered approach for the management of diabetes which is better aligned with a practical and real-world setting.

Methodology

Selection of studies

Original-research studies, that were published in English language, were retrieved and selected through a computer-assisted literature search [i.e., Pubmed https://www.ncbi.nlm.nih.gov/pubmed/, Scopus http://www.scopus.com and Cochrane CENTRAL http://www.cochranelibrary.com]. Computer searches used keywords or combinations of keywords and MESH terms relating to the disease studied: [diabetes management/treatment, glucose control, low carbohydrate/Mediterranean/olive-oil/diet/food/nutrition/vegan-vegetarian/macrobiotic diet and intermittent fasting]. In addition, the reference lists of the retrieved articles were hand searched to find relevant studies to add to the present articles that did not allocate through the searching procedure.

Study selection

Detailed inclusion and exclusion criteria are listed in Table 1.

The present systematic review was performed according to the most current quality standards using the PRISMA guidelines [8]. In Fig. 1, the PRISMA flow diagram illustrates the steps followed during the search procedure. The primary author (DP) collected the relevant papers, risk of bias was assessed using the Cochrane tool by the senior author (CI), and the second author and senior author independently reviewed the literature (DBP, CI); disagreements were resolved by consensus among all authors. The initial search yielded 1987 results and following the application of inclusion/exclusion criteria a final sample of 20 articles were included for review. It is noted that an *a-priori* protocol for this systematic review has not currently been published.

Risk of bias

We used the Cochrane Collaboration's tool for assessing risk of bias in the included studies as a measure of scientific quality of the papers [9]. Refer to supplementary material for assessment (Table 3). Our analysis of risk demonstrated that the majority of papers (14/20) had a moderate risk score of 3.5–4/5 (where a 5/5 score represented a perfect low risk in all risk categories). The main explanation for the majority of studies scoring moderately for risk of bias is due to the relative inability to double-blind dietary intervention trials. In the majority of studies the data analysis was completed by an independent statistician. Expectation bias for participants receiving the intervention diet cannot be ruled out.

Results

Fifteen intervention trials with a duration greater than six months, were identified for LCDs. Four studies reported a

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Adults with T2D (>18 year of age)	Intervention < 6 months
Randomised controlled trials	Not diabetic subjects
Comparison of low carbohydrate, Mediterranean, vegetarian, vegan, intermittent fasting and macrobiotic diets with a conventional low-fat diet	Absence of control group
	Lack of randomization
	Single food or nutrients' effect assessment
	Mediterranean dietary patterns without inclusion of the components of the traditional diet
	Not relevant outcomes
	Control diets with fat intake >30% of TEI
	Papers not published in English

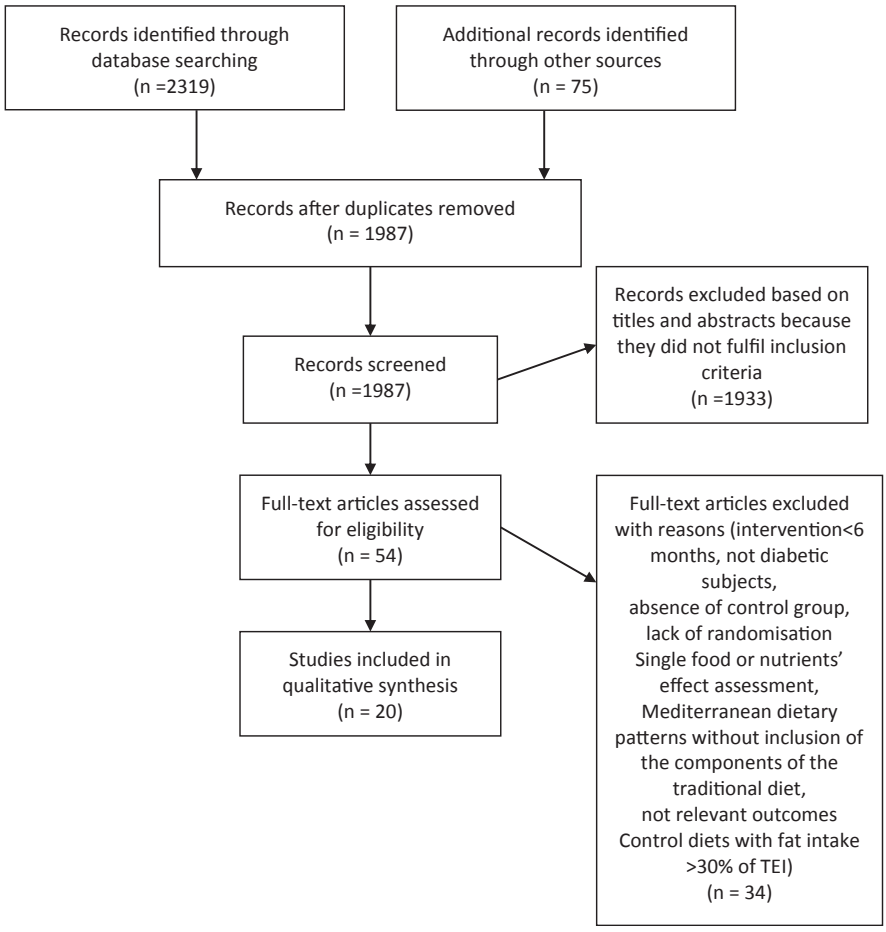

Figure 1 PRISMA flow diagram for the systematic review of clinical trials regarding dietary patterns and their role in the management of type 2 diabetes mellitus.

