Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes 1–3

Olubukola Ajala, Patrick English, and Jonathan Pinkney

ABSTRACT
Background: There is evidence that reducing blood glucose concentrations, inducing weight loss, and improving the lipid profile reduces cardiovascular risk in people with type 2 diabetes.

Objective: We assessed the effect of various diets on glycemic control, lipids, and weight loss.

Design: We conducted searches of PubMed, Embase, and Google Scholar to August 2011. We included randomized controlled trials (RCTs) with interventions that lasted ≥6 mo that compared low-carbohydrate, vegetarian, vegan, low–glycemic index (GI), high-fiber, Mediterranean, and high-protein diets with control diets including low-fat, high-GI, American Diabetes Association, European Association for the Study of Diabetes, and low-protein diets.

Results: A total of 20 RCTs were included (n = 3073 included in final analyses across 3460 randomly assigned individuals). The low-carbohydrate, low-GI, Mediterranean, and high-protein diets all led to a greater improvement in glycemic control [glycated hemoglobin (Hb A1c)] compared with their respective control diets, with the largest effect size seen in the Mediterranean diet. Low-carbohydrate and Mediterranean diets led to greater weight loss [−0.69 kg (P = 0.21) and −1.84 kg (P < 0.00001), respectively] compared with the high-protein diet.

Conclusion: Low-carbohydrate, low-GI, Mediterranean, and high-protein diets are effective in improving various markers of cardiovascular risk in people with diabetes and should be considered in the overall strategy of diabetes management. Am J Clin Nutr 2013;97:505–16.

INTRODUCTION

There is good evidence that complex interventions, including dietary changes, can prevent the progression of impaired glucose tolerance to diabetes (1, 2). However, there is limited evidence on the optimal dietary approach to control hyperglycemia in type 2 diabetes (T2D) 3. It is clear that weight loss and reduced total calorie intake are important in the obtainment of good glycemic control (3–7), but the ideal proportion of the 3 main food components (carbohydrate, fat, and protein) that should be recommended remains unclear.

Several trials (8–10) have documented the potential benefits of carbohydrate restriction and low–glycemic index (GI) and Mediterranean diets on glycemic control and weight loss that are maintained long term (9, 11–14).

Epidemiologic data showed a relation between a high intake of saturated fat and raised glycated hemoglobin (Hb A1c) (15), but randomized studies have failed to corroborate these findings (3–8). Systematic reviews and meta-analyses have shown that low-GI, high-fiber, and Mediterranean diets improve glucose metabolism (16–18).

The British Diabetes Association, European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), American Heart Association, Canadian Diabetes Association, International College of Nutrition, groups from South Africa and Japan, and the National Cholesterol Education Panel (Adult Treatment Panel 3) (19–27) have various recommendations for the optimal diet in people with T2D (summarized in Table 1). Most of these authorities recommend a carbohydrate intake of 50–60% of total energy intake, total fat intake ≤30% of energy (with moderate polyunsaturated fat and restriction of saturated and trans fat intake). However, there is insufficient evidence to justify these recommendations. To our knowledge, there is no systematic review or meta-analysis that has compared the effects of different categories of dietary intervention on glycemic control, weight loss, and lipids in T2D. This systematic review was conducted to provide a succinct but robust evidence base to guide clinicians and patients on the most suitable dietary intervention to induce weight loss and improve glycemic control and the lipid profile.

METHODS

Search strategy and study selection

Electronic searches of PubMed, Embase, and Google Scholar for randomized controlled trials (RCTs), systematic reviews, and...
meta-analyses were undertaken up to July 2011. References of included studies and key review and guideline reports were checked for additional studies. Key search terms included diabetic, atherogenic, carbohydrate restricted, low carbohydrate, ketogenic, fat restricted, low fat, Mediterranean, protein restricted, low protein, vegetarian, and glycemic index (GI).

Studies were considered eligible for inclusion if they were RCTs carried out in adults ($\geq 18$ y of age) with an intervention that lasted $\geq 6$ mo that compared low- and high-carbohydrate, high-protein, vegetarian and vegan, low-glycemic, high-fiber, and Mediterranean diets with any control diet in people with T2D.

**Outcome measures**

The quality of each included trial was assessed based on specific criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and included minimization of selection bias, attrition bias, detection bias, reporting bias, and blinding of outcome assessment (Figure 1; see "Supplemental data" in the online issue). Outcomes of interest were Hb A1c, which was used as the measure of glycemic control, difference in weight lost, and changes in HDL cholesterol, LDL cholesterol, and triglycerides.

**Statistical analysis**

A meta-analysis was undertaken for each dietary-intervention subgroup when appropriate (16 of 20 trials) with Revman 5 software (Cochrane Information Management System) when data were available for more than one trial and were of sufficient quality. The fixed-effect inverse-variance model was used to calculate the weighted mean difference (WMD) and was expressed in terms of the 95% CI and level of statistical significance. Outcomes were extracted by comparing means of the intervention compared with control diets and the SEM at follow-up.

