Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials

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Abstract

High-protein diets are popular for weight management, but the health effects of such diets in diabetic persons are inconclusive. The aim of the present meta-analysis was to examine the effects of high-protein diets on body weight and metabolic risk factors in patients with type 2 diabetes. We searched the PubMed and Cochrane Library databases for relevant randomised trials up to August 2012. Either a fixed- or a random-effects model was used to combine the net changes in each outcome from baseline to the end of the intervention. Overall, nine trials including a total of 418 diabetic patients met our inclusion criteria. The study duration ranged from 4 to 24 weeks. The actual intake of dietary protein ranged from 25 to 52% of total energy in the intervention groups and from 15 to 20% in the control groups. Compared with the control diets, high-protein diets resulted in more weight loss (pooled mean difference: 2 2.08, 95% CI 2 3.25, 2 0.90 kg). High-protein diets significantly decreased glycated Hb A1C (HbA1C) levels by 0.52 (95% CI 2 0.90, 2 0.14) %, but did not affect the fasting blood glucose levels. There were no differences in lipid profiles. The pooled net changes in systolic and diastolic blood pressure were 2 3.13 (95% CI 2 6.58, 0.32) mmHg and 2 1.86 (95% CI 2 4.26, 0.56) mmHg, respectively. However, two studies reported a large influence on weight loss and HbA1C levels, respectively. In summary, high-protein diets (within 6 months) may have some beneficial effects on weight loss, HbA1C levels and blood pressure in patients with type 2 diabetes. However, further investigations are still required to draw a conclusion.

Key words: High-protein diets: Metabolic risk factors: Type 2 diabetes: Randomised controlled trials: Meta-analyses

Type 2 diabetes significantly increases the risk of vascular diseases¹ and mortality in some cancers² and has become a huge public health burden worldwide³. The American Diabetes Association⁴ has reported that lifestyle changes including moderate weight loss and regular physical activity, with dietary strategies such as limiting fat and energy intake, can contribute to the prevention and control of diabetes.

High-protein diets have been proposed to promote weight loss and have been one of the most popular weight loss strategies⁵. These are attractive as weight loss is associated with a reduced risk of developing diabetes and may reduce cardiovascular morbidity and mortality⁶. High-protein diets, compared with high-carbohydrate or high-fat diets, provide a higher level of satiety for a longer period of time, which could lead to long-term reduced energy intake⁷,⁸. On the other hand, increased protein intake, usually accompanied with increased fat intake, raises the concern for the potential harm on blood lipid levels and cardiovascular risk⁹. During recent years, a number of randomised trials that have investigated the health effects of high-protein diets have been published. A further two previous systematic reviews and meta-analyses have demonstrated that high-protein diets have small but significant beneficial effects on body weight and some cardiovascular risk factors in general populations¹⁰,¹¹.

Abbreviation: HbA1C, glycated Hb A1C.

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However, the health effects of high-protein diets in type 2 diabetes are inconclusive. Individual trials conducted among diabetic patients usually have small sample sizes and provide insufficient evidence to draw conclusions\(^{(12–20)}\). The aim of the present meta-analysis was, therefore, to examine the effects of high-protein diets on body weight and metabolic risk factors in patients with type 2 diabetes.

**Methods**

**Data sources**

We followed the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011) for the planning and conduct of the present meta-analysis\(^{(21)}\). The reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines\(^{(22)}\).

We conducted an electronic search of the PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) databases up to August 2012. Search terms included high-protein diet, low-carbohydrate diet, dietary protein, dietary carbohydrate and diabetes. The search was limited to human clinical trials. Reference lists in the published articles retrieved from the electronic search were also manually scanned. No language restriction was imposed.

