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REVIEW ARTICLE

The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background/objectives Recently, the role of a low-carbohydrate diet in diabetes management has generated interest with claims being made regarding its superiority over the traditional high-carbohydrate, low-fat dietary approach. This systematic review and meta-analysis evaluated the interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes.

Subjects/methods Randomised controlled trials were searched for which included adults with type 2 diabetes aged 18 years or more. The intervention was a low-carbohydrate diet as defined by the author compared to a control group of usual care. MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, ISRCTN, ProQuest and opengrey.eu were searched. Independent experts were contacted and reference lists of selected papers were checked. Results were analysed descriptively and meta-analyses were completed to include trials that presented data at 1 year.

Results Eighteen studies ($n = 2204$) were eligible for inclusion within the systematic review. The definition of a low-carbohydrate diet varied. At trial end, the descriptive analysis suggested that the low-carbohydrate intervention arm (LCIA) may promote favourable outcomes in terms of HbA1c, triglycerides and HDL cholesterol. The LCIA demonstrated reduced requirements for diabetes medication, which may have reduced the observed benefit of dietary carbohydrate restriction on HbA1c. Seven studies provided data to be included in the meta-analyses at 1 year. The meta-analyses showed statistical significance in favour of the LCIA for HbA1c (estimated effect = −0.28%, 95% CI −0.53 to −0.02, $p = 0.03$; $\chi^2 = 13.15$, df = 6, $p = 0.03$; $I^2 = 54\%$), HDL cholesterol (estimated effect = 0.06 mmol/L, 95% CI 0.04–0.09, $p < 0.00001$; $\chi^2 = 6.05$, df = 6, $p = 0.42$; $I^2 = 1\%$), triglycerides (estimated effect = −0.24 mmol/L, 95% CI −0.35 to −0.13, $p < 0.0001$; $\chi^2 = 1.88$, df = 6, $p = 0.93$; $I^2 = 0\%$) and systolic blood pressure (estimated effect = −2.74 mmHg, 95% CI −5.27 to −0.20, $p = 0.03$; $\chi^2 = 10.54$, df = 6, $p = 0.10$; $I^2 = 43\%$). Meta-analyses for weight, total cholesterol, LDL cholesterol and diastolic blood pressure did not demonstrate a statistically significant difference between interventions.

Dietary adherence was an issue in most studies. A very low-carbohydrate diet (<50 g/day) seems unrealistic in this population, however, a low-carbohydrate diet (<130 g/day) appears to be achievable. Improved clinical outcomes were observed in some studies as a result of achieving a low- or moderate-carbohydrate diet.

Fifteen out of 18 studies were considered high risk of bias, with performance bias being a common issue.

Conclusions Reducing dietary carbohydrate may produce clinical improvements in the management of type 2 diabetes. Further research is needed to understand the true effect of dietary carbohydrate restriction on HbA1c independent of medication reduction and to address known issues with adherence to this dietary intervention. Clarity is needed regarding appropriate classification of a low-carbohydrate diet.

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Introduction

Diabetes is a condition that remains high on the global health agenda. The global prevalence of diabetes was estimated to be 9% in 2014 [1] and it is predicted that diabetes will be the seventh leading cause of death by the year 2030 [2]. In the United Kingdom, diabetes also poses a significant health concern with ~3.9 million people living with diabetes and around 700 people receiving a new diagnosis of diabetes each day, type 2 diabetes being the most prevalent [3].

Dietary carbohydrate restriction has become a topic of interest to both patients and clinicians alike in recent years [4]. Although it is known that the total amount of carbohydrate consumed has the biggest effect on postprandial blood glucose levels [5], evidence regarding the ideal macronutrient composition for patients with type 2 diabetes is unknown [5, 6].

For the United Kingdom, the Scientific Advisory Committee on Nutrition (SACN) [7] suggest that the national dietary reference value for total carbohydrate intake for the general population should remain at an estimated population average of 50%, which is widely accepted as a high-carbohydrate diet [4, 8]. However, some clinicians and academics have called for a low-carbohydrate diet to be the first-line treatment in type 2 diabetes [8].

Several randomised controlled trials have been completed since the publication of the last systematic review considering the role of a low-carbohydrate diet in the management of type 2 diabetes, which concluded that a low-carbohydrate diet demonstrated no long-term superiority over other dietary interventions for patients with type 2 diabetes [9]. Therefore, the aim of the current systematic review is to consider, in light of emerging evidence, the clinical effect of a low-carbohydrate diet in the management of type 2 diabetes, including an exploration as to the interpretation of what authors understand a low-carbohydrate diet to be.

Materials and methods

Papers were identified by completing an electronic search on the following databases: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, ISRCTN, ProQuest and opengrey.eu. Searches were completed in June 2016. Two independent experts were contacted with the aim of identifying any additional relevant papers. Reference lists of selected papers were then checked for further suitable papers.

The following search terms were used: 'type 2 diabetes' or 't2dm' or 'non-insulin dependent diabetes' or 'niddm' and 'low carbohydrate diet' or 'low CHO diet' or 'carbohydrate restricted diet' or 'CHO restricted diet'. Only papers written in English were accepted and no time limits were imposed. Defined search terms were adhered to where possible but were amended based on the capabilities of each database.

Inclusion criteria were studies recruiting adults aged 18 years or above with a diagnosis of type 2 diabetes. Only randomised controlled trials were selected. The intervention group had to be a low-carbohydrate diet as stated by the author. The LCIA must have achieved a lower-carbohydrate intake than the control group. The control group was usual care, which included a variety of diets that could be offered to patients as part of their diabetes care. Studies that enrolled participants with type 1 diabetes, pre-diabetes or participants who were pregnant as part of the study population were excluded.

Studies were assessed for risk of bias using the Cochrane Risk of Bias tool [10].

The primary outcome was change in HbA1c (%). Secondary outcomes were change in diabetes medications, weight (kg), total, LDL and HDL cholesterol (mmol/L), triglycerides (mmol/L), systolic and diastolic blood pressure (mmHg), and dietary adherence.

Primary outcome data (HbA1c) were extracted at multiple time points including 3 months, 6 months, 12 months and trial end. Weight was also extracted at multiple time points as the trajectory of weight loss and the concept of weight loss maintenance is often of interest within the field [11]. The remaining outcomes were assessed at trial end. All outcomes were analysed descriptively.

For outcomes with continuous data, a statistically significant difference between groups was accepted if $p < 0.05$ or the 95% confidence interval did not include zero. When analysing HbA1c, if a difference of 0.2 or 0.5% was seen between groups, this was noted. An improvement of 0.5% is generally considered to be clinically important [12]; although a 0.2% improvement is of unknown short-term clinical relevance [13], some suggest that such an improvement can improve mortality by 10% [14]. For the purpose of this paper, no clinical difference between groups was classified as <0.2% between groups.

Meta-analyses were performed for change in each outcome at 1 year (to include 48 weeks). Therefore, studies that were under 48 weeks in duration were not included in the meta-analysis. It was agreed to discount any studies that were under a year to decrease study design heterogeneity and to allow for adherence issues that may occur in longer-term studies that is more likely to reflect long-term behaviour of patients. Data from three-arm studies were excluded from the meta-analysis if insufficient detail was reported to allow for a comparison between two arms, for example, significance of the difference between groups was reported across all groups with no reference to the significance of the difference between individual arms.

