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Original Article

Effects of low carbohydrate diets in individuals with type 2 diabetes: systematic review and meta-analysis

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Abstract: Background: Many studies have reported that caloric restriction has been gaining widespread popularity to control weight and lipid. Recently, American Diabetes Association and Diabetes UK recommend low carbohydrate diets (LCD) have favorable effects on the risk factors of type 2 diabetes, but the efficacy of LCD individuals with type 2 diabetes is not unclear. Therefore, the aim of this study was to assess the effect of LCD on glycemic control, lipids, and weight loss on type 2 diabetes individuals. Methods: A structured literature search was undertaken to identify all randomized controlled trials (RCTs) conducted in patients with type 2 diabetes receiving LCD. We performed PubMed, Medline, Embase, and Cochrane Library from Standardized mean difference (SMD) and 95% confidence intervals (CI) were calculated by the random-effects model. Heterogeneity among studies was measured using Cochrane Q-test together with the I^2 statistic. Results: Four studies showed greater weight reduction on low carbohydrate diets and in six there were no significant differences between groups. LCD was more effective in achieving weight loss that control diets were with a WMD in weight loss of -2.356 Kg. There was a significant decrease in the percentage of HbA1c in subjects who consumed LCD compared with other diets and appeared to be beneficial in increasing HDL-C and decreasing TG with no significant reduction in TC or LDL-C. Conclusions: This review shows that there are consistent differences in weight and HbA1c changes over the long-term treatment with LCD.

Keywords: Low carbohydrate diets, Type 2 diabetes, weight, glycaemic control, lipids

Introduction

During the past three decades, the prevalence of type 2 diabetes (T2DM) in the middle-aged has almost doubled [1, 2]. International Diabetes Federation (IDF) has estimated that the prevalence of diabetes was 366 million worldwide, and is expected to increase up to 552 million by 2030 [3]. According to statistics from the US Center for Disease Control and Prevention, 55% of diabetic patients are obese and 85% are overweight [4]. Many studies have reported that weight reduction is a recommended target for the first-line treatment and prevention of diabetes [5-8].

The American Diabetes Association (ADA) recommends that monitoring carbohydrate intake should be a component of diabetes therapy [5]. Systematic reviews and meta-analyses have shown that low-glycemic index, high-fiber, and Mediterranean diets improve glucose metabolism [9-11]. In 2008, the ADA suggests consuming at least about 150 grams of carbohydrates per day for persons with type 2 diabetes [12], this recommendation differs from that reported in 2007. Low carbohydrate diets is low in fiber and fruits, high in protein from animal sources, cholesterol and fat, which are risk factors for obesity and T2DM [13]. Low carbohydrate diets (LCD) have shown beneficial effects on weight reduction programs on obese individuals without diabetes, but the evidence over the efficacy on individuals with type 2 diabetes is not conclusive [14, 15]. Therefore, the aim of this systematic review is to evaluate the effect of low carbohydrate diets on weight reduction, glycemic control, and lipid profile in type 2 diabetes individuals.

Methods

Search strategy

Searches of PubMed, Medline, Embase, and Cochrane Library from their inception until May