reduction in HbA1c concentration following the implementation of a LCD [10–13]. With the exception of Westman et al. [10], there was no significant difference in weight loss between LCDs and LFDs. In regards to lipid profile there were no significant differences between the LCD and LFD, although there were isolated cases in which lipid markers improved in favor of a specific diet (for details, refer to Table 2). LDL cholesterol did not differ between any of the LCD and high carbohydrate diet (HCD) studies. Similar to the observations on the lipid profiles, the majority of studies reported no significant difference in blood pressure between the LCD and HCD. Two studies with a duration >6 months were identified using Mediterranean dietary patterns as the comparator intervention [14,15]. Both trials showed a greater reduction in body weight and HbA1c levels compared with LFDs, with one study showing higher rates of diabetes remission, and delayed need for diabetes medication [14]. In regards to vegetarian and vegan interventions 2 studies were identified. The vegan diet showed improved glycemia and plasma lipids [16] while the vegetarian diet showed greater body weight reduction and increased insulin sensitivity compared with a conventional diabetes diet [17]. Only one study was identified using macrobiotic dietary regimes and participants on this diet achieved better glycemic control compared to those following a control diet [18]. There were no long-term (>6 months) interventions on IF and T2DM management. Studies are described in more detail in Table 2 (summary of trials).

Discussion

Low carbohydrate diets

The use of LCD has attracted a great deal of attention in recent years, with review articles suggesting that a LCD should be the initial management approach for diabetes [19]. However, the definition of a LCD is inconsistent. A 2014 meta-analysis defined a LCD as one that has <45% of total energy intake (TEI) from carbohydrates [20]. Although we included studies with a carbohydrate intake <45% of TEI there is a great variation in LCDs within our review with researchers using different LCD interventions ranking from a very low-carbohydrate intake (20–50 g/d) to a significantly higher intake of 45% of TEI.

Fifteen intervention trials with a duration greater than six months, were identified. In regards to glycemic control, 4 studies reported a reduction in HbA1c concentration following the implementation of a LCD [10–13]. The 12-

Table 2 A summary of trials included in the systematic review of dietary patterns and management of type 2 diabetes mellitus.

Study	n	Dietary intervention	Macronutrient intake at the end of the intervention	Duration	Relevant variables	Significant outcome measures
Davis, 2009 [43]	105	Dietary data at 3 months LCD: 24% carbohydrates, 49%fat, 27% protein LFD: 53% carbohydrates, 25% fat, 22% protein	Dietary data at 12 months LCD: 33.4% carbohydrates, 43.9%fat (28.7% saturated), 22.7% protein, 15.1 g fiber/day LFD: 50.1% carbohydrates, 30.8% fat (30.2% saturated), 18.9% protein, 17.2 g fiber/day	12 months	Weight, blood pressure, lipids, HbA1c	No evidence of superior benefit in either diet Higher HDL for the LCD group ($+0.16 \pm 0.27$) compared to the low-fat group ($+0.06 \pm 0.21$)* Differences in the short-term effects of each diet were not sustained
Tay, 2015 [21]	115 (78 completed the study)	LCD:14% carbohydrates (carbohydrate, 50 g/d), 58%fat, (<10% saturated fat), 28% protein LFD: 53% carbohydrates, 30% fat (<10% saturated fat), 17% protein	37 weeks–12 months LCD:16.6% carbohydrates, 52.5%fat, (11% saturated, 28.8% monounsaturated fat), 25.6% protein, 25.7 g fiber/day LFD:49% carbohydrates, 26.1% fat, (8.5% saturated, 12% monounsaturated fat), 18.4% protein, 31.4 g fiber/day	12 months	Body composition, HbA1c, Fasting glucose	No significant difference in weight loss, HbA1c and several CVD risk markers The LCD (high in unsaturated fat and low in saturated fat) achieved greater improvements in lipid profile [TG (LCD diet: −0.4 mmol/L; LFD: - 0.01 mmol/L),** HDL (LCD: 0.1 mmol/L; LFD: 0.06 mmol/L),* blood glucose stability, reductions in diabetes medication requirements and greater attenuation of diurnal blood glucose fluctuation
Iqbal, 2010 [44]	144 (77 assessed at 1 y)	From baseline at 6 months (aim<30 g carbohydrates/day) LCD: 35.4% (154 g) carbohydrates, 42.7%fat, 19.5% protein LFD:41.9% carbohydrates, 36.6% fat, 21.1% protein	Dietary data at 24 months LCD: 47.9% carbohydrates (188gr), 34.2%fat, 16.9% protein, 23 g fiber/day LFD: 46.7% carbohydrates, 33.6% fat, 17.6% protein, 23 g fiber/day	24 months	Weight, HbA1c, lipids	No significant difference in weight loss, glycemic control and lipids
Guldbrand, 2012 [46]	61	3–6 months (Aim: 20% carbohydrates, 50% fat, 30% protein) LCD:25% carbohydrates, 49%fat, 20% saturated fat, 24% protein LFD:49% carbohydrates, 29% fat, 11% saturated fat, 21% protein	24 months LCD:31% carbohydrates, 44% fat, 19% saturated fat, 24% protein, 24gfiber/day LFD:47% carbohydrates, 31% fat, 13% saturated fat, 20% protein	24 months	Weight, waist, blood pressure, lipids, HbA1c, Medication use	No significant difference in weight loss, glycemic control and lipids
Brinkworth, 2004 [69]	66 (38 completed the study)	High-protein diet: 30% protein, 40% carbohydrates, 30% fat, with extra 21 g protein after 2 months Low-protein diet: 15% protein, 55% carbohydrates, 30% fat, with extra 7 g protein after 2 months	(No dietary data at 12 months)	12 months	Weight, lipids, HbA1c, fasting plasma glucose, blood pressure	No significant difference in weight loss, glycemic control and lipids. Improvement in blood pressure for the high-protein diet