**RESULTS**

**Study selection**

A total of 1601 records were identified from the initial electronic search, with an additional 64 records from other sources (references of reviews and other articles). From the abstracts of these records, we identified 55 articles for examination of full texts. Thirty-five studies were excluded either because the intervention lasted <6 mo or the studies were not randomized controls (Figure 2). Studies were excluded from the meta-analysis but included in the results section (Table 2) if required data were not available or provided after correspondence from the authors (28), if only one study was available in that subgroup that made comparisons impossible (5, 29, 30), and if the study was carried out in both patients with diabetes and nonpatients with diabetes with separate data not available for the diabetic group (31). One study (32) had separate data for change in Hb A1c in patients with diabetes, and another study (33) was included in the qualitative analysis only.

<table>
<thead>
<tr>
<th>Variables</th>
<th>BDA (19)</th>
<th>ADA (22)</th>
<th>EASD (21)</th>
<th>CDA (20)</th>
<th>Japan (24)</th>
<th>South Africa (25)</th>
<th>India (23)</th>
<th>AHA (26)</th>
<th>NCEP (27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates (%)</td>
<td>50–55</td>
<td>Not recommended</td>
<td>45–60</td>
<td>50–60</td>
<td>60</td>
<td>55–60</td>
<td>&gt;65</td>
<td>45–55</td>
<td>50–60</td>
</tr>
<tr>
<td>GI (%)</td>
<td>—</td>
<td>Not recommended for general use</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Recommended</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fiber</td>
<td>&lt;30 g/d</td>
<td>No specific amount</td>
<td>Increase with low-GI foods</td>
<td>25–35 g/d</td>
<td>1 fruit, 400 g vegetables</td>
<td>40 g/d</td>
<td>No specific amount</td>
<td>&gt;25 g/d</td>
<td>20–30 g/d</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>10–15</td>
<td>15–20</td>
<td>10–20</td>
<td>11</td>
<td>15–20</td>
<td>12–20</td>
<td>No specific amount</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

1 ADA, American Diabetes Association; AHA, American Heart Association; BDA, British Diabetic Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; GI, glycemic index; NCEP, National Cholesterol Education Program.
despite not having separate data for the diabetic group because >80% of the study population had diabetes.

The 16 studies included in the quantitative analysis were RCTs with dietary interventions that ranged from 6 mo (30, 32, 34, 35, 42) to 4 y (36). Two of the studies included in the meta-analysis compared 3 separate diets (37, 38). These arms were treated in isolation. Wolever et al (38) compared a low-GI diet compared with a high-GI diet compared with a low-carbohydrate diet. The low-carbohydrate arm was compared with the low-GI arm and labeled Wolever-1, whereas the low-GI arm was compared with high-GI arm and labeled Wolever-2. Elhayany et al (37) compared a low-carbohydrate Mediterranean diet compared with a traditional Mediterranean diet compared with an ADA diet, and thus, the low-carbohydrate Mediterranean arm was compared with the traditional Mediterranean arm in the subgroup “low-carbohydrate compared with other diets.” This comparison was labeled Elhayany-1. The traditional Mediterranean diet was compared with the ADA diet in the “Mediterranean compared with other diets” subgroup, and this comparison was labeled Elhayany-2.

Quality of studies

None of the included trials reported any significant differences in characteristics of participants in the intervention or treatment arm. Except for 3 studies (8, 35, 37), all other studies reported the method of random assignment, 10 studies reported the method of allocation concealment, and 6 studies were analyzed on an intention-to-treat basis (7, 32, 34, 36, 39, 40).

Participants

The 20 studies included 3460 patients with final analyses in 3073 patients. Four of the studies (31–33, 41) included patients with and without diabetes, and one of these studies (32) provided data on the change in glycemic control in the diabetic group, and another study (33) was included in quantitative analysis despite not having separate data for the diabetic group because >80% of the study population had diabetes. All participants were ≥18 y old, and all but one study (35) included both sexes.