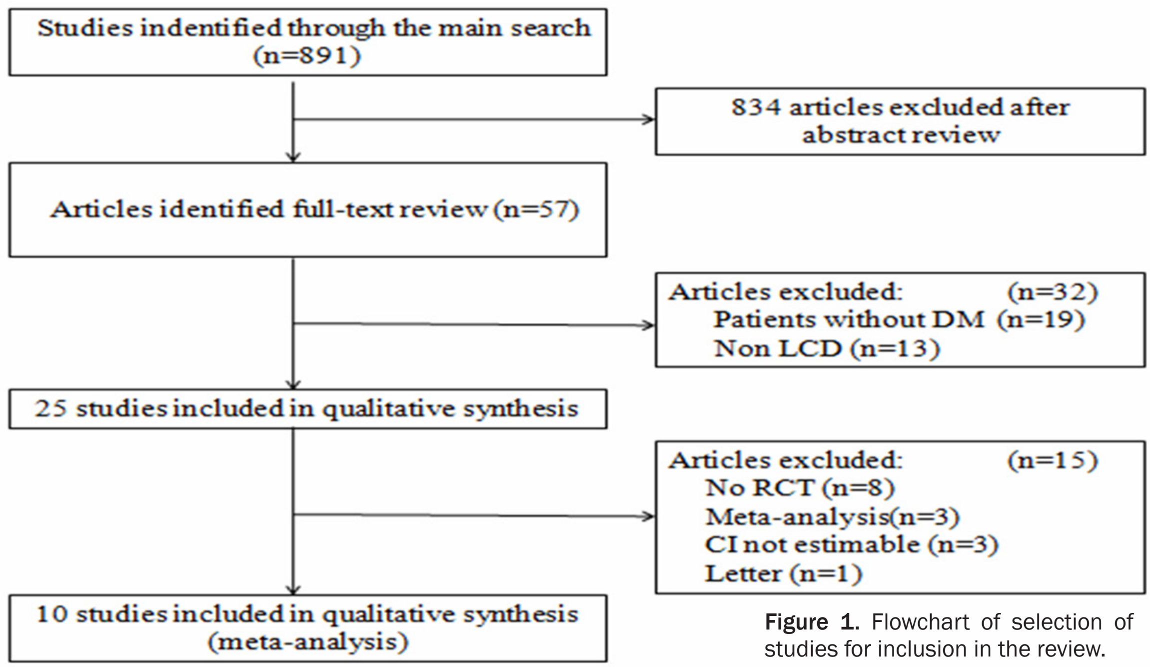


Figure 1. Flowchart of selection of studies for inclusion in the review.

30, 2014, were performed. Key search terms were used individually or combined: "diabetic", "type 2 diabetes", "T2DM", "low carbohydrate diets", "carbohydrate-restricted diet" with no languages restriction.

Trial selection

Only the studies that met the following criteria were included: (1) RCT study design; (2) All participants of T2DM patients; (3) One group received LCD (defined as a diet allowing a maximum intake of 130 g of carbohydrates per day with any other type of diet); (4) The patients should be included 18 years and older individuals with T2DM. Studies were excluded if the participants less than 18 years of age, the treatment allocation was not random and studies did not report data for at least 1 of the clinical outcomes of interest. Also the individuals with type 1 diabetes were excluded. When the results of a paper were published more than once, only the most complete article was included in the analysis.

Quality assessment of primary studies

Two authors independently evaluated the quality of all included RCTs by Jadad scale in the following domains: randomization, blinding and description of withdrawals and drop outs [16]. A cut score of 3 was used to indicate high quality studies as it has been reported to be sufficient to determine high quality versus low quality in previous studies.

Data extraction

Two authors independently extracted data based on a predesigned data extraction form. Information was extracted on baseline characteristics (the primary author, publication date, sample size, country of origin, age range, sex). Outcome measures were extracted for change in weight and the following metabolic markers: HbA1C, total cholesterol (TC), High Density lipoprotein (HDL)-cholesterol, LDL-cholesterol and triglycerides (TG) levels.

Statistical analysis

All meta-analysis were performed using Stata statistical software (STATA version SE-10.1; Stata Corporation, College Station, TX). We assessed the statistical heterogeneity between trials by I^2 statistic [17]. When heterogeneity was confirmed ($P<0.10$, $I^2>50\%$), the random-effect method was used, otherwise the fix-effect model was adopted [18]. 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. A sensitivity analysis was performed to identify potential outliers.

Table 1. Comparative clinical trials of low carbohydrate diets in type 2 diabetes