Krebs, 2012 [48]	419 (294 completed the study)	(Aim: 40% carbohydrates, 30%fat, 30% protein) at 6 months High-protein diet:45% carbohydrates, 31.9% fat, 11.9% saturated fat, 21.9% protein, 25 g fiber High-carbohydrate diet:48.5% carbohydrates, 30.1% fat, 10.9% saturated fat, 20.2% protein, 23.9 g fiber	24 months High-protein diet: 45.5% carbohydrates, 45.4%fat, 12.5% saturated fat, 32.8% protein, 23.2 g fiber High-carbohydrate diet: 48.1% carbohydrates, 30.4% fat, 11.5% saturated fat, 20.3% protein, 23.7 g fiber	24 months	Weight, waist circumference, body fatness, HbA1c, lipids, blood pressure and renal function	No significant differences between groups
Westman, 2008 [10]	97 (49 completed the study)	Low-carbohydrate, Ketogenic Diet (LCKD) Group Intervention Aim for <20 g carbohydrates/day for the LCKD intervention Control diet: Low glycemic index diet (LGID), 55% carbohydrates	Low-carbohydrate diet: 13% (49 g) carbohydrates, 59% fat, 28% protein Control diet (LGID): 44% carbohydrates, 36% fat, 20% protein	6 months	Weight, HbA1c, fasting plasma glucose, lipids, medication changes	Higher weight loss (−11.1 kg vs. −6.9 kg),* lower HbA1c (−1.5% vs. −0.5%),* and higher HDL (+5.6 mg/dL vs. 0 mg/dL),** for the LCD Diabetes medications were reduced or eliminated in 95.2% of LCKD vs. 62% of LGID participants*
Larsen, 2011 [70]	108 (99 completed the study)	At 3 months High-protein diet: 40.4% carbohydrates, 30.1% fat (saturated 40.2%),28.2% protein, 22.5 g fiber Control diet: 49% carbohydrates, 29.3% fat (saturated fat 40.5%), 20.8% protein, 23.4 g fiber	At 12 months High-protein diet: 26.5% protein, 42% carbohydrates, 31% fat (saturated 39%), 22 g fiber Control diet: 48% carbohydrates, 32% fat (saturated 40%),19% protein, 24 g fiber	12 months	Weight, lipids, HbA1c	No evidence of superior benefit in either diet
Elhayany, 2010 [11]	259 (179 completed the study)	LCMD: 35% low-GI carbohydrates, 45% fat rich in MUFAs, 15−20% protein, 30 g fiber TMD: 50−55% low-GI carbohydrates, 30% fat rich in MUFAs, 15−20% protein, 30 g fiber ADA diet: 50−55%carbohydrates, 30% fats, 20% protein	At 6 months LCMD: 41.9% carbohydrates TMD: 45.2%, carbohydrates ADA diet: 45.4% carbohydrates No dietary data at the end of the intervention	12 months	Weight, Hb A1c, lipids	HDL cholesterol increased (0.1 mmol/l ± 0.02) only in the LCMD* HbA1c greater in the LCMD than in the ADA diet (−2.0 and −1.6%, respectively)* Greater reduction in TGs for the LCMD (−1.3 mmol/l) and TMD (−1.5 mmol/l) compared to the ADA diet group (−0.7 mmol/l)** No other significant differences
Wolever, 2008 [71]	162 (156 completed the study)	LCD: 39% carbohydrates, 40% fat, 19% protein, 59GI High GI: 47% carbohydrates, 31% fat, 20% protein, 63GI Low GI:52%, carbohydrates, 27% fat, 21% protein, 55GI	No dietary data at the end of the intervention	12 months	Weight, lipids, HbA1c	No significant difference in glycemic control, weight and lipids Differences in total: HDL cholesterol among diets disappeared by six months Reduction in postprandial glucose and CRP, with LGID