Intervention

Nine studies compared a low-carbohydrate diet to a variety of control diets including low-fat, low-GI, and traditional Mediterranean diets (compared with a low-carbohydrate Mediterranean diet) (7, 8, 32, 37, 38, 43). Four studies (31, 35–37) compared Mediterranean diets with low fat and the ADA diet, 3 studies (34, 38, 39) compared a low-GI diet with the ADA, high-GI, and high-fiber diets, respectively, and 2 studies (40, 44) compared a high-protein diet with low-protein and high-carbohydrate diets, respectively. Other studies compared vegan with ADA diets (29), vegetarian with EASD diets (30), high-carbohydrate with high-MUFA diets (5), and high-fiber with low-fat diets (28). Control diets are described in more detail in Table 2 (summary of trials).
<table>
<thead>
<tr>
<th>First author, year of publication (reference)</th>
<th>Participants</th>
<th>n</th>
<th>Intervention</th>
<th>Duration</th>
<th>Relevant variables</th>
<th>Significant outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-carbohydrate compared with other diets</td>
<td>Severely obese adults; 39% with T2D</td>
<td>51 with diabetes</td>
<td>Low-carbohydrate diet: 37% carbohydrates, 22% protein, 41% fat</td>
<td>6 mo</td>
<td>Weight, lipids, FPG, Hb A₁c</td>
<td>Higher weight loss (−3.9 kg),** lower triglycerides (−0.35 mmol/L),** FPG (−1.16 mmol/L), and* Hb A₁c (−0.6%) NS</td>
</tr>
<tr>
<td>Samaha, 2003 (32)</td>
<td></td>
<td></td>
<td>Control diet (low fat): 51% carbohydrates, 16% protein, 33% fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stern, 2004 (33)</td>
<td>Obese adults; 83% with T2D</td>
<td>109 with diabetes</td>
<td>Low-carbohydrate diet: 120 g carbohydrates, 73 g protein, 93 g fat</td>
<td>1 y</td>
<td>Weight, Hb A₁c, lipids</td>
<td>No significant difference in weight loss, lower Hb A₁c (−0.6%),* better lipid profile triglycerides (−0.6 mmol/L)* and HDL (+0.37 mmol/L)*</td>
</tr>
<tr>
<td>Westman, 2008 (42)</td>
<td>Obese adults with T2D</td>
<td>97 (50 completers)</td>
<td>Low-carbohydrate diet: 13% carbohydrates, 28% protein, 59% fat</td>
<td>6 mo</td>
<td>Weight, Hb A₁c, FPG, lipids,</td>
<td>Higher weight loss (−4.2 kg)* and HDL (+0.14 mmol/L),* lower Hb A₁c (−1%)*</td>
</tr>
<tr>
<td>Wolever-I, 2008 (38)</td>
<td>Adults with T2D managed by diet only</td>
<td>162 (156 analyzed)</td>
<td>Low-carbohydrate diet: 40% fat, 40% carbohydrates, 60% GI</td>
<td>1 y</td>
<td>Weight, lipids, Hb A₁c</td>
<td>No significant difference in glycemic control and weight, better lipid profile in the low-carbohydrate group</td>
</tr>
<tr>
<td>Haimoto, 2008 (8)</td>
<td>Adults with T2D</td>
<td>133 (127 with data at 1 y)</td>
<td>Low-carbohydrate diet: 45% carbohydrates, 33% fat, 18% protein</td>
<td>2 y (results at 1 y used for meta-analysis)</td>
<td>Weight, lipids, Hb A₁c</td>
<td>Higher weight loss (−1.2 kg),** lower Hb A₁c (−0.6%),** lower LDL (−0.44 mmol/L)**</td>
</tr>
<tr>
<td>Davis, 2009 (7)</td>
<td>Overweight adults with T2D</td>
<td>105</td>
<td>Low-carbohydrate diet: 20–25 g carbohydrates/day with 5-g increments/wk</td>
<td>1 y</td>
<td>Weight, lipids, Hb A₁c</td>
<td>Higher HDL (+0.1 mmol/L),** no other significant differences</td>
</tr>
<tr>
<td>Elhayany-I, 2010 (37)</td>
<td>Overweight adults with T2D</td>
<td>174 (124 completers)</td>
<td>Low-carbohydrate diet (Mediterranean): 35% low-GI carbohydrates, 45% fat rich in MUFAs, 15–20% protein</td>
<td>1 y</td>
<td>Weight, Hb A₁c, lipids</td>
<td>Higher HDL (+0.13 mmol/L),** no other significant differences</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>First author, year of publication (reference)</th>
<th>Participants</th>
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<th>Intervention</th>
<th>Duration</th>
<th>Relevant variables</th>
<th>Significant outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yancy, 2010 (41)</td>
<td>Overweight adults 32% with T2D</td>
<td>146 (45 with diabetes)</td>
<td>Low-carbohydrate diet: 50–60 g carbohydrates, 50–60 g fat, 50–55 g protein Low-fat diet: 190 g carbohydrates, 35–40 g fat, 120 mg orlistat 3 time/day, 73–80 g protein</td>
<td>1 y</td>
<td>Weight, lipids, Hb A1c</td>
<td>No significant difference in weight lost or glycemic control in entire study population</td>
</tr>
<tr>
<td>Iqbal, 2010 (43)</td>
<td>Obese adults with diabetes</td>
<td>144 (77 assessed at 1 y)</td>
<td>Low-carbohydrate diet: 35 g carbohydrate, 20 g protein, 40 g fat Control diet (low fat): 40 g carbohydrate, 23 g protein, 34 g fat</td>
<td>2 y (results at 1 y used for meta-analysis)</td>
<td>Weight, Hb A1c, lipids</td>
<td>No significant difference in weight lost or change in glycemic control</td>
</tr>
<tr>
<td>Vegan and vegetarian compared with other diets</td>
<td>Barnard, 2009 (29)</td>