Study	Country	Sample size	Duration	Intervention		Jadad scores
		LCD/Control		LCD	Control	
Guldbrand H, 2012	Sweden	30/31	24 months	1600 kcal/day for women and 1800 kcal/day for men; 50 energy per cent (E%) was from fat, 20 E% was from carbohydrate and 30 E% was from protein	1600 kcal/day for women and 1800 kcal/day for men; 30 E% from fat (less than 10 E% from saturated fat), 55-60 E% from carbohydrate and 10-15 E% from protein	5
Esposito K, 2009	Italy	108/107	48 months	1500 kcal/d for women and 1800 kcal/d for men, with the goal of no more than 50% of calories from complex carbohydrates and no less than 30% calories from fat	1500 kcal/d for women and 1800 kcal/d for men, with the goal of no more than 30% of calories from fat and no more than 10% of calories from saturated fat	5
Samaha FF, 2003	U.S.	64/68	6 months	Restrict carbohydrate intake to 30 g per day or less. No instruction on restricting total fat intake was provided. Vegetables and fruits with high ratios of fiber to carbohydrate were recommended	Caloric restriction sufficient to create a deficit of 500 calories per day, with 30 percent or less of total calories derived from fat	3
Nielsen JV, 2005	Sweden	16/15	6 months	1800 kcal for men and 1600 kcal for women, distributed as 20% carbohydrates, 30% protein and 50% fat	1600-1800 kcal for men and 1400-1600 kcal for women, consisted of approximately 60% carbohydrates, 15% protein and 25% fat	0
Stern L, 2004	U.S.	44/43	12 months	Carbohydrate intake to less than 30 g per day	Caloric intake by 500 calories per day, with less than 30% of calories derived from fat	3
Davis NJ, 2009	U.S.	55/50	12 months	Carbohydrate restriction of 20-25 g daily depending on baseline weight 35% LGI	A fat gram goal, which was 25% of energy needs, based on baseline weight	3
Elhayany A, 2010	Israel	61/63	12 months	Carbohydrates, 45% fats-high inmonounsaturated fat content, 15-20% proteins	50-55% LGI carbohydrates, 30% fats-high in monounsaturated fat content, 15-20% proteins	3
Elhayany A, 2010	Israel	61/55	12 months	35% LGI carbohydrates, 45% fats-high inmonounsaturated fat content, 15-20% proteins	50-55% carbohydrates, 30% fats and 20% proteins	3
Daly ME, 2005	UK	51/51	3 months	A diet consisting of up to 70 g of carbohydrate per day	Reducing fat intake	4
Yamada Y, 2014	Japan	12/12	6 months	The total carbohydrate intake to be <130 g/day	The target intake of specific macronutrients was as follows: carbohydrates =50-60%, protein =1.0-1.2 g/kg (<20%) and fat ≤25%	3
Iqbal N, 2009	U.S.	70/74	24 months	30 g/day (without restrictions on total fat or caloric intake)	≤30% calories from fat and a deficit of 500 kcal/day	3

LCD: low carbohydrate diets; M: male; F: female; LGI: Low Glicemic Index.

Funnel plots, Egger's test and Begg's test were used to evaluate publication bias.

Results

Description of studies

A flow diagram of our search strategy and results is listed in **Figure 1**. The main search strategy identified 891 articles. By scanning titles or abstracts, 834 articles were discarded. The full texts of the remaining 57 articles were reviewed, 32 were excluded since they did not included T2DM (n=19) and a LCD (n=13). 25 studies were included in qualitative synthesis, but 15 articles were excluded since eight non-RCT; three meta-analysis; three lack of the CI; one letter. At last, a total of 10 studies [19-28] with 1080 participants were included in the systematic review and meta-analysis. Sample size varied between 24 and 215 participants. Follow-up ranged from 3 months to 4 years.

Table 1 shows the characteristics of each included study. The 10 selected studies included in this review were highly heterogeneous in terms of population demographics, carbohydrate intake parameter, and the assessment of confounding factors. Intervention diets included a low carbohydrate diet compared with either a low fat diet [19-21, 24, 26, 28], high carbohydrate diet [22], a conventional diet [23, 25, 27], a ADA diet [25].

Quality of studies

The all of the studies included in our analysis were methodologically good in quality. Most of the studies included in the systematic review were conducted in the US and European countries and their follow-up. The characteristics of the retained RCTs and the Jadad scores are shown in **Table 1**. The quality scores ranged from 3 to 5 points out of a theoretical maximum of 5 points, except the quality score in one study [22] was 1. 10 articles adopted random assignment of patients, 9 RCTs stated the detailed randomized method and the follow-up steps [19-21, 23-28]. The double-blinded was performed in 3 RCT [19, 20, 26].