(*continued on next page*)

Table 2 (*continued*)

Study	n	Dietary intervention	Macronutrient intake at the end of the intervention	Duration	Relevant variables	Significant outcome measures
Jonasson, 2017 [72]	61	LCD: 20% carbohydrates LFD:55–60% carbohydrates, <30% fat	LCD:25% carbohydrates, 49%fat, 20% saturated fat, 24% protein LFD:49% carbohydrates, 29% fat, 11% saturated fat, 21% protein	6 months	Weight, lipids, HbA1c, inflammatory markers	No significant difference in glycemic control, weight and lipids Improved inflammatory markers for the LCD
Goldstein, 2011 [73]	52 (30 completed the study)	Modified Atkins diet: 25 g of carbohydrates/day for the first 6 weeks increasing to 40 g/day ADA calorie-restricted diet: 10–20% protein, <30% fat, 35 g fiber 1500 kcal/day for men and 1200 kcal/day for women	Modified Atkins diet: 85 g (20%) carbohydrates/day, 23% protein, 57% fat ADA calorie-restricted diet: 41% carbohydrates, 19% protein, 40% fat	12 months	Weight, fasting blood glucose, lipid profile, blood pressure	No significant difference in HbA1c weight loss and lipids
Sato, 2017 [45]	66 (62 completed the study)	LCD: 130gr/day carbohydrates Calorie restricted diet: 50–60% carbohydrates, 1.0–1.2 g/kg protein	LCD: 54% carbohydrates, 17% protein, 29% fat Calorie restricted diet: 55% carbohydrates, 16% protein, 29% fat	18 months	HbA1c and BMI	No significant difference in HbA1c and BMI
Yamada, 2013 [12]	24	LCD: 70–130 g/day carbohydrates Calorie restricted diet: 50–60% carbohydrates, <25% fat, <20% protein	LCD: 30% carbohydrates, 35% fat, 25% protein Calorie restricted diet: 51% carbohydrates, 32% fat 17% protein	6 months	Weight, HbA1c, lipids, blood pressure	Better glycemic control for the LCD compared to calorie restricted diet (HbA1c 7% and 7.5% respectively)* No significant differences in weight, lipids and blood pressure
Rock, 2014 [13]	227 (198 completed the study)	Low fat weight loss program: 60% carbohydrates, 20% fat, 20% protein Low carbohydrate weight loss program: 45% carbohydrates, 30% fat, 25% protein Usual care: 55% carbohydrates, 30% fat, 15% protein	No dietary data	12 months	Weight, HbA1c, lipids, blood pressure	Greater weight loss, improved glycemic control and lower triglyceride levels for low carbohydrate and low fat intervention groups compared with usual care group Lower HbA1c for the lower versus higher carbohydrate group (6.6% vs. 7.2% respectively)*
Esposito, 2009 [14]	215	LCMD: <50% of energy from carbohydrates, >30% fat (30–50 g olive oil) Control diet (low-fat): <30% of energy from fat, <10% saturated fat	LCMD Year 4: 44.2% carbohydrates 18% protein, 10% saturated fat, 17.6% monounsaturated fat, 11.5% polyunsaturated fat Low fat diet Year 4: 51.6% carbohydrates, 17.9% protein, 9.4% saturated fat, 12.4% monounsaturated fat, 7.6% polyunsaturated fat	48 months	Time to introduction of antidiabetic medication Weight, HbA1, lipids, insulin, adiponectin	Greater reduction in body weight, HbA1c levels, higher rate of diabetes remission, and delayed need for diabetes medication for the LCMD compared with the low-fat diet At the end of the intervention 44% of patients in the LCMD group and 70% in the LFD group required treatment** Greater improvements in glucose, HOMA-IR and HbA1c levels for the LCMD