<td>Overweight adults with T2D</td>
<td>99</td>
<td>Vegan diet: 10% fat, 15% protein, 75% carbohydrates Control diet (ADA): 15–20% protein, 60–70% carbohydrates and MUFAs</td>
<td>74 wk</td>
<td>Weight, lipids, Hb A1c</td>
</tr>
<tr>
<td>Kahleova, 2011 (30)</td>
<td>Adults with T2D</td>
<td>74</td>
<td>Vegetarian diet: 60% carbohydrates, 15% protein, 25% fat Control diet (EASD): 50% carbohydrates, 20% protein, &lt;30% fat</td>
<td>6 mo</td>
<td>Weight, lipids, Hb A1c</td>
<td>Reduced diabetes medication (43% compared with 5% of participants),** higher weight loss (&lt;3 kg)**</td>
</tr>
<tr>
<td>Low-GI compared with other diets</td>
<td>Ma, 2008 (39)</td>
<td>Adults with poorly controlled T2D</td>
<td>40</td>
<td>Low-GI diet: 37% carbohydrates, 76 GI, 42% fat, 20% protein ADA diet: 38% carbohydrate, 80 GI, 43% fat, 20% protein</td>
<td>10 mo</td>
<td>Weight, Hb A1c, lipids</td>
</tr>
<tr>
<td>Wolever-2, 2008 (38)</td>
<td>Adults with T2D managed by diet only</td>
<td>162</td>
<td>Low-GI diet: 20% protein, 25% fat, 50% carbohydrates with 55% high GI High-GI diet: 20% protein, 30% fat, 45% carbohydrates with 63% high GI</td>
<td>1 y</td>
<td>Weight, FPG, 2HPPG, triglycerides, HDL</td>
<td>Lower postprandial glucose, no other significant differences</td>
</tr>
<tr>
<td>Jenkins, 2008 (34)</td>
<td>Overweight adults with T2D</td>
<td>210 (155 completers)</td>
<td>Low-GI diet: 69.6 GI, 33% fat, 21% protein High-fiber cereal diet: 83.5 GI, 30.5% fat, 21% protein</td>
<td>6 mo</td>
<td>Weight, FPG, Hb A1c, lipids</td>
<td>Lower Hb A1c with high fiber (–0.32%)** Higher HDL (+2 mmol/L)** in low-GI group</td>
</tr>
<tr>
<td>Mediterranean compared with other diets</td>
<td>Toobert, 2003 (35)</td>
<td>Postmenopausal women with T2D</td>
<td>279 (245 completers)</td>
<td>Mediterranean lifestyle program compared with usual care</td>
<td>6 mo</td>
<td>Hb A1c, lipids, BMI</td>
</tr>
<tr>
<td>First author, year of publication (reference)</td>
<td>Participants</td>
<td>n</td>
<td>Intervention</td>
<td>Duration</td>
<td>Relevant variables</td>
<td>Significant outcome measures</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Salas-Salvadó, 2008 (31)</td>
<td>Adults at high risk of cardiovascular disease</td>
<td>1224, 819 of whom were diabetic</td>
<td>Mediterranean diet + olive oil: 50 g olive oil/d, 15 g nuts, 9.8 MedDiet Score, 41% fat compared with Mediterranean diet + nuts: 28 g olive oil/d, 39 g nuts, 9.9 MedDiet Score; 43% fat compared with Control diet (low fat): 8.7 MedDiet score, 38% fat</td>
<td>12 mo</td>
<td>Weight, waist circumference, triglycerides, blood pressure</td>
<td>Greater reduction in triglycerides in MedDiet + nuts group*</td>
</tr>
<tr>
<td>Esposiò, 2008 (36)</td>
<td>Overweight adults with newly diagnosed T2D</td>
<td>215</td>
<td>Mediterranean diet: &lt;50% of energy from carbohydrates, rich in vegetables and whole grains, and low in red meat Control diet (low-fat ADA): &lt;30% of energy from fat</td>
<td>4 y (results at 1 y used for meta-analysis)</td>
<td>Time to introduction of antidiabetic medication, weight, FPG, Hb A1c, lipids</td>
<td>Fewer patients needed antidiabetic medication at 4 y (44% compared with 70%)*</td>
</tr>
<tr>
<td>Elhayany-2, 2010 (37)</td>
<td>Overweight adults with T2D</td>
<td>174 (118 completers)</td>
<td>Mediterranean diet: 50–55% low-GI carbohydrates, 30% fat rich in MUFAs, 15–20% protein Control diet (ADA): 15–20% protein, &lt;7% saturated fat, 60–70% carbohydrates</td>
<td>1 y</td>
<td>Weight, FPG, Hb A1c, lipids</td>
<td>Higher HDL (+0.07 mmol/L)* lower triglycerides (~0.35 mmol/L)* Lower triglycerides (~0.58 mmol/L)**</td>
</tr>
<tr>
<td>Brinkworth, 2004 (44)</td>
<td>Obese adults with T2D</td>
<td>66 (38 completers)</td>
<td>High-protein diet: 30% protein, 40% carbohydrates, 30% fat, with extra 21 g protein after 2 mo Low-protein diet: 15% protein, 55% carbohydrates, 30% fat, with extra 7 g protein after 2 mo</td>
<td>12 mo</td>
<td>Weight, lipids, Hb A1c, FPG</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Larsen, 2011 (40)</td>
<td>Overweight/obese adults with T2D</td>
<td>108 (99 completers)</td>
<td>High-protein diet: 26.5% protein, 45% carbohydrates, 31% fat Control diet (high carbohydrates): 19% protein, 48% carbohydrates, 32% fat</td>
<td>12 mo</td>
<td>Weight, lipids, Hb A1c</td>
<td>No evidence of superior benefit in either diet</td>
</tr>
<tr>
<td>Brehm, 2009 (5)</td>
<td>Overweight/obese adults with T2D</td>
<td>124 (95 completers)</td>
<td>High-carbohydrate diet: 54% carbohydrate, 15% protein, and 28% fat (9% MUFAs) Control diet (high MUFAs): 46% carbohydrates, 15% protein, and 38% fat (14% MUFAs)</td>
<td>12 mo</td>
<td>Weight, Hb A1c, lipids</td>
<td>No significant difference in any measured variables</td>
</tr>
</tbody>
</table>