Weight change

Figure 2A provides a summary of weight change. Four studies showed greater weight reduction on low carbohydrate diets and in six there were no significant differences between groups. LCD was more effective in achieving weight loss that control diets were with a WMD in weight loss of -2.356 Kg (95% CI: -3.652, -1.06 kg; $P<0.001$), when all studies were included in the analysis.

Glycemic control

Data from 10 studies were pooled and compared LCD with a variety of control diets. There was a significant decrease in the percentage of HbA1c in subjects who consumed LCD compared with other diets (WMD: -0.33%; 95% CI: -0.51%, -0.151%; $P<0.001$, $I^2=88.4\%$) (**Figure 2B**).

Change in lipids

Low-carbohydrate diets appeared to be beneficial in increasing HDL-C (WMD: 0.094 mmol/L; 95% CI: 0.043, 0.144 mmol/L; P<0.001) and decreasing TG (WMD: -0.28 mmol/L; 95% CI: 0.393, -0.167 mmol/L; P<0.001) with no significant reduction in TC (WMD: 0.051 mmol/L; 95% CI: -0.144, 0.246 mmol/L; $P=0.61$) or LDL-C (WMD: -0.027 mmol/L; 95% CI: -0.108, 0.053 mmol/L; P=0.508) .

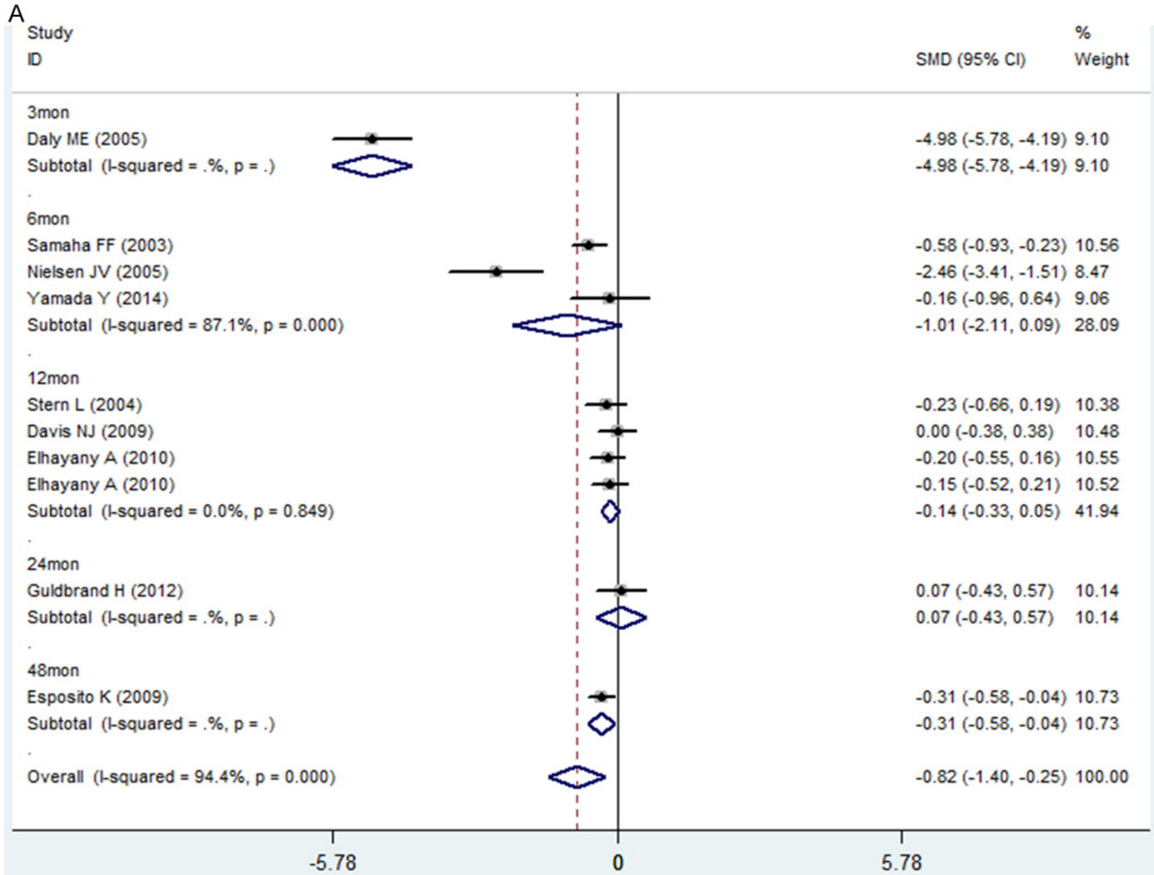
Sensitivity analysis

Sensitivity analyses were performed to explore potential sources of heterogeneity and to examine the influence of various exclusion criteria on the overall result. Further exclusion of any single study did not materially alter the overall result (**Figure 3**).

Discussion