Toobert, 2003 [15]	279 (245 Completed the study)	Mediterranean lifestyle program (MLP) (diet, physical activity, stress management) Usual care	No dietary data at the end of the intervention	6 months	HbA1c, lipids, BMI	HbA1c decreased from 7.43 to 7.07 mg/dl** in the MLP, whereas that of the control subjects remained at 7.4 mg/dl. BMI decreased 0.37 in the MLP and increased 0.20 for the usual care group*
Barnard, 2009 [16]	83	Vegan diet: 75% carbohydrate 10% fat, 15% protein Conventional diet: 60–70% carbohydrates, <7% saturated fat, 15–20% protein	Vegan diet: 22.3 fat (5% saturated fat), 66.3% carbohydrates, 14.8% protein, 21.7 g/1000cal fiber Conventional diet: 33.7% fat (10%, saturated fat), 46.5% carbohydrates, 21% protein, 13.4 g/1000cal fiber	12 months and 22 weeks	Weight, HbA1, fasting plasma glucose, lipids, blood pressure	Improved glycemia (HbA1c (%) −0,4 compare to +0.01,** and plasma lipids (LDL mg/dL, −13.5 compare to −3.4),* for the vegan diet (After controlling for medication changes)
Kahleova. 2011 [17]	74 (62 completed the study)	Vegetarian diet: 60% carbohydrates, 25% fat, 15% protein Conventional diabetic diet: 50% carbohydrates, 30% fat, 20% protein	High adherence 55% in the vegetarian diet and 32% in the control group Medium adherence 22.5% in the vegetarian diet and 39% in the control group Low adherence 22.5% in the vegetarian diet and 29% in the control group	6 months	Weight, body composition, blood pressure, HbA1c, fasting plasma glucose, lipids, oxidative stress,	Decreased body weight (−6.2 kg vs. −3.2 kg),** and increased insulin sensitivity (30% increased metabolic clearance rate of glucose (using euglycemic clamp technique) vs. 20%)* for the experimental group Greater reduction in visceral fat (4% vs. 0%)* and subcutaneous fat* for the vegetarian diet 43% of participants in the experimental group and 5% of participants in the control group reduced diabetes medication** Improvement in oxidative stress markers for the vegetarian diet
Soare, 2016 [18]	40	Ma-Pi 4 diet: 67% carbohydrate, 21% fat, 12% protein, fiber 27 g/1000 kcal Control diet: 50% carbohydrate, 30% fat, 20% protein, fiber 20 g/1000 kcal	(No assessment of dietary intake was performed during the 6-month follow-up)	6 months	Weight, HbA1c, lipids	Better glycemic control with Ma-Pi 4 diet. HbA1c (%) −11.27 compare to −5.88 for the control diet** No other significant differences

*$P < 0.05$; **$P < 0.00$.

LCD, low carbohydrate diet; LFD, low fat diet; HbA1c, glycated haemoglobin; HDL, HDL cholesterol; CVD, cardiovascular disease; TG, triglycerides; LCMD, low carbohydrate Mediterranean diet; TMD, traditional Mediterranean diet; ADA diet, American Diabetes Association diet; GI, glycemic index; CRP, C-reactive protein; BMI, body mass index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, LDL cholesterol.

month three arm intervention [Low carbohydrate Mediterranean diet (LCMD), traditional Mediterranean diet (TMD) and ADA diet] [11] showed greater improvements in HbA1c following a LCMD compared to the ADA diet (Table 2). However, it is unlikely that this improvement in HbA1c was due to the carbohydrate intake because the mean intake differed by only 16 g and the use of low GI foods was encouraged in the LCMD but not addressed in the ADA diet. Additionally, the lack of improvement in HbA1c between high- and low-carbohydrate Mediterranean diets further suggests that the results were due to a focus on the low-GI Mediterranean eating pattern rather than total carbohydrate intake [11]. Yamada et al. reported lower HbA1c levels for the LCD group in comparison with the calorie-restricted diet (7.0 ± 0.7 and 7.5 ± 1.0 respectively) [12]. Nevertheless, the number of subjects enrolled was small (24 participants) therefore studies with a larger sample size are needed to confirm these findings. Another 12-month intervention trial showed greater mean [95% CI] reductions in diabetes medication for the LCD group compared with the HCD group [LCD: −0.5 arbitrary units (−0.7, −0.4 arbitrary units); HCD:−0.2 arbitrary units (−0.4, −0.06 arbitrary units)] [21].

With the exception of Westman et al., there was no significant difference in weight between LCDs and LFDs at the time of completion of the studies. However, fat intake for participants on the LFD was 36% of TEI at the end of the intervention which is not consistent with a LFD [10]. These findings are consistent with a meta-analysis that examined participants with diabetes following a LCD or a balanced weight loss diet. The study revealed little or no difference in weight loss and changes in cardiovascular risk factors up to two years of follow-up in overweight or obese adults with or without T2DM [20].

There were no significant differences in lipid profiles between the LCDs and LFDs, although there were isolated cases in which lipid markers improved in favor of a specific diet (refer to Table 2 for details). Similar to the observations on the lipid profiles, the majority of studies reported no significant difference in blood pressure between the LCDs and HCDs.

Mediterranean diet

The Mediterranean diet, a dietary pattern inscribed on the Representative List of the Intangible Cultural Heritage of Humanity, by the UNESCO [22], is a mostly but not exclusively plant-based diet [23].