(Continued)
Meta-analyses

**Glycemic control**

Low-carbohydrate compared with other diets (Figure 3). Data from 8 studies (7, 8, 32, 33, 38, 39, 43, 44) were pooled and compared low-carbohydrate with a variety of control diets. There was a significant decrease in the percentage of Hb A1c in subjects who consumed low-carbohydrate compared with other diets (WMD: $-0.12\%$; 95% CI: $-0.24\%$, $-0.00\%$; $P = 0.04$, $I^2 = 75\%$).

Low-GI compared with other diets. Data from the 3 studies that compared low-GI with other diets (34, 38, 39) showed a $-0.14\%$ decrease in Hb A1c in subjects who consumed low-GI compared with control diets (95% CI: $-0.23\%$, $-0.03\%$; $P = 0.008$, $I^2 = 80\%$).

Mediterranean compared with other diets. The 3 studies that compared Mediterranean with other diets (35–37) showed a WMD in Hb A1c of $-0.47\%$ in favor of the Mediterranean diet (95% CI: $-0.64\%$, $-0.30\%$; $P < 0.00001$, $I^2 = 82\%$).

High-protein compared with other diets. Data pooled from 2 studies that compared high-protein with other diets (40, 44) showed a significant decrease in the percentage of Hb A1c in subjects who consumed high-protein diets (WMD: $-0.28\%$; 95% CI: $-0.38\%$, $-0.18\%$; $P < 0.00001$, $I^2 = 60\%$).

**Weight loss**

Low-carbohydrate compared with other diets. There was no significant difference in weight loss when low-carbohydrate diets were compared with control diets (WMD: $0.69\,\text{kg}$; 95% CI: $1.77$, $0.39\,\text{kg}$; $P = 0.21$).

Low-GI compared with other diets. There was no significant difference in weight loss with low-GI compared with control diets (+1.39 kg; 95% CI: $1.58$, $4.36\,\text{kg}$; $P = 0.36$).

Mediterranean compared with other diets. The Mediterranean diet was more effective in achieving weight loss that control diets were with a WMD in weight loss of $1.84\,\text{kg}$ (95% CI: $2.54$, $1.15\,\text{kg}$; $P < 0.00001$).

High-protein compared with other diets. Data pooled from 2 studies showed no benefit of high-protein diet compared with control diets for achieving weight loss (WMD: $0.44\,\text{kg}$; 95% CI: $-0.96$, $1.84\,\text{kg}$; $P = 0.54$).

**Change in lipids**

Low-carbohydrate compared with other diets. Low-carbohydrate diets appeared to be beneficial in increasing HDL (WMD $+0.08\,\text{mmol/L}$; 95% CI: $0.05$, $0.11\,\text{mmol/L}$; $P < 0.00001$) with no significant reduction in LDL (WMD: $0.03\,\text{mmol/L}$; 95% CI: $-0.12$, $0.07\,\text{mmol/L}$; $P = 0.57$) or triglycerides (WMD: $-0.04\,\text{mmol/L}$; 95% CI: $-0.15$, $0.07\,\text{mmol/L}$; $P = 0.47$).

Low-GI compared with other diets. Low-GI diets were effective in increasing HDL (WMD: $+0.05\,\text{mmol/L}$; 95% CI: $0.02$, $0.07\,\text{mmol/L}$; $P < 0.00001$), but the reductions in LDL and triglycerides were not significant compared with those for control diets (for low-GI diets, WMD: $-0.07\,\text{mmol/L}$; 95% CI: $-0.16$, $0.02\,\text{mmol/L}$; $P = 0.15$; for control diets, WMD: $-0.01\,\text{mmol/L}$; 95% CI: $-0.04$, $0.03\,\text{mmol/L}$; $P = 0.69$).