Review Manager 5.3 software was used for the meta-analyses, which calculated a pooled mean difference between the change from baseline in the intervention and control arms, and estimated its 95% confidence interval. Along with the number of participants included in the analysis of each study, the mean change and the associated standard deviation in the intervention and control arm were used when completing the meta-analysis; when the standard deviation was not available, 95% confidence intervals were used where possible. For studies that did not provide the necessary data, the authors were contacted to ask for the provision of the relevant data; studies were excluded if this data was not provided. For studies that provided end-point data as opposed to mean change from baseline, if sufficient data available, mean change from baseline and the standard deviation of the change was calculated by applying published formulae [15]. The calculator function on Review Manager 5.3 was used to generate the results of the meta-analyses. The random-effects model was used as there were variations within the methodologies of the trials [16]. Studies with marked study design heterogeneity were not included in the meta-analyses. Statistical heterogeneity was assessed using the χ^2-test for heterogeneity interpreted using the I^2 statistic, which was interpreted according to Higgins and Green [17]. In the meta-analyses, studies were inversely weighted according to their study size, variance and the inter-study variance statistic τ^2, giving more weight to larger studies with smaller variance.

Data regarding carbohydrate prescription advised to participants in the LCIA and their mean final carbohydrate consumption were extracted, where data were available. Consumption was recorded in both g/day and %TEI (total energy intake). When only one of these values were given in a study, the corresponding value was calculated on the basis of 1 g carbohydrate = 4 kcal, using the mean calorie intake at trial end.

Nutritional data were extracted from the intervention and control diets where data were available at trial end to include mean percentage TEI from carbohydrate, protein, fat, saturated fat, polyunsaturated fat, mono-unsaturated fat and mean total intake of calories (kcal) and fibre (g). Means and standard deviations were presented for each outcome of each arm. A paired *t* test was used to compare the means of both groups. Trials that used enteral or formula feeds and three-arm trials with no obvious control were excluded from this analysis. Papers that did not report nutritional data for both the control and intervention diet were excluded from the comparative analysis. See Fig. 1 for details of the study selection process.

The protocol of this review was published on the PROSPERO database prior to the commencement of the review; registration ID: CRD42016035935.

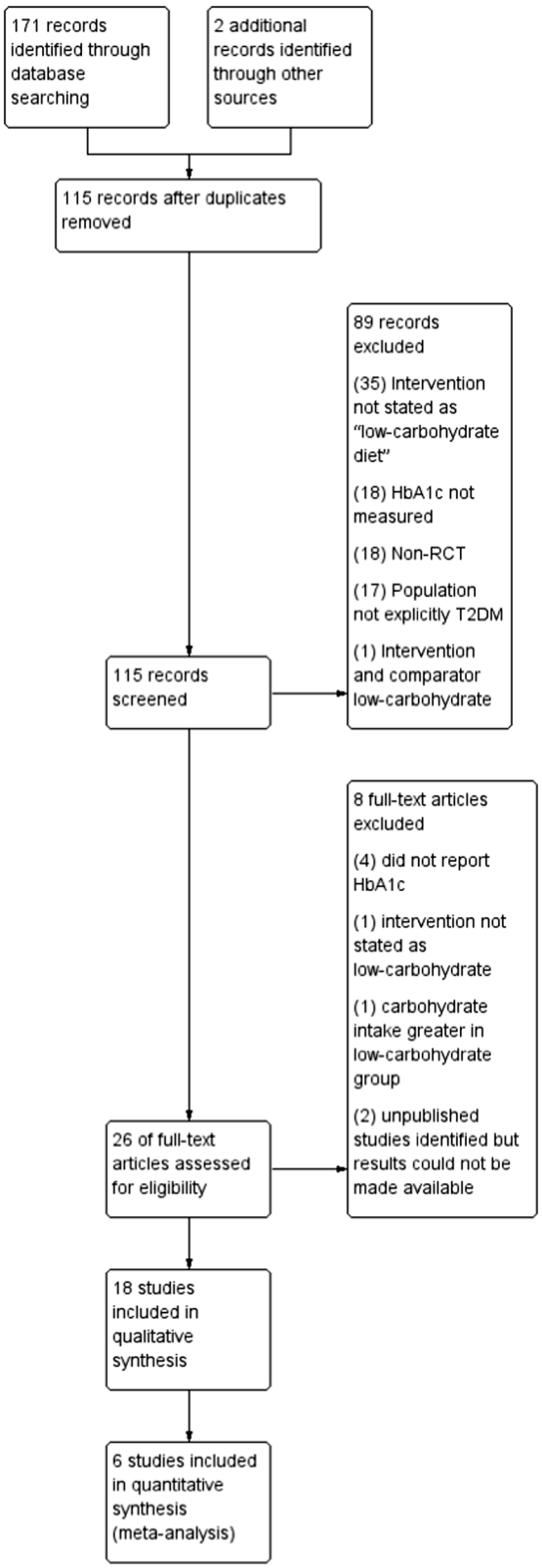

Fig. 1 PRISMA flow diagram

Results

Characteristics of included studies

Eighteen studies were selected for this review within which 2204 participants were randomised and data were analysed for 1937 participants as some attrition was evident and not all studies used intention-to-treat analysis.

Trial duration varied (Table 1). Three studies consisted of three arms [18–20], with the remaining studies an intervention arm and control arm.

Two studies used enteral feeds [21, 22] and one study included partial use of formula feeds [24].

Risk of bias assessment

Fifteen out of the 18 studies were considered high risk of bias in one or more of the six criteria (Supplementary Fig. 1). The risk of performance bias was a common issue for these trials with 15 out of 18 trials (83%) at high risk. Due to the nature of the intervention, authors had difficulty in blinding the participants and study personnel to the intervention with many authors discussing this issue. Some studies were found to be at risk of detection bias, whereby outcome assessors were not sufficiently blinded; whereas assessment of objective measures was not deemed as threatening, a lack of blinding of those assessing nutritional composition of diets was observed in some studies. Insufficient detail of study processes often resulted in the categorisation of unclear risk of bias.

HbA1c (primary outcome)

Data from 17 studies were included in the descriptive analysis of change in HbA1c. One study [25] was not included within this analysis as the figures provided by this study did not report change in HbA1c for the whole study sample: outcomes were categorised by baseline HbA1c and insufficient data were provided to include their findings in the analysis.

Three months

Seven studies analysed HbA1c at 3 months. There appeared to be a trend within the results: out of the seven studies reporting at this time point, five reported an average difference of ≥0.2% favouring the LCIA with three of these reporting a difference of ≥0.5%. The two remaining studies showed no difference between groups. Two studies reported a statistically significant difference in favour of the low-carbohydrate intervention arm (LCIA) ($p < 0.05$) [21, 26]; however, when one of these studies adjusted the results for differences in baseline HbA1c, statistical significance was lost ($p = 0.06$) [26].

Six months

Eight studies reported change in HbA1c at 6 months. Seven out of the eight studies reported an improvement of ≥0.2% in favour of the LCIA with three studies reporting improvements of ≥0.5%. The remaining study showed no difference between groups. Four studies reported a statistically significant difference between groups in favour of the LCIA regarding change in HbA1c at this time point [19, 24, 26, 28]; similarly here, after one study accounted for differences in baseline HbA1c, statistical significance was lost. Although differences between groups were not statistically significant, two studies considered the within group improvements in HbA1c [27, 34], both of which found a statistically significant improvement in HbA1c in the LCIA but not in the control group.

One year

Ten studies reported change in HbA1c at 1 year. Six studies showed an improvement of ≥0.2% favouring the LCIA, of which three studies showed an improvement of ≥0.5% in the LCIA. Conversely, one study [20] showed an improvement of 0.2% in the control group; interestingly, the baseline HbA1c for both the intervention and control arms was considerably lower in this study than any other (Table 1). Three studies showed no difference between groups. Four studies showed a statistically significant improvement in HbA1c in the LCIA [18, 19, 29, 35].

Trial end

HbA1c was analysed at trial end with data available from 17 studies (Supplementary Table 1). A difference of ≥0.2% was seen in 12 of the 17 studies (70.6%) in favour of the LCIA; within these 12 studies, four studies found a difference of ≥0.5% favouring the LCIA. Four studies showed no difference between groups. One study reported a difference of 0.2% in favour of the control group [20]. Eight studies showed a statistically significant difference between groups in favour of the LCIA at trial end.