This review provides evidence that a low carbohydrate diet (restrict carbohydrate intake to 20-60 g/d) can improve glycemic control, weight, and lipids in people with T2DM. LCD reduced HbA1c by 0.33% compared with other diets and it can led to significant improvements in the lipid profile with up to a 9.4% increase in HDL-C, 28% reduction in TG and 2.7% reduction in LDL-C, in contrast the result of TC increased 5.1%.

From a physiological point of view, carbohydrate diet should be avoided to achieve good glycemic control in type 2 diabetes, increased


A
Study
ID
SMD (95% CI)
%
Weight
3mon
Daly ME (2005)
-4.98 (-5.78, -4.19) 9.10
Subtotal (I-squared = .%, p = .)
-4.98 (-5.78, -4.19) 9.10
6mon
Samaha FF (2003)
-0.58 (-0.93, -0.23) 10.56
Nielsen JV (2005)
-2.46 (-3.41, -1.51) 8.47
Yamada Y (2014)
-0.16 (-0.96, 0.64) 9.06
Subtotal (I-squared = 87.1%, p = 0.000)
-1.01 (-2.11, 0.09) 28.09
12mon
Stern L (2004)
-0.23 (-0.66, 0.19) 10.38
Davis NJ (2009)
0.00 (-0.38, 0.38) 10.48
Elhayany A (2010)
-0.20 (-0.55, 0.16) 10.55
Elhayany A (2010)
-0.15 (-0.52, 0.21) 10.52
Subtotal (I-squared = 0.0%, p = 0.849)
-0.14 (-0.33, 0.05) 41.94
24mon
Guldbrand H (2012)
0.07 (-0.43, 0.57) 10.14
Subtotal (I-squared = .%, p = .)
0.07 (-0.43, 0.57) 10.14
48mon
Esposito K (2009)
-0.31 (-0.58, -0.04) 10.73
Subtotal (I-squared = .%, p = .)
-0.31 (-0.58, -0.04) 10.73
Overall (I-squared = 94.4%, p = 0.000)
-0.82 (-1.40, -0.25) 100.00
-5.78
0
5.78