Mediterranean compared with other diets. The Mediterranean diet significantly reduced triglycerides (WMD: $-0.21\,\text{mmol/L}$; 95% CI: $-0.29$, $-0.14\,\text{mmol/L}$; $P < 0.00001$) and increased...
Difference in low carbohydrate vs. 'other' diets. 'Other' diets compared were low fat (Samaha [32], Haimoto [8], Davis [7] and Iqbal [43]), Low GI (Westman [42] and Wolever-1 [38]), Mediterranean (Elhayany-1 [37]) and conventional high CHO (Stern [33]).

Wolever-1 [38] is the comparison between the low-CHO and low-GI arms of the study.

Elhayany-1 [37] is the comparison between the traditional Mediterranean and low-CHO arms of the study.

### B Difference in low-GI versus other diets

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Low GI</th>
<th>Other diets</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenkins 2008 [14]</td>
<td>-0.32</td>
<td>0.0784</td>
<td>106</td>
<td>104</td>
<td>43.3%</td>
<td>-0.32 [-0.47, -0.17]</td>
</tr>
<tr>
<td>Ma 2008 [39]</td>
<td>0.08</td>
<td>0.28</td>
<td>20</td>
<td>20</td>
<td>3.4%</td>
<td>0.08 [-0.47, 0.63]</td>
</tr>
<tr>
<td>Wolever-2 2008 [38]</td>
<td>0.0707</td>
<td>55</td>
<td>48</td>
<td>55</td>
<td>53.3%</td>
<td>0.00 [-0.14, 0.14]</td>
</tr>
</tbody>
</table>

Total (95% CI) 181 172 100.0% -0.14 [-0.24, -0.03]

Heterogeneity: $\chi^2 = 9.80$, df = 2 ($P = 0.007$); $I^2 = 80$

Test for overall effect: $Z = 2.63$ ($P = 0.008$)

Difference in low-GI vs. 'other' diets. 'Other' diets compared were high fiber (Jenkins [35]), high GI (Wolever-2 [38]), ADA (Ma [39]).

Wolever-2 [38] is the comparison between the low-GI and high-GI arms of the study.

### C Difference in Hb A1c Mediterranean versus other diets

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mediterranean</th>
<th>Other diets</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elhayany-2 2010 [37]</td>
<td>0.2</td>
<td>0.2164</td>
<td>63</td>
<td>65</td>
<td>15.8%</td>
<td>0.20 [-0.22, 0.62]</td>
</tr>
<tr>
<td>Esposito 2008 [36] (1)</td>
<td>-0.6</td>
<td>0.1124</td>
<td>108</td>
<td>107</td>
<td>58.5%</td>
<td>-0.60 [-0.82, -0.38]</td>
</tr>
<tr>
<td>Toobert 2003 [35]</td>
<td>-0.34</td>
<td>0.1693</td>
<td>137</td>
<td>108</td>
<td>25.8%</td>
<td>-0.34 [-0.67, -0.01]</td>
</tr>
</tbody>
</table>

Total (95% CI) 308 280 100.0% -0.41 [-0.58, -0.24]

Heterogeneity: $\chi^2 = 10.97$, df = 2 ($P = 0.004$); $I^2 = 82$

Test for overall effect: $Z = 4.73$ ($P < 0.00001$)

(1) For Esposito 2008, data for outcome at 1 year

Difference in Mediterranean vs. 'other' diets. 'Other' diets were 'usual care' (Toobert [36]), ADA (Esposito [36] and Elhayany-2 [37]).

Elhayany-2 [37] is the comparison between the traditional Mediterranean and ADA arms of the study.

### D Difference in Hb A1c high-protein versus other diets

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>High Protein</th>
<th>Other diets</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinkworth 2004 [44]</td>
<td>-0.3</td>
<td>0.051</td>
<td>19</td>
<td>19</td>
<td>94.4%</td>
<td>-0.30 [-0.40, -0.20]</td>
</tr>
<tr>
<td>Larsen 2011 [40]</td>
<td>0.04</td>
<td>0.0292</td>
<td>53</td>
<td>46</td>
<td>5.6%</td>
<td>0.04 [-0.37, 0.45]</td>
</tr>
</tbody>
</table>

Total (95% CI) 72 65 100.0% -0.28 [-0.38, -0.18]

Heterogeneity: $\chi^2 = 2.49$, df = 1 ($P = 0.11$); $I^2 = 60$

Test for overall effect: $Z = 5.67$ ($P < 0.00001$)

Difference in high protein vs. 'other' diets. 'Other' diets compared were low protein (Brinkworth [44]) and high carbohydrate (Larsen [40]).