Meta-analysis for change in HbA1c at 1 year

Seven studies provided data for change in HbA1c at 1 year appropriate for use in a meta-analysis (Fig. 2a). The meta-analysis showed a statistically significant effect on HbA1c in favour of the LCIA (effect estimate = −0.28%, 95% CI −0.53 to −0.02, $p = 0.03$). Significant statistical

Table 1 Characteristics of the intervention and control groups

Author	Participants randomised (*n*)	Study duration	Baseline HbA1c (%)		Daily carbohydrate prescribed to LCIA	Control diet	Calorie difference between groups
			LCIA	Control			
Pohl et al. [21]	78	12 weeks	7.7	7.3	37% TEI	52% CHO, 30% fat	No difference
Pohl et al. [22]	105	12 weeks	6.9	6.9	37% TEI	52% CHO, 30% fat	No difference
Daly et al. [23]	102	3 months	9.0	9.1	70 g	Healthy eating: reducing fat and portion sizes	No focus on calories
Shirai et al. [24]	240	24 weeks	7.7	7.7	52% TEI	60% CHO, 25% fat	No difference
Tay et al. [25]	131	24 weeks	7.3	7.4	<50 g/14% TEI	53% CHO, <30% fat	No difference
Westman et al. [26]	97	24 weeks	8.8	8.3	<20 g	Low GI (55% CHO)	Reduced in control by 500 kcal deficit
Jonasson et al. [27]	61	6 months	7.3	7.4	20% TEI	Low fat (30% fat)	No difference
Yamada et al. [28]	24	6 months	7.6	7.7	<130 g	50–60% CHO, <25% fat	Non-specified kcal reduction in control
Mayer et al. [29]	46	48 weeks	7.6	7.6	<20 g	Low fat (<30% fat and Orlistat)	Reduced in control by 500–1000 kcals
Davis et al. [30]	105	1 year	7.5	7.4	20–25 g increasing by 5 g increments	Low fat (25% fat)	No focus on calories
Elhayany et al. [18]	259	1 year	8.3	8.3/8.3	35% TEI	Mediterranean and ADA (50–55% CHO; 30% fat)	Similar calories in all groups
Goldstein et al. [31]	52	1 year	9.0	8.8	25–40 g	ADA—unclear constituency	Reduced in control to 1200–1500 kcals
Larsen et al. [32]	108	1 year	7.9	7.8	40% TEI	High CHO (55% CHO; 30% fat)	No difference
Rock et al. [19]	227	1 year	7.3	7.5/7.4	45% TEI	Low-fat and usual care (60% CHO; <20% fat)/(55% CHO; 30% fat)	Calorie deficit applied to all groups
Tay et al. [33]	131	1 year	7.3	7.4	<50 g/14% TEI	53% CHO, <30% fat	No difference
Wolever et al. [20]	162	1 year	6.1	6.2/6.2	Raise total fat intake by 10%*	High GI and low GI (20–25% CHO)*	500 kcal deficit applied to control group if weight loss desired
Guldbrand et al. [34]	61	2 years	7.5	7.2	20% TEI	Low fat (55–60% CHO; 30% fat)	No difference
Esposito et al. [35]	215	4 years	7.8	7.7	<50% TEI	Low fat (<30% fat)	No difference

LCIA low-carbohydrate intervention arm, *CHO* carbohydrate, *TEI* total energy intake, *GI* glycaemic index

*These targets correspond to key foods that were recommended, other foods were consumed in addition, but there were no pre-specified targets reported for additional food

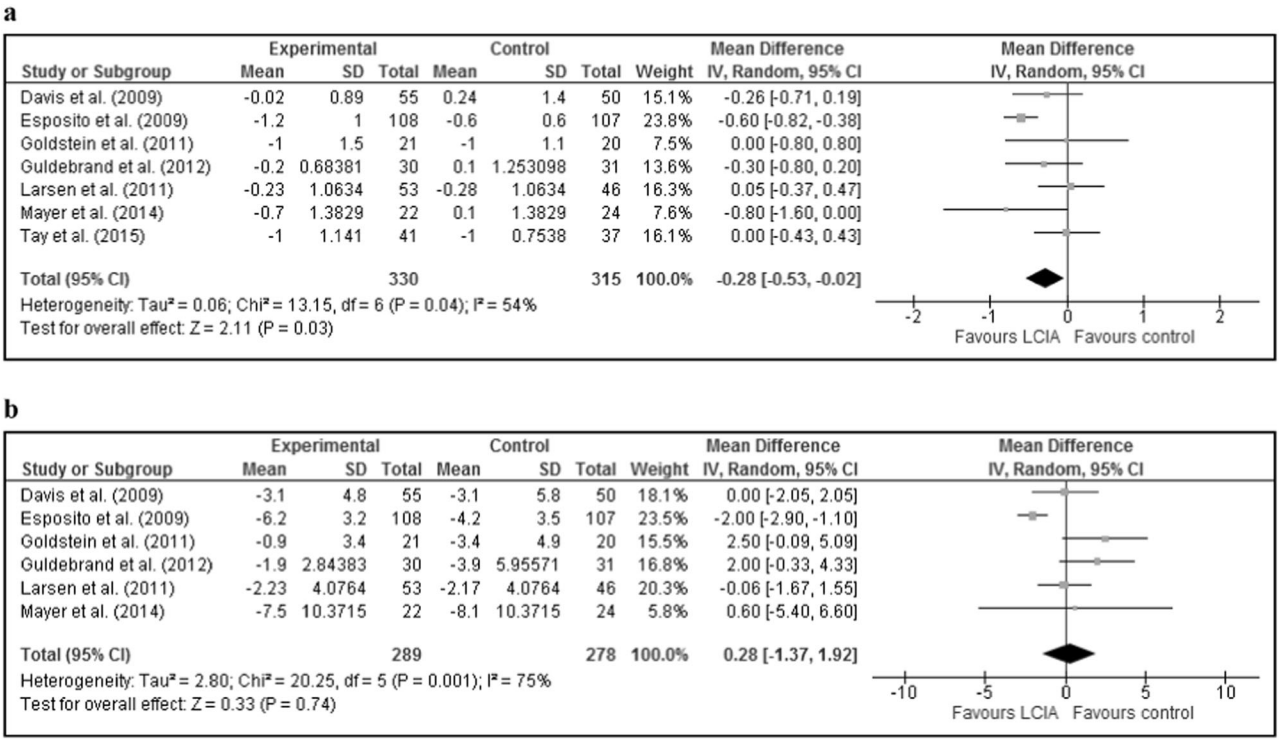

Fig. 2 **a** Meta-analysis of change in HbA1c at 1 year. **b** Meta-analysis of change in weight at 1 year

heterogeneity was evident ($\chi^2 = 13.15$, df = 6, $p = 0.04$; $I^2 = 54\%$).

The three-arm trials [18–20] were not included in the meta-analyses as significance of the difference between individual arms was not reported. However, their inclusion would not have affected the outcome of this result. While one study [20] found a marginal but statistically non-significant difference in favour of the control group, the two other papers [18, 19] found a statistically significant difference between groups in favour of the LCIA. Therefore, inclusion of the data from these three trials, had the data been available, may have further promoted the superiority of the LCIA in improving glycaemic control.

Medication changes

Out of the 18 studies included in this review, all but two studies included participants on diabetes medication at trial start [20, 35]. Two studies did not report on medication changes [18, 28]. Out of the remaining 14 studies, every study reported a reduced requirement for diabetes medication in the LCIA compared to the control group. Eleven studies discussed the statistical significance of the difference in medication reduction between groups. Nine of these studies (82%) reported a statistically significant reduction in diabetes medication in the LCIA ($p \leq 0.05$)—finding a statistically significant reduction in insulin [21, 22], oral hypoglycaemic agents [24, 34] or a combined diabetes medication score [25, 26, 19, 32, 33] in the LCIA.