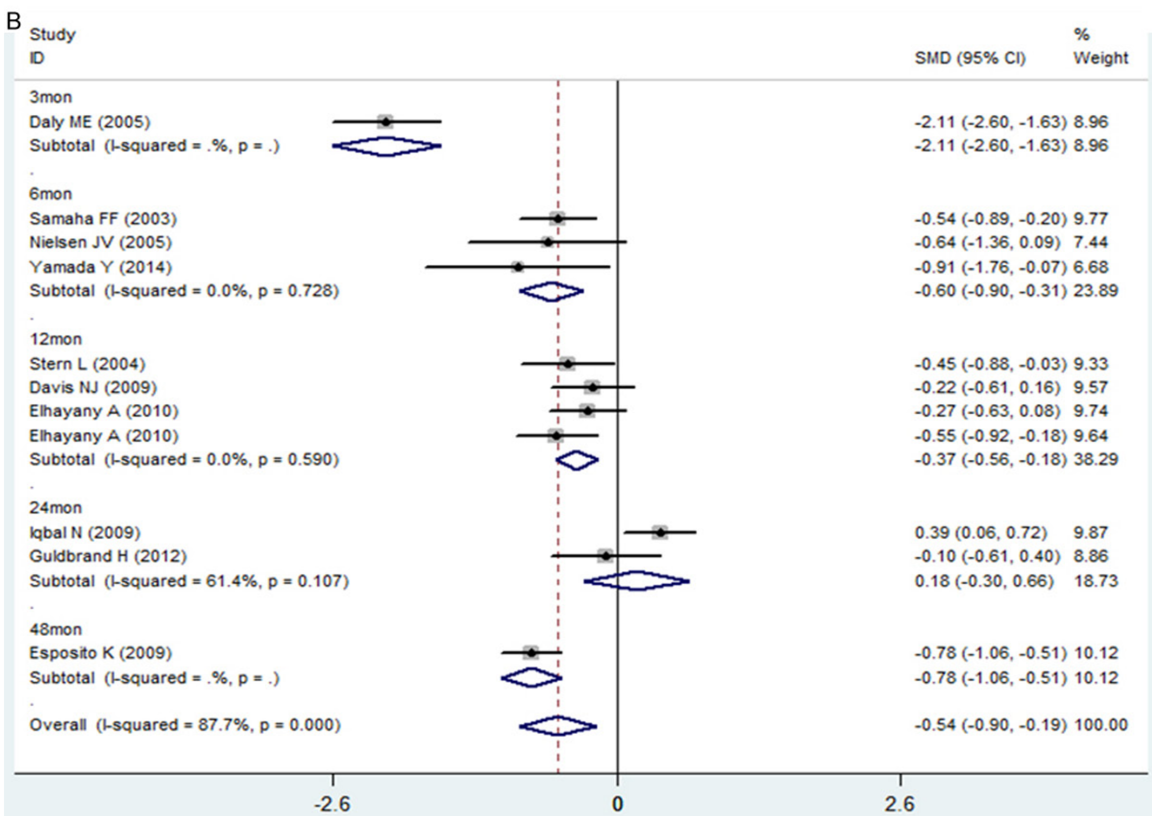

B
Study
ID
SMD (95% CI)
%
Weight
3mon
Daly ME (2005)
-2.11 (-2.60, -1.63) 8.96
Subtotal (I-squared = .%, p = .)
-2.11 (-2.60, -1.63) 8.96
6mon
Samaha FF (2003)
-0.54 (-0.89, -0.20) 9.77
Nielsen JV (2005)
-0.64 (-1.36, 0.09) 7.44
Yamada Y (2014)
-0.91 (-1.76, -0.07) 6.68
Subtotal (I-squared = 0.0%, p = 0.728)
-0.60 (-0.90, -0.31) 23.89
12mon
Stern L (2004)
-0.45 (-0.88, -0.03) 9.33
Davis NJ (2009)
-0.22 (-0.61, 0.16) 9.57
Elhayany A (2010)
-0.27 (-0.63, 0.08) 9.74
Elhayany A (2010)
-0.55 (-0.92, -0.18) 9.64
Subtotal (I-squared = 0.0%, p = 0.590)
-0.37 (-0.56, -0.18) 38.29
24mon
Iqbal N (2009)
0.39 (0.06, 0.72) 9.87
Guldbrand H (2012)
-0.10 (-0.61, 0.40) 8.86
Subtotal (I-squared = 61.4%, p = 0.107)
0.18 (-0.30, 0.66) 18.73
48mon
Esposito K (2009)
-0.78 (-1.06, -0.51) 10.12
Subtotal (I-squared = .%, p = .)
-0.78 (-1.06, -0.51) 10.12
Overall (I-squared = 87.7%, p = 0.000)
-0.54 (-0.90, -0.19) 100.00
-2.6
0
2.6

Figure 2. Forest plots for different factors between low carbohydrate diets and control diets. A: Weight reduction on LCD and other diets; B: HbA1c changes on LCD and other diets.