**Study selection**

Articles were selected for the pooled analyses based on the following criteria regarding participants, interventions, comparisons, outcomes and study designs: (1) the study was conducted in adults with type 2 diabetes; (2) the study intervention was a high-protein diet with daily protein intake \(>20\%\) of total energy; (3) the intervention and control groups had a \(\geq 5\%\) difference in dietary protein intake; (4) the outcomes included net changes in weight loss, glycated Hb \(\text{A}_1\text{C}\) (HbA\(_1\text{C}\)) levels, fasting blood glucose levels, blood lipids and blood pressure, with their associated standard deviations; (5) the study design was a randomised controlled trial.

Studies that were not randomised, had study duration \(<4\) weeks, lacked the required data for statistical analysis and lacked the necessary differences in total protein intake between groups were excluded. In the case of multiple publications with duplicate/overlapped data for the same trial, the article with the more detailed information was selected.

**Data extraction and quality assessment**

We recoded the following characteristics of each study using an electronic form: first author's last name, publication year and country of origin; study design details (sample size, randomisation, parallel or cross-over, and blinding); actual intake of dietary macronutrient; intervention duration; net changes in metabolic risk factors. We also extracted data of patient characteristics at study baseline, including age, sex, body weight, BMI, HbA\(_1\text{C}\) levels, fasting blood glucose levels, lipid profiles and blood pressure. If more than one time period for follow-up was reported, data from the longest follow-up time period were recorded. However, in one trial with 1 year of follow-up\(^{(20)}\), data from the intermediate time period (at 8 weeks) were extracted because the intervention was changed in the latter period. Study quality was assessed based on the following items: randomisation; allocation concealment; blinding; withdrawal; availability of the intention-to-treat analysis.

**Statistical analysis**

For parallel trials, the net changes in each outcome in the intervention and control groups were reported as differences between mean values before and after treatment. For cross-over trials, net changes were calculated as differences in post-treatment values of each group. Standard deviations for the net changes in each group were obtained. If not reported, they were derived from the standard errors, CI or \(P\) values using a standard formula\(^{(22)}\). If only standard deviations for the baseline and final values were provided, standard deviations for the net changes were imputed according to the method of Follmann et al.\(^{(23)}\) using a correlation coefficient (\(R\)) of 0·50. The between-study heterogeneity was tested using the Cochran \(Q\) test at a significance level of \(P<0·1\) and quantified by the \(I^2\) statistic, which is a quantitative measure of inconsistency across studies\(^{(24,25)}\). In the presence of significant heterogeneity, a random-effects model was used to calculate the pooled effect size, and a meta-regression analysis was conducted to explore the possible sources of heterogeneity; otherwise, a fixed-effects model was applied.

Because of the limited number of studies included in the present meta-analysis (less than ten for most outcomes), a subgroup analysis was planned, but not performed. To test

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Design</th>
<th>Sample size (M %)</th>
<th>Duration (weeks)</th>
<th>Ratio (carb:pro:fat)*</th>
<th>Protein intake difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gannon et al.(^{(13)})</td>
<td>2003</td>
<td>USA</td>
<td>X, O</td>
<td>11 (100 %)</td>
<td>5</td>
<td>40:30:30 v. 55:15:30</td>
<td>15</td>
</tr>
<tr>
<td>Gannon &amp; Nuttall(^{(14)})</td>
<td>2004</td>
<td>USA</td>
<td>X, O</td>
<td>102(48 %)</td>
<td>12</td>
<td>34:26:40 v. 46:20:33</td>
<td>6</td>
</tr>
<tr>
<td>Daly et al.(^{(15)})</td>
<td>2005</td>
<td>USA</td>
<td>P, O</td>
<td>12(25 %)</td>
<td>8</td>
<td>43:27:30 v. 51:19:30</td>
<td>8</td>
</tr>
<tr>
<td>Sargrad et al.(^{(16)})</td>
<td>2005</td>
<td>USA</td>
<td>P, O</td>
<td>84 (21 %)</td>
<td>24</td>
<td>13:28:59 v. 44:20:36</td>
<td>8</td>
</tr>
<tr>
<td>Wycherley et al.(^{(17)})</td>
<td>2010</td>
<td>Greece</td>
<td>X, O</td>
<td>17 (29 %)</td>
<td>4</td>
<td>50:30:20 v. 50:15:35</td>
<td>15</td>
</tr>
<tr>
<td>Macdonald et al.(^{(18)})</td>
<td>2010</td>
<td>Australia</td>
<td>P, O</td>
<td>83 (NA)</td>
<td>16</td>
<td>47:32:18 v. 53:18:22</td>
<td>14</td>
</tr>
<tr>
<td>Khoo et al.(^{(19)})</td>
<td>2011</td>
<td>Australia</td>
<td>P, O</td>
<td>31 (100 %)</td>
<td>8</td>
<td>40:30:30 v. 55:15:30</td>
<td>15</td>
</tr>
</tbody>
</table>