Regarding the two studies that did not include participants prescribed medication at trial start and one study found no difference in commencement of diabetes medications at trial end (1 year) [20]. The other study found no difference in commencement of diabetes medications between groups at 1 year, however, at 4 years, 44% of participants in the LCIA in comparison to 70% of participants in the control group required treatment [35].

Weight change

Fifteen studies were included in the analysis for weight change.

Three months

Five studies reported weight change at 3 months, of which three reported a statistically significant difference between groups in favour of the LCIA [23, 26, 30]; no study showed a statistical significant superiority of the control group.

Six months

Out of the eight studies that reported this outcome at 6 months, four reported a statistically significant improvement in favour of the LCIA [19, 24, 26, 30]. Four studies

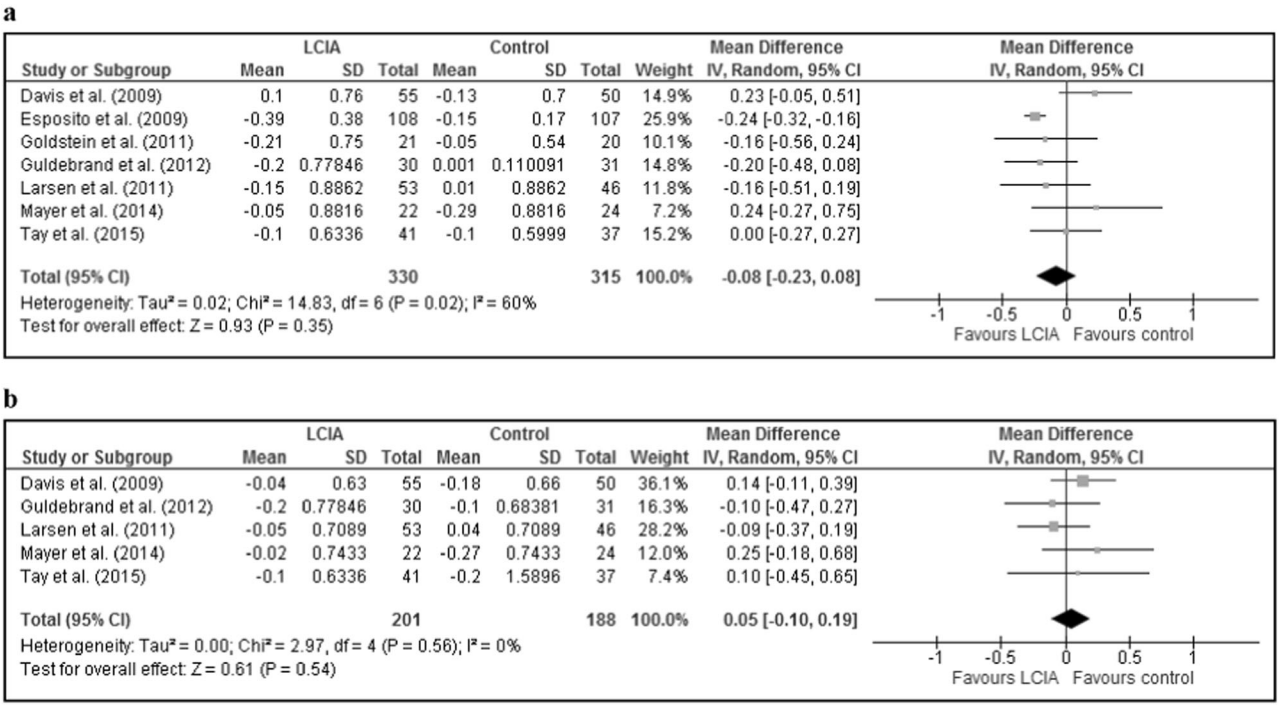

Fig. 3 **a** Meta-analysis of change in total cholesterol at 1 year. **b** Meta-analysis of change in LDL cholesterol at 1 year

showed no statistically significant difference between groups.

One year

Out of 10 papers that reported weight change at 1 year, three reported statistical significance in favour of the LCIA [19, 30, 35]. However, one paper reported significance across all time points simultaneously, whereas the absolute difference between these two groups at 1 year was zero [30]. No study showed statistical significance in favour of the control group.

Trial end

At trial end out of 15 studies, five reported a statistically significant effect in favour of the LCIA at trial end; this includes the above-mentioned study where significance was across all time points [30] (Supplementary Table 2). No study favoured the control group in terms of statistical significance.

Meta-analysis for change in weight at 1 year

For the six studies that provided appropriate data at 1 year, the summary effect between interventions was not statistically significant (estimated effect = 0.28 kg, 95% CI −1.37 to 1.92, $p = 0.74$) (Fig. 2b). Heterogeneity was statistically significant ($\chi^2 = 20.25$, df = 5, $p = 0.001$; $I^2 = 75\%$).

Total cholesterol

Fifteen studies collected data for total cholesterol (Supplementary Table 3). No study found a statistically significant difference between groups, suggesting no superior effect of the LCIA or the control group regarding this outcome.

The meta-analysis including seven studies at 1 year also concluded no superior effect of either intervention (estimated effect = −0.08 mmol/L, 95% CI −0.23 to 0.08, $p = 0.35$). Heterogeneity was statistically significant ($\chi^2 = 14.83$, df = 6, $p = 0.02$; $I^2 = 60\%$) (Fig. 3a). When transforming the data from the paper by Guldbrand et al. [34] as per published formulae [15], a clinically irrelevant difference of 0.001, instead of no observed difference, in the control group was used to allow the data to be utilised in the meta-analysis (Fig. 3a).

LDL cholesterol

Fifteen papers reported LDL cholesterol outcomes (Supplementary Table 4). One study showed a statistically significant difference across all groups with the best results seen in the LCIA [18]. The remaining studies showed no statistically significant difference between intervention groups.

Five studies provided appropriate data to be included in the meta-analysis at 1 year for this variable, which also concluded no superior effect of either intervention (estimated effect = 0.05 mmol/L, 95% CI −0.10 to 0.19, $p =$