**FIGURE 3.** Forest plots that show differences in Hb A1c between low-carbohydrate and other diets (A), low-GI and other diets (B), Mediterranean and other diets (C), and high-protein and other diets (D). A meta-analysis was done with Revman 5 software (Cochrane Information Management System). A fixed-effect inverse-variance model was used to calculate the weighted mean difference and expressed in terms of 95% CIs and level of significance. ADA, American Diabetes Association; CHO, cholesterol; GI, glycemic index; Hb A1c, glycated hemoglobin; IV, inverse variance.
HDL (WMD: +0.04 mmol/L; 95% CI: 0.01, 0.07 mmol/L; \(P = 0.004\)). One of the 3 studies did not provide data on the change in LDL cholesterol (49), but pooled data from the other 2 studies showed no significant reduction in LDL (WMD: -0.08 mmol/L; 95% CI: -0.24, 0.08 mmol/L; \(P = 0.34\)).

High-protein compared with other diets. High-protein diets had no effects on markers of the lipid profile (LDL WMD: -0.16 mmol/L; 95% CI: -0.41, 0.09 mmol/L; \(P = 0.22\)); triglyceride WMD: -0.11 mmol/L; 95% CI: -0.56, 0.33 mmol/L; \(P = 0.61\); HDL WMD: +0.01 mmol/L; 95% CI: -0.08, 0.10 mmol/L; \(P = 0.89\)).

Studies excluded from meta-analyses

Six studies were excluded from meta-analyses; 4 of these studies had no other studies for comparison within their subgroup (5, 28–30), and 2 studies included participants with and without diabetes with no separate data provided for subjects with diabetes (31, 41).

Barnard et al (36) compared a vegan diet with the low-fat ADA diet and showed a significantly greater reduction in total cholesterol, LDL, and Hb A1c in the vegan group after 74 wk. A similar-sized study (30) that compared a vegetarian diet with the EASD diet showed greater weight loss and reduced requirements for diabetes medication in the vegetarian arm. No significant benefit was shown in studies that compared high-carbohydrate with high-MUFA diets (5) and high-fiber with low-fat diets (28).

Yancy et al (32) compared a low-carbohydrate diet with a low-fat diet in 146 patients, 45 of whom had diabetes. There was no significant difference in the amount of weight loss or glycemic control in the whole group (41). Salas-Salvado et al (31) compared 2 variations of the Mediterranean diet with a low-fat diet in 1224 participants with high cardiovascular risk. Approximately two-thirds of participants had diabetes, and the major significant finding was a greater reduction in triglycerides in the group who consumed the Mediterranean diet with nut supplementation.

DISCUSSION

This review provides evidence that modifying the amount of macronutrients can improve glycemic control, weight, and lipids in people with diabetes. Low-carbohydrate, low-GI, Mediterranean, and high-protein diets reduced Hb A1c by 0.12–0.5% compared with comparison or control diets. These Hb A1c reductions were significant, with a reduction of 0.5% that was similar to that achieved by using medication (44, 45) and associated with lower risk of microvascular complications (46).

Low-carbohydrate, low-GI , and Mediterranean diets lead to significant improvements in the lipid profile with up to a 4–10% increase in HDL (4% in Mediterranean, 5% in low-GI, and 10% in low-carbohydrate diets), 1–4% reduction in LDL (1% in low-carbohydrate, 3% in low-GI, and 4% in Mediterranean diets), and 9% reduction in triglycerides.

Low-carbohydrate diets restrict carbohydrate intake to 20–60 g/d. The studies in this review compared diets low in carbohydrates with low-fat and low-GI diets. The low-carbohydrate diets appeared to provide superior weight loss, glycemic control, and lipid profile compared with low-fat diets and, in one of 2 studies (42), was superior to the low-GI diet for all 3 variables. However, the carbohydrate content of these diets was as low as 20g carbohydrates/d and ranged from 13–45% of the daily energy intake. In contrast, international authorities recommend a carbohydrate intake from 45 to >65% of total energy intake.

A recently published review by Wheeler et al (47) that looked at literature between 2001 and 2010 also showed that low-carbohydrate diets appeared to improve markers of glycemic control with nonsignificant improvements in lipoproteins.

A vegetarian diet includes mainly cereal products, nuts, seeds, fruit, and vegetables and, occasionally, dairy products and eggs. Vegans avoid dairy products, eggs, or any other foods derived from animals.

The study that compared a vegan diet to the low-fat ADA diet showed significantly lower total cholesterol, LDL, and Hb A1c in the vegan arm (29). These differences were attributed to the weight-loss effect of the diet. Additional analysis at 18 mo (29) showed an advantage of vegetarian diets in terms of glycemic control and lipid profile but not in weight loss (48).

Kahleova et al (30) randomly assigned a similar number of participants to receive either a vegetarian or EASD diet and showed significant reductions in diabetes medication, greater weight loss, and increased insulin sensitivity in the vegetarian arm but no significant difference in Hb A1c.

Therefore, there is a suggestion that vegan and vegetarian diets might be beneficial in improving glycemic control and inducing weight loss. However, there is a need for more studies to support the wider use of these diets in people with diabetes.