M, male; carb, carbohydrate; pro, protein; P, parallel; O, open label; X, cross-over; NA, not available.

* Actual dietary intake.
Other baseline characteristics of the study participants include studies that reported the duration of diabetes. Profiles and blood pressure are given in Table 2. Only three samples. Several studies reported good or excellent compliance was determined using daily food records or urine samples. Twenty-seven were excluded because of varied reasons such as non-randomisation design, study duration <1 month or difference in actual protein intake <5% (detailed in Table S1, available online). Finally, nine randomised trials were selected for the final analysis.

Results

Literature search

The flow of the literature search is presented in Fig. S1 (available online). The initial search of the PubMed and CENTRAL databases identified 1803 records, of which the majority were excluded based on the title and abstract scan, mainly because they were reviews and animal studies, enrolled non-diabetic individuals or used other dietary interventions. After full-text review of the remaining thirty-six articles, twenty-seven were excluded because of varied reasons such as non-randomisation design, study duration <1 month or difference in actual protein intake <5% (detailed in Table S1, available online). Finally, nine randomised trials were selected for the final analysis.

Study characteristics

An overview of the included trials addressing the effects of high-protein diets in type 2 diabetes is given in Table 1. Of the nine trials published from 2002 to 2011, four were conducted in the USA, three in Australia and one each in the UK and Greece. The sample sizes ranged from 11 to 102 participants, with a sum of 418; four trials reported study power analysis and estimated required sample size. Study durations ranged from 4 to 24 weeks, with a median of 12 weeks. All trials were open-label (non-blinded) studies, with six using a parallel design and the remaining a cross-over design. The actual intake of dietary protein ranged from 25 to 32% of total energy in the intervention groups and from 15 to 20% in the control groups, and the differences between the two groups within each trial varied from 6 to 15%. Dietary compliance was determined using daily food records or urine samples. Several studies reported good or excellent compliance with the diets, while others had no judgement.

All participants were overweight or obese adults with type 2 diabetes (mean age 46–63·3 years and mean BMI 31–38·6 kg/m²). Other baseline characteristics of the study participants including weight, fasting blood glucose levels, HbA1C levels, lipid profiles and blood pressure are given in Table 2. Only three studies reported the duration of diabetes.

Study qualities of these trials are given in Table SII (available online). All trials reported random allocation, but a few of them reported the details of sequence generation and

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Intervention</th>
<th>Control</th>
<th>Baseline characteristics</th>
<th>Study duration</th>
<th>Sample size</th>
<th>Metabolites</th>
<th>BMI (kg/m²)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parker et al.</td>
<td>2002</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
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<tr>
<td>Gannon et al.</td>
<td>2003</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
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<td>DBP (mmHg)</td>
</tr>
<tr>
<td>Sargrad et al.</td>
<td>2004</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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<tr>
<td>Daly et al.</td>
<td>2005</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
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</tr>
<tr>
<td>Westman et al.</td>
<td>2006</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
</tr>
<tr>
<td>Wycherley et al.</td>
<td>2007</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
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<tr>
<td>Wycherley et al.</td>
<td>2008</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
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<tr>
<td>Papakonstanti et al.</td>
<td>2009</td>
<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
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<tr>
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<td>2010</td>
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<td>Wycherley et al.</td>
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<td>Intervention</td>
<td>Control</td>
<td>Age (years)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
</tr>
</tbody>
</table>