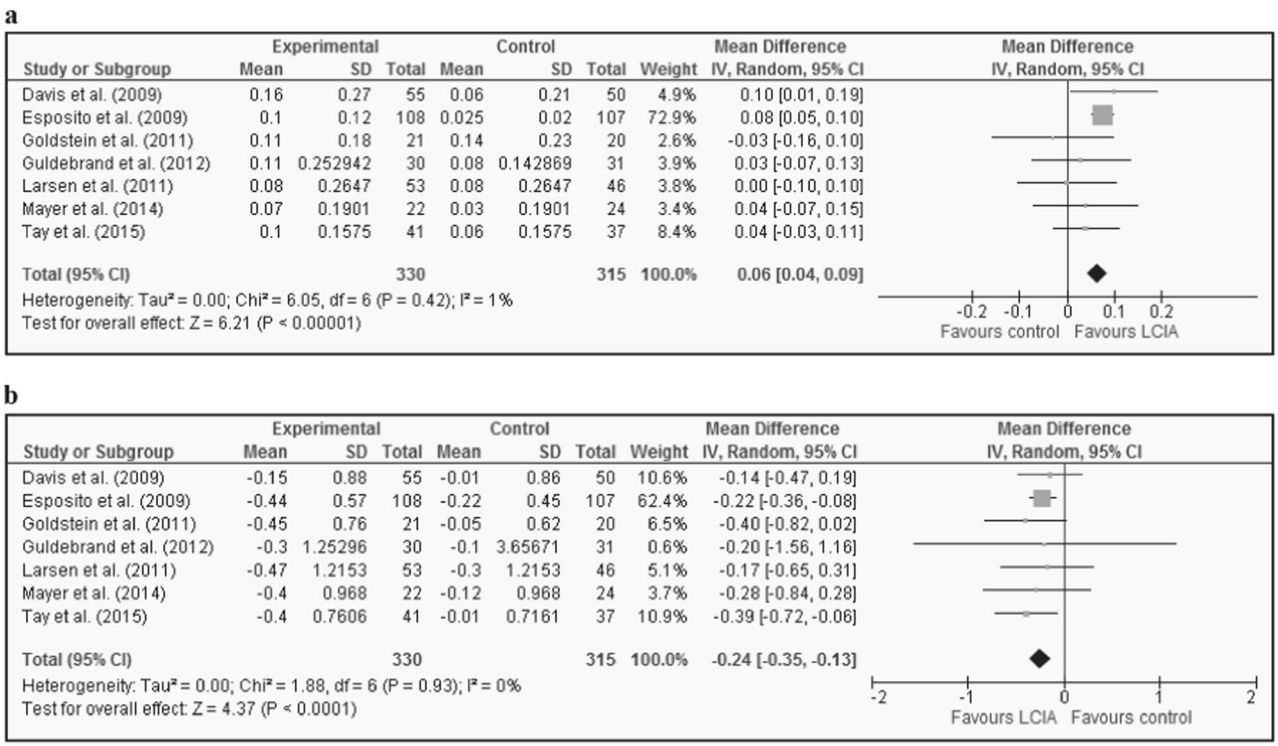

Fig. 4 **a** Meta-analysis of change in HDL cholesterol at 1 year. **b** Meta-analysis of change in triglycerides at trial end

0.54). Heterogeneity was not statistically significant ($\chi^2 = 2.97$, df = 4, $p = 0.56$; $I^2 = 0\%$) (Fig. 3b).

HDL cholesterol

Data from 16 studies concerning HDL cholesterol appeared to show a trend in favour of the LCIA with seven out of the 16 studies reporting a statistically significant difference in favour of the LCIA (Supplementary Table 4). No studies reported statistical significance in favour of the control group. In one study, although the difference between groups was not statistically significant, change in HDL cholesterol within the LCIA was statistically significant but was not in the control group [27]. Authors of one paper did not report on the cholesterol outcomes covered in this review, but there was a statistically significant difference between groups for total: HDL cholesterol in favour of the LCIA [23]. One paper did not provide HDL cholesterol results for the group as a whole, their analysis categorised participants into those with a baseline HDL cholesterol level of below 1.3 or above or equal to 1.3. In the latter group, the difference in HDL cholesterol improvement was statistically significant in favour of the LCIA; statistical significance was not reported for the former group [25].

The pooled analysis of seven studies showed a statistically significant effect favouring the LCIA in improving HDL cholesterol levels at 1 year (estimated effect = 0.06 mmol/L, 95% CI 0.04–0.09, $p < 0.00001$). There was no evidence of statistical heterogeneity ($\chi^2 = 6.05$, df = 6, $p = 0.42$; $I^2 = 1\%$) (Fig. 4a).

Triglycerides

Eighteen studies provided change in triglyceride level data (Supplementary Table 5). Eight studies found a statistically significant difference between groups in favour of the LCIA. No studies found a statistically significant difference in favour of the control group. One study found no significant difference between groups, but found the change within the LCIA to be statistically significant but the change in the control group was not [26].

The results of the pooled analysis at 1 year that includes seven studies suggest that the LCIA was favoured with a high statistical significance (estimated effect = −0.24 mmol/L, 95% CI −0.35 to −0.13, $p < 0.0001$). There was no evidence of statistical heterogeneity ($\chi^2 = 1.88$, df = 6, $p = 0.93$; $I^2 = 0\%$) (Fig. 4b).

Blood pressure

Fourteen studies reported blood pressure outcomes (Supplementary Table 6). Two studies found the LCIA demonstrated statistically significant improvements in systolic blood pressure [29, 32] and two studies found that the LCIA demonstrated statistically significant improvements in diastolic blood pressure [20, 29] over a control diet. The

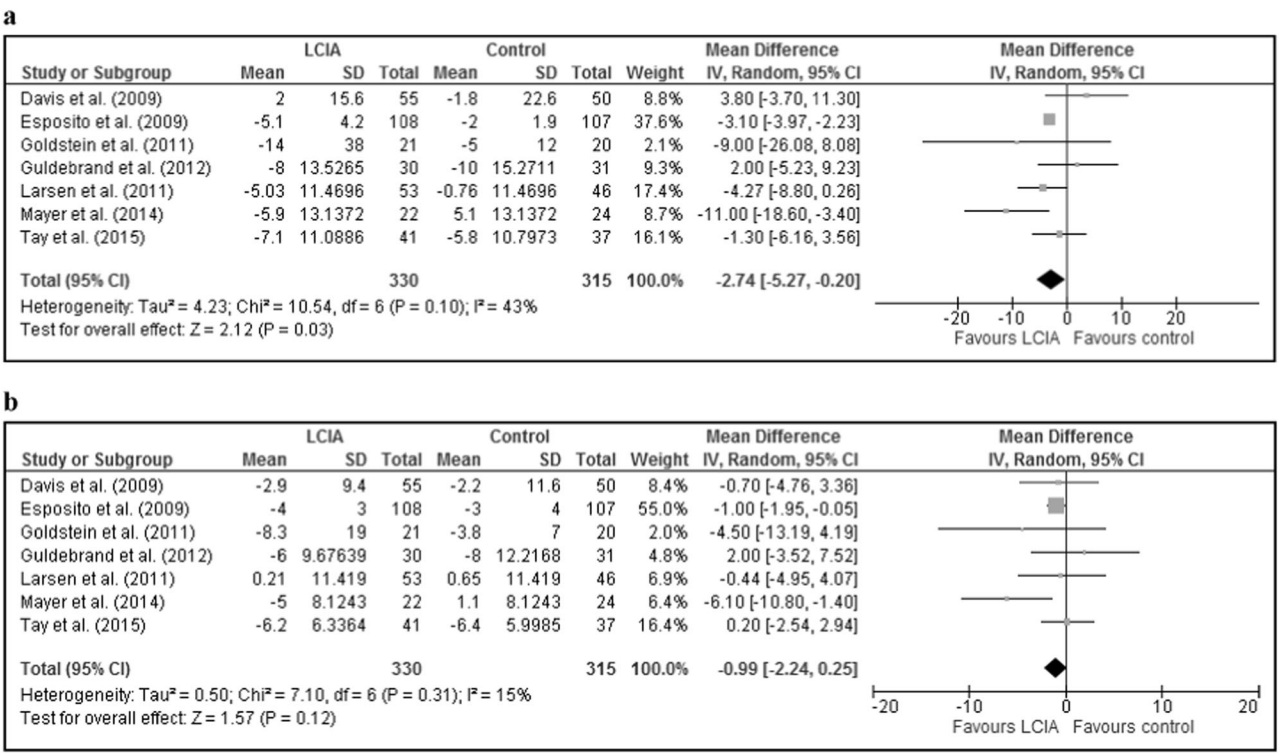

Fig. 5 **a** Meta-analysis of change in systolic blood pressure at trial end. **b** Meta-analysis of change in diastolic blood pressure at trial end

remaining studies found no statistically significant difference between intervention and control groups.

However, when results from seven studies were pooled together at 1 year, a statistically significant superiority was seen in the LCIA with regard to systolic blood pressure (estimated effect = −2.74 mmHg, 95% CI −5.27 to −0.20, $p = 0.03$). There may be evidence to suggest moderate heterogeneity ($\chi^2 = 10.54$, df = 6, $p = 0.10$; $I^2 = 43\%$) (Fig. 5a).