Research on the role of the Mediterranean diet on T2DM though limited, has provided some preliminary encouraging results. A Meta-analysis of 10 prospective studies showed a significant 23% reduction in the risk of developing T2DM for the highest versus the lowest centile of the Mediterranean diet adherence score [24]. Epidemiologic and interventional studies have revealed a protective effect of a Mediterranean diet against chronic inflammation [25], insulin resistance, and the metabolic syndrome [26]. Moreover, one of the most desirable features of a Mediterranean diet has been the ability to improve coronary risk factors. As chronic inflammation is predictive of the future occurrence of both T2DM and cardiovascular events [27], it is likely that the proposed anti-inflammatory effects of a Mediterranean diet may play an important role in mediating their benefits on both glycemic status and cardiovascular risk [28,29].

Two RCTs were identified to evaluate the long-term effect of the Mediterranean diet on T2DM patients [14,15]. The findings of these studies demonstrated the beneficial effect of a Mediterranean dietary pattern on glycemic control and insulin sensitivity in patients with T2DM, as well as their superiority over control diets such as low-fat diet or usual dietary habits. As seen in the paper by Esposito et al. [14,30], the longest to date study to assess the effects of a Mediterranean diet in patients with newly diagnosed T2DM (total follow-up: 8.1 years), a LCMD postponed the introduction of diabetes medications by two years independent of weight loss compared with a traditional low-fat diet. Moreover, a substantial long-term reduction of HbA1c levels was observed. At year 4 the LCMD group achieved a −0.4% (95% CI: −0.9 to −0.1%) greater reduction in HbA1c compared to the LFD. Partial or complete remission of diabetes occurred in 14.7% (95% CI:13.0−16.5%) of LCMD participants within the first year of intervention and 5% (95% CI: 4.4−5.6%) after six years; these rates were two to four times greater than those of participants assigned to the low-fat diet group. In another RCT with 6-month duration 279 postmenopausal women with T2DM were assigned to either a Mediterranean lifestyle program-(MLP) or usual care. Subjects allocated to the MLP group exhibited lower HbA1c levels, compared with the control group. However, the relative role of the Mediterranean diet in the context of the program that also included exercise, group support, smoking cessation and stress management training was unclear [15]. As previously mentioned, while examining the effects of low carbohydrate interventions on the management of T2DM a significantly greater reduction in HbA1c was observed for the LCMD in a 12 month/three-arm intervention trial compared to a low-fat (based on the 2003 ADA guidelines) diet (−2.0 and −1.6%, respectively). A reduction in serum triglycerides was also observed for patients allocated to the LCMD (−1.3 mmol/l) and TMD group (−1.5 mmol/l), compared with patients in the ADA diet (−0.7 mmol/l) whereas changes in glucose, insulin, and HOMA-IR levels were similar among groups [11].

Vegan and vegetarian diets

Well planned vegetarian diets [31] may offer an advantage over non-vegetarian diets with respect to prevention and management of diabetes. The 7th Day Adventist Health Studies found that vegetarians have approximately half the risk of developing diabetes compared with non-vegetarians [32]. Vang et al. [33] reported that non-vegetarians were 74% more likely to develop diabetes over a 17-year period than vegetarians. A low-fat, plant-based diet with no or little meat may help prevent and treat diabetes, possibly by improving insulin sensitivity

and decreasing insulin resistance [34]. Fruits, vegetables, whole grains and legumes may contribute to a decreased incidence of T2DM through their low energy density, low glycemic load, and high fiber and antioxidant content. These foods have been shown to improve glycemic control, slow the rate of carbohydrate absorption and the risk of diabetes [35,36]. Vegetarian and vegan diets have also shown to improve plasma lipid concentrations and reverse atherosclerosis progression [37]. A recent meta-analysis of 9 RCTs has shown that vegetarian dietary patterns in comparison with non-vegetarian dietary patterns have benefits for glycemic control and other established cardiometabolic risk factors over a median follow-up of 12 weeks [38].

A 6-month randomised, open, parallel study comparing a vegetarian diet with a conventional diabetic diet (50% carbohydrates, 20% protein and <30% fat) showed a vegetarian diet alone or in combination with exercise is more effective in increasing insulin sensitivity, reducing body weight [−6.2 kg (95% CI −6.6 to −5.3) for the intervention group vs. −3.2 kg (95% CI −3.7 to −2.5) for the control group] and diabetes medication [43% for the experimental group and 5% for the control group; 38% difference between groups (95% CI 17−58%)]. However, the number of subjects (37 in the experimental group and 37 in the control group) did not provide sufficient power to confirm the superior effect of the vegetarian diet on HbA1c. Furthermore, lower adherence to the prescribed diet in the control group points to a potential weakness of the conventional diabetic diet [17].

In individuals with T2DM participating in a 74-week RCT, both a low-fat vegan diet and a diet based on ADA guidelines, facilitated long-term weight reduction. In analyses controlling for medication changes, a vegan diet appeared to be more effective for control of glycemia and plasma lipid concentrations [16]. Vegetarian diets may provide a beneficial alternative for nutritional therapy in T2DM however, as there are only two RCTs with a duration >6 months, further studies should explore the long-term effects of vegetarian diets in patients with T2DM.