FBG, fasting blood glucose; HbA1C, glycated Hb A1C; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; DGP, diabetic blood pressure; NA, not available.
allocation concealment. No trial was blinded. Dropout rates ranged from 0 to 40%. Common reasons for dropout included loss to follow-up, personal issues and dietary non-compliance. Only one trial\(^{19}\) analysed data according to an intention-to-treat principle.

Effects on weight loss

Fig. 1 shows the effects of high-protein diets on weight loss. The net changes in weight loss between the intervention and control groups ranged from \(-2.4.2\) to \(4.7\) kg among the nine comparisons, with one trial (16) reporting a significant result. A meta-analysis of these data comparing high-\(v\). low-protein diets reported a significant weight loss of \(2.2.08\) (95% CI: \(-3.25, 0.90\)) kg. There was no evidence of between-study heterogeneity (\(P = 0.84\) and \(I^2 = 0\%\)).

Effects on glycaemic control

Fig. 2 shows the effects of high-protein diets on fasting blood glucose and HbA\(_1C\) levels. The meta-analysis showed that high-protein diets did not affect fasting blood glucose levels (pooled effect size = \(-0.10\) mmol/l, 95% CI: \(-0.49, 0.29\) mmol/l) but significantly decreased HbA\(_1C\) levels by \(0.52\) (95% CI: \(-0.90, -0.14\))%. There was no heterogeneity for fasting blood glucose levels (\(P = 0.77\) and \(I^2 = 0\%\)), whereas significant heterogeneity was observed for HbA\(_1C\) levels (\(P = 0.02\) and \(I^2 = 57.2\%\)). A univariate meta-regression analysis exploring the possible sources of heterogeneity indicated that there was a trend towards greater reductions in HbA\(_1C\) levels among individuals with higher HbA\(_1C\) levels at baseline (\(\beta = -0.34\) and \(P = 0.13\)).

Effects on lipid profiles

Fig. 3 shows the effects of high-protein diets on lipid profiles. The pooled treatment effects for TAG, total cholesterol, HDL-cholesterol and LDL-cholesterol were \(-0.35\) (95% CI: \(-0.17, 0.02\)) mmol/l, \(-0.04\) (95% CI: \(-0.27, 0.19\)) mmol/l, \(0.0\) (95% CI: \(-0.06, 0.05\)) mmol/l and \(0.05\) (95% CI: \(-0.12, 0.22\)) mmol/l, respectively. No evidence of heterogeneity was observed for these outcomes (\(P\) values ranged from 0.46 to 0.96 and all \(I^2 = 0\%\)).

Effects on blood pressure

Fig. 4 shows the effects of high-protein diets on blood pressure. The pooled analyses suggested that high-protein diets borderline significantly reduced both systolic blood pressure (\(-3.13\) mmHg, 95% CI: \(-6.58, 0.32\) mmHg) and diastolic blood pressure (\(-1.86\) mmHg, 95% CI: \(-4.26, 0.56\) mmHg). There was little evidence of heterogeneity for either outcome (both \(P > 0.28\) and both \(I^2 < 20\%\)).