The pooled analysis from seven studies for diastolic blood pressure did not demonstrate a statistically significant difference between groups (estimated effect = −0.99 mmHg, 95% CI −2.24 to 0.25, $p = 0.12$). There was no evidence of statistical heterogeneity ($\chi^2 = 7.10$, df = 6, $p = 0.31$; $I^2 = 15\%$) (Fig. 5b).

Interpretation of a low-carbohydrate diet

All authors described the intervention diet to be low-carbohydrate. However, although 10 out of the 18 studies prescribed a low-carbohydrate diet (six prescribing a very low-carbohydrate diet), five studies prescribed a moderate-carbohydrate diet, one study prescribed a high-carbohydrate diet with one another study prescribing up to 50% TEI from carbohydrates that encompasses a range of up to and including a high-carbohydrate diet (Table 1). Please see defined categorisations in Table 2. One study did not specify the quantity of carbohydrate prescribed to the low-carbohydrate group, but had the aim of increasing total fat intake by 10% [20].

Table 2 Classification of dietary carbohydrate contribution [4, 8]

Classification	g/day	%TEI
Very low-carbohydrate diet	<50	<10
Low-carbohydrate diet	<130	<26
Moderate-carbohydrate diet	130–225	26–45
High-carbohydrate diet	>225	>45

Dietary adherence

Excluding trials involving enteral or formula feeds, 12 trials specified a carbohydrate prescription and reported carbohydrate intake at trial end in the LCIA. Two trials managed to achieve their set carbohydrate intake target in the intervention arm, one which prescribed a low-carbohydrate diet [28] and one that prescribed up to and including a high-carbohydrate diet [35]. Adherence appeared to be particularly problematic for those studies who set out to achieve a very low-carbohydrate diet (<50 g carbohydrate per day), with only one out of the six trials that prescribed a very low-carbohydrate diet being able to achieve this target as an average value in the LCIA [26]; this study prescribed <20 g/day and achieved an average carbohydrate intake of 49 g/

Table 3 Comparative nutritional breakdown of intervention and control diets

Component	Number of studies	Low carbohydrate Mean (SD)	Control Mean (SD)	Mean difference	95% CI for difference	*P*-value
Calories (kcal)	12	1577.8 (188.3)	1613.4 (194.0)	−35.6	−137.4 to 66.2	0.458
Carbohydrate	12	26.65 (10.60)	47.68 (3.01)	−21.03	−27.15 to −14.92	<0.001
Protein	11	24.56 (2.77)	19.02 (1.19)	5.55	3.76–7.33	<0.001
Fat	11	48.26 (8.47)	31.79 (4.22)	16.47	10.63–22.32	<0.001
SFA	9	13.92 (3.79)	10.40 (1.86)	3.52	1.28–5.77	0.007
PUFA	7	8.81 (2.73)	5.50 (1.28)	3.31	0.38–6.25	0.033
MUFA	8	17.90 (7.80)	10.44 (2.88)	7.46	1.86–13.06	0.016
Fibre (g)	5	19.52 (6.57)	23.58 (7.82)	−4.06	−6.50 to −1.62	0.010

day. It does appear that a low-carbohydrate diet of <130 g carbohydrate per day is achievable as the average carbohydrate intake at trial end from the aforementioned 12 studies was 106 g per day (Supplementary Table 7).

Nutritional breakdown of intervention and control diets

Twelve studies were included in this comparative analysis (Table 3). Comparative analysis of the intervention and control diet showed that the difference between mean daily calorie intake of both groups was not statistically significant ($p = 0.458$). Carbohydrate and fibre intake was lower in the LCIA. Protein and fat intake was higher in the LCIA. Within the dietary fats analysed, the greatest difference was the increase observed in mono-unsaturated fat intake in the LCIA, with a difference of 7.46% seen between groups ($p = 0.016$); the LCIA demonstrated increased consumption of saturated and polyunsaturated fats. The total percentage increase seen in unsaturated fats in the LCIA was 10.77% and saturated fats intake increased on average by 3.52%.

Discussion

Glycaemic control

Results from the descriptive and meta-analyses suggest that reducing carbohydrate intake may have a favourable effect on HbA1c.

The previous systematic review concluded there was no superiority of a low-carbohydrate diet in improving HbA1c while assessing interventions with a maximum intake of 130 g carbohydrate [9]. A previous meta-analysis that considered a reduced-carbohydrate intake to <45% TEI reported the superiority of a carbohydrate-restricted diet compared to a control in improving HbA1c [36]. The current review considered low-carbohydrate dietary interventions as defined by the author; therefore, although there was a carbohydrate reduction, this was not always limited to <130 g carbohydrate/day.

From all 14 papers that included participants on diabetes medication at trial start and reported changes in diabetes medication, there was a unanimous report of the superior effect of medication reduction in the LCIA in comparison to the control group, with nine out of 11 studies that discussed statistical significance of the difference between groups, finding a statistically significant reduction in diabetes medication in the LCIA. Similarly, a recent review [37] also found that the majority of studies considering the role of a low-carbohydrate diet in type 2 diabetes management do not account for medication changes making it difficult to assess the efficacy of this dietary intervention.

The term glycaemic control is often used interchangeably with HbA1c; however, this review proposes that a reduced need for diabetes medication may also be an indicator of glycaemic control as was suggested by several authors of the included studies within this review [21, 22, 25, 33]. In one study with insulin-treated participants [22], baseline HbA1c was 6.9% (Table 1). Insulin requirements were less in the LCIA but there was no difference in HbA1c between groups at trial end. Guidelines suggest that patients taking hypoglycaemia-inducing medication should be supported to aim for an HbA1c of 7% [38], so arguably on average, this group was already at glycaemic target at baseline and to aim for a lower HbA1c may not have been clinically responsible or necessary. Therefore, it should be acknowledged that for participants on hypoglycaemia-inducing medication, when HbA1c is close to or at glycaemic target HbA1c reduction in HbA1c would not necessarily be a treatment aim, however reduction in medication could be. When glycaemic control is considered solely from the perspective of HbA1c, the significance of diabetes medication reduction is ignored. Several authors of studies included within the review stated that if medications had not been reduced, greater reductions in HbA1c would have been seen in the LCIA [23, 25, 30].

Only one study included in the review did not demonstrate an improved HbA1c or superior medication reduction

in the LCIA [20]. The mean baseline HbA1c was considerably lower in this study compared to the other trials (6.1–6.2%) (Table 1) and no participants were taking diabetes medications at trial start. The mean baseline HbA1c, in fact, was below the diagnostic criteria for diabetes of 48 mmol/mol or 6.5%, which may suggest that reducing dietary carbohydrate may not have as significant an effect on glycaemic control at lower HbA1c levels.

Lipid profile and blood pressure

The current review suggests that there is no significant superior overall effect of either intervention arm regarding total, LDL cholesterol or diastolic blood pressure. However, improved triglyceride and HDL cholesterol levels were seen in the LCIA across the included studies, demonstrated by both the descriptive and meta-analyses. Meta-analyses also showed improved systolic blood pressure outcomes within the LCIA at 1 year. Results from other reviews [39, 40] have also found that reducing carbohydrate intake can have favourable effects on cardiovascular disease-related outcomes.

Concerns regarding a lower-carbohydrate, higher-fat diet have existed for some time due to the fear of the potential adverse cardiovascular implications that may result from an increased fat intake, more specifically saturated fat. A recent systematic review suggested that saturated fats are not associated with all-cause mortality, CHD and CHD mortality as had been previously thought [41]. However, a 2015 Cochrane review [42] suggests that a small but potentially important reduction in cardiovascular risk can be observed when reducing saturated fat. The consensus remains to continue to recommend replacing saturated fats with unsaturated fats due to their known superiority of the latter in promoting cardiovascular health [43]. Interestingly, this review found that the main increase in dietary fats came from unsaturated fats, in particular mono-unsaturated fats, which we do not believe has been evidenced before when considering dietary carbohydrate restriction for patients with type 2 diabetes.