Intermittent fasting and macrobiotic diets

"*Intermittent*" fasting (IF) is a relatively new dietary approach to weight management that involves interspersing usual daily energy intake with a short period of severe calorie restriction or fasting.

IF has shown to enhance autophagy, reduce levels of Advance Glycation End-Products [AGEs], increase adiponectin levels and improve metabolic parameters in non-diabetic individuals. There are many physical and potentially psychological benefits of fasting or intermittent calorie restriction [39]. However, as fasting for weight control purposes has shown to be a more potent and consistent predictor of risk for future onset of binge eating and bulimic pathology, some behavioural modifications related to abstinence of over eating are crucial in maintaining weight loss [40]. Short-term interventions revealed superior decreases in body weight by caloric restriction (CR) vs. IF/alternate day fasting (ADF) regimens, yet comparable reductions in visceral fat mass, fasting insulin, and insulin resistance have been observed [41]. However as there are no long-term interventions on IF regimes and T2DM more research is required before robust conclusions can be reached.

The macrobiotic Ma-Pi 2 diet (12% protein, 18% fat and 70% carbohydrate), a predominantly vegetarian, whole-food diet has shown benefits in adults with T2DM by improving fasting blood glucose, plasma lipids and plasma insulin. The Ma-Pi 2 and Ma-Pi 4 diets are plant-based diets rich in fibre and fermented foods with a prebiotic potential [42]. The Ma-Pi 4 diet (a recent version of the Ma-Pi 2 diet that includes additional fish-derived protein) has been reported to be more efficient in glycemic control than a control diet [18].

The median percentage reduction in HbA1c levels was significantly greater for patients in the Ma-Pi 4 group [−11.27% (95% CI: −10.17; −12.36)] compared with the control group [−5.88% (95% CI: −3.79; −7.98)]. These results suggest that a macrobiotic diet could be a valid alternative treatment for patients with T2DM. However, as there is only one study with a 6 month follow up examining the effects of a macrobiotic diet on patients with T2DM further research is needed to validate these results.

Adherence and safety of dietary approaches

This review shows that there are no consistent differences in weight and HbA1c changes over the long-term treatment with LCD compared to LFD. Thus, a possible explanation for the lack of improvements in HbA1c might be that people are unable to achieve a strictly prescribed carbohydrate intake. As seen in Davis et al. [43], at 6 and 12 months, there was an increase in energy and macronutrients (carbohydrates for the LCD group and fat for the LFD group), suggesting decreased adherence. Carbohydrate intake at 3 months was 24% of TEI but this increased to 33.5% and 33.4% at 6 and 12 months, respectively. Iqbal et al. [44] aimed for a carbohydrate intake of <30 g while examining the effects of a LCD vs. a LFD in obese, diabetic participants. However, the lowest mean carbohydrate intake was 154 g and the final carbohydrate intake 188 g, far less compared to the aim of <30 g. In addition, Westman et al. [10] aimed for a carbohydrate intake of <20 g, significantly lower from the 49 g consumed by the low carbohydrate ketogenic diet (LCKD) group over the 24-week duration of the intervention. As observed in Iqbal et al. and Sato et al. dietary intake with respect to carbohydrate intake was similar for both groups at the end of the intervention with both groups failing to achieve their dietary targets throughout the study [44,45]. Reduced compliance with the LCD was also observed after six months in a two-year intervention. More specifically participants found it hard to restrain from carbohydrates as well as change from low-fat to high fat products [46,47]. Krebs et al. highlighted how difficult it is to achieve and maintain any prescribed change in dietary composition, and how individuals turn back to habitual intakes over

time. The prescribed intervention diet in this study recommended replacing some carbohydrate with protein. The target of 30% protein was achieved in only 12 of the 207 (6%) participants in the high-protein group [48]. This review suggests that LCDs in a real-world setting may be difficult to sustain. In line with our observations, meta-analyses have shown that LCDs were more effective in HbA1c and body weight reduction in the short-term compared to other diets, whereas no superiority was observed in the long-term [49,50]. Another meta-analysis revealed that a moderate carbohydrate reduction seems to be a more realistic approach in improving glycemic control in patients with T2DM compared to a very low-carbohydrate intervention [51].

Furthermore, the overall effect on long-term atherosclerosis risk is not clear. Although LCD are focused on improving glycemic control in T2DM, the negative consequences of severely restricting carbohydrate is often a concomitant increase in saturated fats which in turn can increase atherosclerosis risk. Low carbohydrate diets high in saturated fat may accelerate the progression of coronary artery disease (CAD) through increases in lipid deposition and inflammatory and coagulation pathways [52,53]. As seen in a study of two cohorts the high animal protein/low-carbohydrate score was associated with higher all-cause mortality, cardiovascular mortality and cancer mortality whereas a higher vegetable low-carbohydrate score was associated with lower all-cause and cardiovascular mortality [54]. Wycherley et al. revealed that maintaining a relatively low level of saturated fat as part of a LCD could possibly mitigate potential impairments in vascular function as measured by flow mediated dilatation and the associated increased cardiovascular disease (CVD) risk [55].