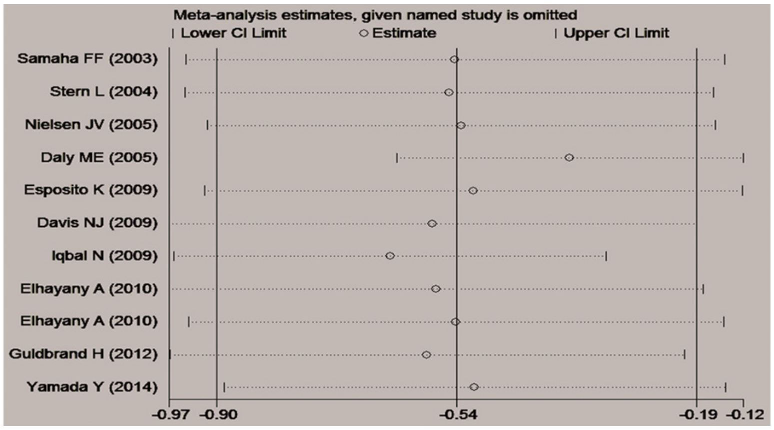


Figure 3. The pooled sensitivity of low carbohydrate diets for type 2 diabetes patients. CI: Confidence interval.

insulin sensitivity and recovered the function of beta cell. However, LCD contains a high intake of fat, which has traditionally been linked with increased risk for arteriosclerosis. So now many studies begin to discuss the role of LCD in patients with T2DM [19]. In a Swedish observational study, they found neither a high fat intake nor an intake of large amounts of saturated fat (22 E%) was linked with an increased risk for cardiovascular disease [29, 30]. Dietary structure change can promote weight loss and increase activity levels, which is included as part of diabetes management [31]. Recently some short-term studies have shown LCD has the positive effects on glycemic control and weight in obese patients with T2DM [32, 33]. A total of 2906 patients with newly diagnosed T2DM received LCD before giving them oral drugs or insulin. After 3 months, weight decreased by a mean of 4.5 kg, and HbA1c levels decreased by 2% from a baseline 9% [34]. But some studies have different viewpoints about the effect of LCD. Yancy et al [33] compared a LCD with a LFD in 45 patients with T2DM. There was no significant difference in the amount of weight loss or HbA1c control in the whole group. A study by Daly et al [26] showed that LCD appeared to decrease weight with non-significant reduction in HbA1c.

LCD is designed to limit energy intake and the normal physiological activity is increased to supply fat needs, ultimately lead to weight loss [35]. Weight reduction may be primarily caused by decreased caloric intake and energy efficiency [36-39]. Since HbA1c represents average fasting blood glucose over a period of three months, the time of the intervention should be observe with a follow-up than 3 months. In our analysis, all included studies lasted for at least three months. Our result reported significant HbA1c reduction with LCD in patients with type 2 diabetes, only six out of 11 studies reported significant differences between groups, in contrast, Iqbal et al found LCD increased the level of HbA1c [28]. So, overall effects of the LCD on HbA1c levels were inconsistent [30].

Two previous meta-analyses, respectively, showed worsening of the TC and LDL-C levels and improvements in the TG and HDL-C levels with LCD [40, 41]. However, another meta-analysis showed no deterioration in the TC or LDL-C levels and significant improvements in the TG and HDL-C levels with LCD [42], this conclusion is the same to our result. Due to, patients with LCD consumed less carbohydrates, more protein and more fat than other diets, questions remain over the longer-term effectiveness, sustainability and safety of LCD, particularly with respect to cardiovascular, renal and bone health [26].

There are several limitations to this systematic review. There are significant confounders in performing a meta-analysis of such varied interventions, and a publication bias and a residual confounding bias may have existed. The diets were different in terms of the composition, different baseline, the duration of the studies, and some studies failed to assessor blinding, these feature may introduced heterogeneity. Furthermore, it is difficult to distinguish the effects of individual nutritional component. Meanwhile, the lack of long-term follow-up data limits our understanding of the efficacy and safety of LCD, eg. fasting serum glucose, fasting serum insulin levels and blood pressure. We also know that exercise can have a significant effect on weight loss and serum glucose, but many studies do not have the data on exercise. Finally, some studies only reported the number of participants who completed the dietary intervention, very few studies performed the intention-to-treat analysis.

Conclusion

Our review of the existing literature indicates that differences on weight, HbA1c and lipid profiles changes over the long-term comparing a LCD with other diets. 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. Therefore, further investigation on the long-term effects over cardiovascular outcomes and safety in subjects with T2DM is needed.

Disclosure of conflict of interest

None.

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