Interpretation of a low-carbohydrate diet

This review assessed the effect of a 'low-carbohydrate diet' as interpreted by the authors of the studies, resulting in a varied carbohydrate prescription across the studies, including prescription of a high-carbohydrate diet in two cases [24, 35] when following the more commonly used classifications (Table 2). One study classified the dietary intervention as low-carbohydrate but did not specify a carbohydrate prescription [20].

There seems to be a general agreement that there are two ways to categorise a low-, moderate- or high-carbohydrate diet: g/day or %TEI (Table 2). However, the two methods of categorisation do not always work synergistically alongside each other. If somebody is following a reduced-calorie diet, a low-carbohydrate diet in grams per day could also be categorised as a moderate-carbohydrate diet if using %TEI. For example, participants in the LCIA in one study in this review [23] consumed 109.5 g carbohydrate/day (low-carbohydrate diet), but due to a lower-calorie intake, this was 33.5% TEI (moderate-carbohydrate diet). In another study [34], participants in the LCIA consumed 96.9 g carbohydrate per day (low-carbohydrate diet), but again, due to a lower-calorie intake, this constituted a moderate-carbohydrate diet in terms of TEI (31%).

This point should be acknowledged when delivering or reporting on interventions and perhaps a consensus is needed with regard to the most appropriate way to categorise a low-carbohydrate diet.

Adherence

Guidelines currently suggest that the ideal proportion of carbohydrates in the diet for patients with type 2 diabetes is unknown due to the lack of existing evidence, so guidance remains to individualise treatment [44, 6], but national non-diabetes-specific dietary guidelines provided by SACN [7] continue to promote a high-carbohydrate diet, a dietary reference value of 50%, which is coincidentally higher than the estimated carbohydrate intake of adults in the United Kingdom (46%) [7].

The majority of studies in this review demonstrated that participants in the LCIA were not able to achieve the carbohydrate prescription as set out by the investigators. However, the average carbohydrate consumption across LCIAs was 106 g/day showing that achievement of a low-carbohydrate diet is realistic and its demonstration was seen in many studies. Adherence to a very low-carbohydrate diet (<50 g/day), although achieved in one study, seems an unrealistic target for the majority of patients within this population group.

This review suggests that the prescription or achievement of a low-carbohydrate diet is not necessarily required to achieve improved clinical markers such as glycaemic control; reducing carbohydrate to achieve a moderate-carbohydrate diet can result in improved glycaemic control as was seen in several of the featured studies [18, 21, 24, 35].

Other nutritional considerations of a low-carbohydrate diet

Calories

The difference in daily calorie intake was not statistically significant between groups, which may explain why the results of this review did not find either intervention to be superior in terms of weight loss, as was also found in other systematic reviews and meta-analyses [36, 9]. The LCIA

appeared superior in promoting weight loss at earlier time points, but the descriptive and meta-analyses failed to show an obvious superiority at 1 year. It is known that low-carbohydrate diets can see greater initial weight losses due to loss of water [45], but ultimately it is likely that the total calorie intake will determine change in weight, as has been discussed elsewhere [37].

Fibre

SACN recommend that the dietary reference value for fibre for adults in the United Kingdom should be 30 g/day [7]. By restricting dietary carbohydrate, the likelihood of reaching such targets is reduced, as was evidenced in this review. Evidence from the SACN report concludes that diets rich in dietary fibre are associated with lower incidences of cardiovascular disease, coronary events, stroke, colorectal, colon and rectal cancer; therefore, not reaching suggested targets could increase the likelihood of the onset of these conditions [7]. This review demonstrated that neither the control or intervention diet achieved this target, with a lower fibre intake observed in the LCIA. It is considered feasible to achieve fibre targets while following a low-carbohydrate diet [46], however, the importance of achieving fibre intake should be highlighted when offering dietary advice to support a low-carbohydrate diet, encouraging the consumption of high-fibre carbohydrate alternatives.

Protein

This review demonstrated a slight but statistically significant increase in relative protein contribution to the diet in the LCIA. Proposed benefits of a higher protein diet include increased satiety, promoting favourable weight management effects [47], but concerns exist regarding the effect that a high-protein intake may have on the kidneys. Diabetic kidney disease is among the most frequently seen complications of diabetes, with diabetes accounting for ~50% of all cases of end-stage renal disease [48]. Currently, there is little evidence to suggest that a high-protein intake would be detrimental to those with good kidney function, however, a high-protein diet may be detrimental to those with existing renal dysfunction [49]. Therefore, if patients with type 2 diabetes wish to increase their protein intake to complement a reduced-carbohydrate diet, kidney function should first be assessed.

Overall nutritional adequacy of a low-carbohydrate diet

Concerns have been raised regarding the provision of certain vitamins and minerals when reducing the amount of carbohydrate in the diet [50]. Achieving a nutritionally adequate diet, although not realistically achievable while following a very low-carbohydrate diet without supplementation [51], is achievable following a low-carbohydrate diet of <130 g/day [46]; however, wider nutritional messages to ensure overall nutritional adequacy of a low-carbohydrate diet beyond carbohydrate consumption are not often well relayed [52]. Therefore, it is recommended that if prescribing any carbohydrate restriction of <45% TEI, nutritional adequacy of the diet should be considered ensuring that an adequate amount of vitamins, minerals and fibre are supplied by the diet [53].

Limitations

In terms of study design, the main issue in terms of internal validity of these studies is the lack of blinding of participants and study personnel, something that is difficult to achieve given such an intervention; however, this should be acknowledged when interpreting results. Furthermore, the true effect of a reduced-carbohydrate diet on HbA1c could not be observed due to medication adjustments; it is likely that a greater reduction in HbA1c would have been seen in the LCIA. There was study design heterogeneity present; some studies prescribed a lower-calorie allowance to the control group that adds another dimension of consideration when comparing interventions as opposed to comparing macronutrient composition of diets.

Several studies provided insufficient information and could not be included in the meta-analyses, limiting the number of studies and participants that could be included in the pooled analysis. Authors should be reminded to follow the reporting guidelines of the CONSORT statement, and editors and reviewers of academic journals should refer to CONSORT when reviewing manuscripts submitted for publication.

Recommendations for future research

Based on the findings of this review, the authors recommend the following areas for future research:

- Exploration of the optimal level of dietary carbohydrate for patients with type 2 diabetes.
- The effect of carbohydrate reduction on HbA1c independent of diabetes medication changes.
- An economic evaluation of the cost savings made by reducing diabetes medication as a result of dietary carbohydrate reduction.

Conclusion

The aim of this systematic review was to explore the interpretation and effectiveness of a low-carbohydrate diet

in the management of type 2 diabetes. The review, which was shaped by Cochrane principles, sourced randomised controlled trials that compared a low-carbohydrate diet, as defined by the author, to a control diet representative of usual care. The intervention and control arms were compared against HbA1c, change in diabetes medications, weight, lipid profile and blood pressure; dietary adherence within the LCIA was considered in addition to a comparison of the nutritional composition of the LCIA and control diets.

Descriptive analyses suggested that the LCIA may offer superiority over control diets in improving HbA1c, HDL cholesterol and triglyceride levels. The meta-analyses confirmed statistically significant superiority of the LCIA in improving HbA1c, HDL cholesterol, triglyceride and systolic blood pressure levels at 1 year. Reducing carbohydrate intake demonstrated a strong superiority over control diets in reducing diabetes medication, which may have diminished the observed effects of a reduced-carbohydrate intake on HbA1c. The LCIA appeared superior to control diets regarding weight loss at earlier time points, but by 1 year the difference was not notable. No significant difference was observed in total cholesterol, LDL cholesterol or diastolic blood pressure between groups.