However, there is a growing convergence of scientific evidence that an optimal diet is mostly plant-based, containing a host of food and nutrients known to have independent health benefits. Both vegetarian diets and prudent diets (diets characterised by increased consumption of plant foods and small amounts of red meat in addition to fish and dairy products) are associated with reduced risk of chronic diseases, particularly CAD and T2DM. Evidence linking red meat intake, particularly processed meat, and increased risk of CAD, cancer and T2DM is convincing and provides indirect support for consumption of a plant-based diet [34,56]. Results from the Attica study in Greece showed that meat and meat products, among all food groups, were the ones mostly associated with poor insulin resistance and hyperinsulinemia [57]. There are various reasons for suspecting that a plant-based diet can reduce the risk for other major complications of diabetes - retinopathy, nephropathy, and macrovascular disease - independent of its tendency to improve glycemic control in diabetic patients [58]. Researchers from the Melbourne Collaborative Cohort Study showed that adherence to a Mediterranean diet may reduce total and CVD mortality risk associated with diabetes [59]. Maria Ida Maiorino et al. examined the influence of a Mediterranean diet compared to a low-fat diet on the inflammatory milieu in T2DM for 215 newly diagnosed men and women. At 1 year, C-reactive protein (CRP) fell by 37% and 12% in the Mediterranean diet and low-fat diet groups, respectively and the between-group difference was significant [−0.8, (95% CI: −1.3 to −0.3 mg/L)] while adiponectin rose by 43% in the Mediterranean diet group and 11% in the low-fat diet group [difference between groups: 1.9 lg/mL, (95% CI: 0.8−3.0 lg/mL)] [60].This review suggests that the adoption of vegetarian or Mediterranean dietary patterns can be an effective strategy for managing diabetes. The TMD is an example of a mostly but not exclusively plant-based diet which is healthy, economically affordable [61] and environmentally sustainable [62]. It encourages consumption of a variety of palatable foods, optimising adherence and sustainability and therefore is considered an effective approach for management of T2DM [63−65]. Moreover a 2018 Systematic review and meta − analysis has shown that olive oil intake, an integral part of the Mediterranean diet, may be associated with a decreased risk for developing T2DM as well as improving glucose metabolism [66]. The findings of our review are consistent with a recent meta − analysis that assessed the comparative efficacy of various dietary patterns on glycaemic control in patients with T2DM. The network meta − analysis revealed that the Mediterranean diet is the most effective and efficacious dietary approach to improve glycaemic control in T2DM patients [67]. In addition the ADA and the European Association for the Study of Diabetes (EASD) report suggests the Mediterranean eating pattern as the greatest in improving glycemic control compared to low-carbohydrate, low glycemic index, high-protein diets, and the Dietary Approaches to Stop Hypertension (DASH) diet [5]. Besides, the Mediterranean dietary pattern results in lower environmental footprints due to the greater emphasis on plant-over animal-derived products [62].

Another possible approach in managing diabetes may be IF and macrobiotic diets. IF regimens have gained considerable popularity in recent years, as some people find these diets easier to follow than a daily or continuous energy restriction [68]. Despite the recent popularity of IF, the supporting evidence base in humans remains small therefore more research is required, in particular, long-term RCTs, before robust conclusions can be reached. In regards to macrobiotic diets as there is only one long term intervention in T2DM management further research is needed to validate the effectiveness of this dietary pattern.

It is noteworthy to mention that the majority of patients with T2DM have reported difficulties in adhering to conventional low fat diets. Nine out of thirteen trials with sufficient nutrition data show a fat intake >30% at the end of the intervention. This supports the view that guidelines should focus more on dietary pattern-based approaches for the management of T2DM rather than nutrient-based approaches.

Conclusion

LCDs have demonstrated beneficial effects on short-term weight reduction for obese individuals without diabetes,

but the evidence for long-term efficacy on individuals with T2DM is inconclusive. Thus, a possible explanation might be that people are unable to achieve a strictly prescribed carbohydrate intake. Moreover, our review suggests that vegetarian and Mediterranean dietary patterns may be more effective in improving glycemic control and selected cardiovascular risk markers in people with diabetes. Considering that LCDs are high in saturated fat that may accelerate the progression of CAD, strategies aiming to promote adherence to vegetarian or Mediterranean dietary patterns low in saturated fat are of fairly strong public health interest. Nevertheless, further long-term intervention trials are needed to validate the beneficial effects of plant-based diets for diabetes management. Preliminary findings on the effectiveness of IF and macrobiotic regimes in weight loss and diabetes control although promising, the supporting evidence remains small therefore more research is required before being considered as valid alternative treatments for patients with T2DM.

Conflicts of interest

The authors have no relevant conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.02.004.

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