Sensitivity analyses

Omission of one trial during sensitivity analyses, in turn, suggested that no single study materially influenced fasting glucose levels, blood lipids or blood pressure. However, two studies\(^{14,16}\) reported a large influence on weight loss and HbA1C levels, respectively. When the study\(^{16}\) that accounted...
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for 64% of total weight was excluded, the pooled net change in weight loss was increased to −1.09 (95% CI −3.04, 0.85) kg and became non-significant. As for HbA1C levels, when the study that reported the highest baseline HbA1C levels was excluded, the pooled effect size became smaller but remained significant (−0.30%, 95% CI −0.53%, −0.09%). In addition, when one comparison in which both the intervention and control groups were in conjunction with exercise training was excluded, the pooled effect sizes for systolic and diastolic blood pressure were −5.99 (95% CI −10.30, −1.68) mmHg and −3.57 (95% CI −6.62, −0.52) mmHg, respectively. Additional sensitivity analyses using different values of the correlation coefficient R (0.25 and 0.75) did not materially alter the pooled effect sizes. For example, the pooled net changes in weight loss were −2.22 (95% CI −3.47, −0.98) kg and −2.06 (95% CI −3.25, −0.87) kg.

Publication bias

The Egger regression test suggested no evidence of publication bias for the outcomes of weight loss, fasting blood glucose levels, HbA1C levels and lipid profiles, but there was some indication of publication bias for systolic blood pressure (P = 0.04).

Discussion

To the best of our knowledge, the present study is the first meta-analysis of randomised controlled trials examining the health effects of high-protein diets in patients with type 2 diabetes. The findings of the present study suggested that a high-protein diet intervention (within 6 months) may exert some beneficial effects on weight loss, HbA1C levels and blood pressure, but has no adverse effects on fasting blood glucose levels and lipid profiles.

During the past few decades, high-protein diets have received considerable attention for weight loss. A previous meta-analysis of thirteen trials among overweight and obese populations has reported that high-protein/low-carbohydrate diets resulted in weight loss by 4 kg at 6 months, yet the weight change decreased to −1 kg at 12 months. Notably, that meta-analysis only included trials with duration > 6 months and, therefore, had no shared trial with the present meta-analysis. A more recent meta-analysis combining data from thirty-eight trials has confirmed the improvements of body weight brought about by high-protein diets, although the effect appeared to be small. Unfortunately, that study focused on the general population and excluded trials conducted among diabetic patients.
The present meta-analysis is generally in line with these two reports, showing a net change of $-2$ kg in body weight among diabetic patients. However, this finding should be treated with caution as the effect tended to be driven by only one trial\(^{16}\). As for body composition indicators (e.g. fat mass, lean body mass and waist circumference), a meta-analysis for these outcomes was not conducted because the numbers of eligible trials were rather small.

High-protein diets significantly lowered HbA\(_{1C}\) levels in the present meta-analysis. Although the decrease in HbA\(_{1C}\) levels was only 0.52%, such a reduction has potential clinical importance. Lowering HbA\(_{1C}\) levels by 0.6% was demonstrated to reduce the risk of diabetes-related clinical endpoints (by 32%), diabetes-related deaths (by 42%) and all-cause mortality (by 36%)\(^{27}\). However, one trial\(^{14}\) appeared to have a considerable influence on the pooled effect size.
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In that trial, the baseline \( \text{HbA}_{1c} \) level (9.6%) was higher than that of other trials and the reported net change (−2.2%) was also extremely high.

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not ideal and might result in some inaccuracies. However, results from the sensitivity analysis using different values of correlation coefficients did not alter the results. Third, all the included studies were short-term intervention trials with study duration ≤ 6 months. As a result, the long-term health effects of high-protein diets as well as the adverse effects could not be determined in the present meta-analysis. Fourth, the results on weight loss appeared to be non-significant when one trial(16) was excluded, making the finding less stable. Finally, publication bias was a common problem in all the meta-analyses. The Egger regression test suggested possible publication bias in the meta-analysis of systolic blood pressure. However, there were only five trials for blood pressure analysis, and blood pressure was not the primary outcome in these trials. In addition, none of them observed a significant effect. These facts, at least in part, argued against the presence of publication bias.

In summary, high-protein diets (within 6 months) may have some beneficial effects on weight loss, HbA1C levels and blood pressure in patients with type 2 diabetes. However, considering the limitations mentioned above, these findings are inconclusive and need to be confirmed in further investigations.

Supplementary material

To view the supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513002055

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