The GI is a way of ranking foods according to their glycemic effect. It is defined as the area under the 2-hour blood glucose response curve (AUC) after the ingestion of 50 g carbohydrates. The AUC of the test food is divided by the AUC of the standard (usually glucose or white bread) and multiplied by 100 (49, 50).

The definition of low GI in these trials was variable. Ma et al (39) defined low GI as “choosing predominantly low-GI foods,” which translated to foods that had, on average, a 3-point lower GI than those in the control arm (the ADA diet); in the study of Wolever et al (38), the low-GI group had 8% less high-GI foods than the high-GI group did, whereas the low-GI group in the study of Jenkins et al (34) consisted of foods with a GI that was, on average, 14 points less than in the control arm (high-fiber diet).

Low-GI diets resulted in a lower Hb A1c and higher HDL but no significant difference in weight loss (34, 38, 39). The Hb A1c reduction was only 0.14% and might not have been clinically relevant.

Anderson et al (51) performed a meta-analysis that compared low-GI with high-GI diets and showed significant benefits in terms of glycemic control and lipid profile. However, these studies included subjects those with type 1 diabetes and children and enrolled a mean of just 14 participants for an average of 33 d per trial, which made it difficult to extrapolate the findings to the prevalently older T2D population and made it impossible to predict if these benefits would be sustained over time. The findings of Wheeler et al (47) were similar to ours with only little differences in glycemic control between low- and high-GI and other diets.

The Mediterranean diet is rich in olive oil, legumes, unrefined cereals, fruit, and vegetables, low in meat and meat products, and with moderate contents of dairy products (mostly cheese and yogurt), fish, and wine. The total fat in this diet is typically 25–35% of calories, with saturated fat at ≤8% of calories (52, 53).
The 3 trials included in the meta-analysis compared a Mediterranean diet with a conventional diet (ie, no change to the current diets of participants) and ADA diet (35–37) and showed better glycemic control, greater weight loss, and a more-favorable lipid profile in the Mediterranean-diet arm.

An important difference between the Mediterranean and ADA diets is likely to be the content of MUFAs, which has been shown to have an impact on the lipid profile (54, 55), insulin sensitivity (56–58), and postprandial glucose concentrations (59). Our conclusion regarding the Mediterranean diet is similar to that in a review by Esposito et al (60), which showed improved glycemic control, and Kastorini et al (61), whose meta-analysis showed an association between the Mediterranean diet and improved lipid profile and lower blood glucose.

High-protein diets are diets in which 20–30% or more of the total daily calories come from proteins (62). Of 2 studies, one study compared a high-protein diet with a low-protein diet (44), and the other study compared a high-protein diet with a high-carbohydrate diet (40). Neither study showed any significant differences in weight, glycemic control, or lipids, but pooled data showed significantly lower HbA1c concentrations in the high-protein–diet group. This impact on glycemic control might have been due to previous suggestions that protein has effects on appetite suppression (63) and insulin sensitivity (64–68). The concern of the development of diabetic nephropathy (69) with a high-protein diet was not substantiated by Brinkworth et al (44) who showed no change in urinary albumin excretion in either the high- or low-protein–diet arms. These data suggest a possible role for high-protein diets, but additional studies are probably required to examine the long-term effects in patients with renal disease.

The studies that compared a diet high in carbohydrates to one high in MUFAs and high-fiber with low-fat diets showed no significant differences in weight, glycemic control, and lipid profile (5, 28).

There are significant confounders in performing a meta-analysis of such varied interventions. The control diets were different in terms of the specific macronutrient composition, study participants sometimes had different baseline characteristics (eg, weight and HbA1c), the duration of the studies ranged between 6 mo and 4 y (although we performed the meta-analysis by using data at 6 mo or 1 y), and, although all studies included in the meta-analysis were RCTs, some studies failed to report on allocation concealment and assessor blinding. Thus, all of these features introduced heterogeneity and confounding effects in the analysis. Additional research should involve large trials that compared all of these diets in participants with similar characteristics for the same duration. The favorable results from the Mediterranean and high-protein categories should be interpreted with caution, particularly because few studies were analyzed.

Another major confounder was the independent effect of weight change on the other measured variables (glycemic control and lipid profile). It is difficult to isolate the effect of weight change on these markers of cardiovascular risk, and thus, these benefits could be falsely attributed to the change in quantity of a macronutrient when the change was due to the impact of weight loss alone. This possibility might be of particular relevance when the effect of low-carbohydrate diets is interpreted. Future studies that aim to keep weight constant or ensure an equal caloric intake in all study arms would be useful to help clarify this issue.

In conclusion, our review of the existing literature on low-carbohydrate, low-GI, Mediterranean, and high-protein diets suggests that these diets may be effective in improving various markers of cardiovascular risk in people with diabetes and could have a wider role in the management of diabetes. Dietary behaviors and choices are often personal, and it is usually more realistic for a dietary modification to be individualized rather than to use a one-size-fits-all approach for each person. The diets reviewed in this study show that there may be a range of beneficial dietary options for people with T2D.

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