Few studies were able to demonstrate achievement of carbohydrate targets as set out by the authors of the studies. However, findings suggest that although adherence to a very low-carbohydrate diet is likely to be unrealistic for patients with type 2 diabetes, achievement of low- and moderate-carbohydrate diets is achievable. Where clinical benefit was seen, it was not limited to the achievement of a low-carbohydrate diet, reducing carbohydrate intake to achieve a moderate-carbohydrate diet also demonstrated improved clinical outcomes in some studies. This review does highlight the lack of clarity surrounding the term 'low-carbohydrate diet'. Moving forward, categorisation of diets in terms of their carbohydrate provision needs to be more consistent.

Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention; however, this is commonplace in many trials comparing dietary interventions.

Therefore, this review concludes that reducing carbohydrate intake may promote favourable health outcomes in the management of type 2 diabetes in the context of a healthy diet. Guidance remains to individualise dietary advice to patients with diabetes. However, more research is needed to determine whether there is an optimal intake of dietary carbohydrate for patients with type 2 diabetes, and to challenge whether the UK national dietary reference value of 50% is appropriate for patients with type 2 diabetes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1 World Health Organization. Global status report on noncommunicable diseases. Geneva: World Health Organization; 2014.
2 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:e442.
3 Diabetes UK. Diabetes: facts and stats. https://www.diabetes.org.uk/Documents/Position%20statements/Facts%20and%20stats%20June%202015.pdf. Accessed 10 Jan 2016.
4 Dyson P. Low carbohydrate diets and type 2 diabetes: what is the latest evidence? Diabetes Ther. 2015;6:411–24.
5 Diabetes UK. Evidence-based nutrition guidelines for the prevention and management of diabetes. London: Diabetes UK; 2011.
6 Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz EJ, Neumiller JJ, et al. Position statement: nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2013;36:3821–42.
7 Scientific Advisory Committee on Nutrition. (2015) Carbohydrates and Health. TSO, London, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf
8 Feinman RD, Pogozelskim WK, Astrip A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutr. 2015;31:1–13.
9 Castañeda-Gonzales LM, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systematic review of RCT greater than 12 weeks. Nutr Hosp. 2011;26:1270–6.
10 Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928
11 Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. Am J Prev Med. 2014;46:17–23.
12 Little RR, Rohlfing CL, Sacks DB, National Glycohemoglobin Standardization Program(NGSP) Steering Committee Status of haemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem. 2011;57:205–14

13 NHS Diabetes. (2009) Self-monitoring of blood glucose in non-insulin treated type 2 diabetes. Aberdeen Health Technology Assessment Group, Aberdeen, http://webarchive.nationalarchives.gov.uk/20130513172055/http:/www.diabetes.nhs.uk/document.php?o=238
14 Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). Br Med J. 2001;322:15–18.
15 Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthingtond HV, Vail A, Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002;31:140–9
16 Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. Chichester: Wiley; 2009.
17 Higgins JPT, Green S on behalf of The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). http://www.cochrane-handbook.org. Accessed 9 Jan 2016.
18 Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab. 2010;12:204–9.
19 Rock CL, Flatt SW, Pakiz B, Taylor KS, Leone AF, Brelje K, et al. Weight loss, glycemic control, and cardiovascular disease risk factors in response to differential diet composition in a weight loss program in type 2 diabetes: a randomized controlled trial. Diabetes Care. 2014;37:1573–80.
20 Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated haemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87:114–25.
21 Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Lerch M, Eriksen J, et al. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. Eur J Clin Nutr. 2005;59:1221–32.
22 Pohl M, Mayr P, Mertl-Roetzer M, Lauster F, Haslbeck M, Hipper B, et al. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. JPEN J Pareneter Enter Nutr. 2009;33:37–49.
23 Daly ME, Paisey R, Paisey R, Milward BA, Eccles C, Williams K, et al. Short-term effects of severe dietary carbohydrate-restriction advice in type 2 diabetes – a randomised controlled trial. Diabet Med. 2006;23:15–20.
24 Shirai K, Saiki A, Oikawa S, Teramoto T, Yamada N, Ishibashi S, et al. The effects of partial use of formula diet on weight reduction and metabolic variables in obese type 2 diabetic patients – multicenter trial. Obes Res Clin Pract. 2013;7:e43–54.
25 Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care. 2014;37:2909–18.
26 Westman EC, Yancy WS, Mayropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab. 2008;5:36.
27 Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH. Advice to follow a low-carbohydrate diet has favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med. 2014;46:182–7.
28 Yamada Y, Uchida J, Izumi H, Tsukamoto Y, Inoue G, Watanabe Y, et al. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Intern Med. 2013;53:13–19.
29 Mayer SB, Jeffreys AS, Olsen MK, McDuffie JR, Feinglos MN, Yancy WS. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. Diabetes Obes Metab. 2014;16:90–93.
30 Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, Stein D, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care. 2009;32:1147–52.
31 Goldstein T, Kark JD, Berry EM, Adler B, Ziv E, Raz I. The effect of a low carbohydrate energy-unrestricted diet on weight loss in obese type 2 diabetes patients – a randomized controlled trial. E Spen Eur E J Clin Nutr Metab. 2011;6:e178–86.
32 Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. Diabetologia. 2011;54:731–40.
33 Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102:780–90.
34 Guldbrand H, Dizdar B, Bunjaku B, Lindstrom T, Bachrach-Lindström M, Fredrikson M, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012;55:2118–27.
35 Esposito K, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med. 2009;151:306–14.
36 Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 2008;108:91–100.
37 Van Wyke HJ, Davis RE, Davis JS. A critical review of low-carbohydrate diets in people with type 2 diabetes. Diabet Med. 2015. https://doi.org/10.1111/dme.12964
38 National Institute of Health and Care Excellence. Type 2 diabetes in adults: management. NG28. London: NICE; 2015.
39 Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M, et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 2009;32:959–65.
40 Hu T, Bazzano LA. The low-carbohydrate diet and cardiovascular risk factors: evidence from epidemiologic studies. Nutr Metab Cardiovasc Dis. 2014;24:337–43.
41 De Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. Br Med J. 2015;351:h3978.
42 Hooper L, Marin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev. 2015;10:CD011737.
43 National Institute of Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. CG181. London: NICE; 2016.
44 American Diabetes Association. Standards of medical care in diabetes – 2016 Abridged for primary care providers. Clin Diabetes. 2016;34:3–21.
45 Pogozelski W, Arpaia N, Priore S. The metabolic effects of low-carbohydrate diets and incorporation into a biochemistry course. Biochem Mol Biol Educ. 2005;33:91–100.

46 Spritzler F. A low-carbohydrate, whole-foods approach to managing diabetes and prediabetes. Diabetes Spectr. 2015;25:238–43.
47 Paddon-Jones D, Westman E, Mattes RD, Wolfe RR, Astrup A, Westerterp-Plantenga M. Protein weight management, and satiety. Am J Clin Nutr. 2008;87:1558S–61S.
48 National Institutes of Health. US Renal Data System, USRDS 2010. Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. United States: National Institute of Diabetes and Digestive and Kidney Diseases; 2010.
49 Cuenca-Sánchez M, Navas-Carrillo D, Orenes-Piñero E. Controversies surrounding high-protein diet intake: satiating effect and kidney and bone health. Adv Nutr. 2015;16:260–6.
50 Bowman SA, Spence JT. A comparison of low-carbohydrate vs. high-carbohydrate diets: energy restriction, nutrient quality and correlation to body mass index. J Am Coll Nutr. 2002;21:268–74.
51 Calton JB. Prevalence of micronutrient deficiency in popular diet plans. J Int Soc Sports Nutr. 2010;7:24.
52 Crowe TC. Safety of low-carbohydrate diets. Obes Rev. 2005;6:235–45.
53 Diabetes UK. Low-carbohydrate diets for people with type 2 diabetes. London: Diabetes UK; 2011.