Review

Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

ABSTRACT

Aims: The objective of this systematic review and meta-analysis is to assess the efficacy of Low Carbohydrate Diet (LCD) compared with a normal or high carbohydrate diet in patients with type 2 diabetes.

Methods: We searched MEDLINE, EMBASE, and Cochrane Library database for randomized controlled trials. Researches which reported the change in weight loss, blood glucose, and blood lipid levels were included.

Results: A total of 9 studies with 734 patients with diabetes were included. Pooled results suggested that LCD had a significantly effect on HbA1c level (WMD: −0.44; 95% CI: −0.61, −0.26; P = 0.00). For cardiovascular risk factors, the LCD intervention significantly reduced triglycerides concentration (WMD: −0.33; 95% CI: −0.45, −0.21; P = 0.00) and increased HDL cholesterol concentration (WMD: 0.07; 95% CI: 0.03, 0.11; P = 0.00). But the LCD was not associated with decreased level of total cholesterol and LDL cholesterol. Subgroup analyses indicated that short term intervention of LCD was effective for weight loss (WMD: −1.18; 95% CI: −2.32, −0.04; P = 0.04).

Conclusions: The results suggested a beneficial effect of LCD intervention on glucose control in patients with type 2 diabetes. The LCD intervention also had a positive effect on triglycerides and HDL cholesterol concentrations, but without significant effect on long term weight loss.

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Contents

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1. Introduction

Diabetes mellitus is the dominant cause of a range of complications and death worldwide. Approximately 422 million people are living with diabetes in 2014 [1]. Type 2 diabetes patients usually accompanied with overweight or obesity, and excessive body mass index (BMI) increases result in the risk of diabetes rises [2]. A traditional diet of energy-restriction, high-carbohydrate, low-fat and low-protein have been recommended for the weight loss of diabetes patients [3]. However, in recent years, studies demonstrate that dietary carbohydrates are a major factor in blood glucose control, and it can aggravate postprandial glucose responses [4,5]. Therefore, the program of carbohydrate restriction was proposed to use to lose weight in many studies, and the efficacy of low carbohydrate diet (LCD) for diabetes management also has been widely discussed by researchers.

The LCD is a program which carbohydrate intake is less than 130 g/day or 26% of daily energy from carbohydrates [4]. Previous studies indicate that LCD can reduce blood glucose and body fat, improve insulin sensitivity, and decrease triglyceride and cholesterol levels among patients with diabetes [6–9]. In a randomized controlled trial (RCT), intervention with LCD has been found to reduce weight, HbA1c, and the level of fasting insulin [10]. Moreover, based on the present researches, the American Diabetes Association (ADA) considers that LCD is similarly effective for weight loss compared with low-fat calorie-restricted diets [11].

But, over the past decades, the issue of carbohydrate restriction has still been a controversial problem, particularly in patients with type 2 diabetes. Although dietary carbohydrates increase postprandial blood glucose levels, total carbohydrate restriction will not return the blood glucose to the normal range [5]. According to the research by Davis et al., one year LCD intervention has a similar effect on weight loss and glycemic control compared with a low-fat diet [12]. Other several studies concern that low-carbohydrate high-fat diet may aggravate the lipid profile, cardiovascular risk factors of patients with diabetes [13]. Two cohort studies indicate that the LCD group based on animal source protein has a greater increase in all-cause mortality [14].

Thus, considering the potential efficacy of LCD in type 2 diabetes management, we conducted this systematic review and meta-analysis of RCTs to evaluate the overall effect of LCD on weight loss, blood glucose, and blood lipid concentrations in diabetic patients.

2. Materials and methods

2.1. Literature search

We searched MEDLINE, EMBASE, and the Cochrane Library database from inception through January 2017. There were no publication time and language restriction. The relevant articles were identified using the following search items: ("low carbohydrate diet" OR "ketogenic diet" OR "Atkins diet") AND ("diabetes" OR "diabetes mellitus"). In addition, we searched reference lists of included studies and other potentially relevant studies. We would request original information from the authors by e-mail if research data was incomplete.

2.2. Study selection

The following inclusion criteria were implemented to identify studies to be included in our meta-analysis: (1) RCTs; (2) target population was patients with type 2 diabetes mellitus; (3) the patients received low carbohydrate diet (less than130 g carbohydrate/day or 26% of daily energy from carbohydrates); (4) the patients in the control group received normal or high carbohydrate diet; (5) studies that reported the change in body weight, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-c) and LDL cholesterol (LDL-c). Two investigators (HB and YM) independently screened the titles and abstracts of the articles according to the inclusion criteria. In the full-text screening stage, the authors must reach a consensus to determine which study should be included or removed. Any disagreements in the results of studies screened were resolved by discussion with a third author (ZPL).

2.3. Data extraction and quality assessment

The following information was independently extracted by two authors (HB and Zhaoping Li) from eligible studies (author, publication year, country, sample size, intervention measures, length of follow-up, and outcome). We extracted the outcomes of mean differences based on changes from baseline. When the studies measure outcomes in a variety of ways, we would convert the results to a uniform scale. The former unit was converted to conventional units (e.g., TC, HDL-c and LDL-c: 1 mg/dl converted to 0.02586 mmol/l; TG: 1 mg/dl converted to 0.0113 mmol/l; blood glucose: 1 mg/dl converted to 0.0555 mmol/l). The quality assessment of included studies was preformed by the modified Jadad scale [15], in which the random sequence generation, concealment of allocation, double blinding, withdrawals, and dropouts were evaluated. Each study received a score from 0 to 7, and a score of more than 4 was considered to be of high quality.

2.4. Statistical analysis

The continuous variable outcomes from the included studies were extracted. We used these data to calculate the WMD with the 95% CI. In the process of analysis, all the standard error of the mean (SEM) were transformed into the standard deviation (SD) by using the formula $SD = SE \times \sqrt{N}$ [16]. The Q tests and I^2 statistics were used to assessed the statistical heterogeneity between the included studies. $P < 0.10$ or $I^2 > 50\%$ was considered to represent significant heterogeneity, and the random-effects model was used. Otherwise, the fixed-effects model would be selected. If significant heterogeneity was shown, subgroup analysis was preformed to explore the potential source of heterogeneity. If more than 10 studies were included, the sensitivity analysis was evaluated using single study remove approach, and then we recalculated the results [17]. Publication bias was assessed by visual inspection of funnel plots and Egger linear regression test. All Data was analyzed using STATA version 12.0 (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Results of the literature search

Fig. 1 shows the flow diagram of the study selection process. We initially identified 2322 potentially study in the literature search, of which 611 were duplicates articles. After title and abstract review, 1676 were excluded because the studies did not meet the inclusion criteria. Among the remaining studies, 6 were non-RCTs, 3 were systematic review and 2 trials did not report the relevant outcomes. The target population of 3 studies was not type 2 diabetes. Finally, full-text assessment of relevant articles resulted in 9 studies were considered to be selected for the meta-analysis.

3.2. Study characteristics

The baseline characteristics of the 9 trials are listed in Table 1. The total participants of included studies were 734 cases and the number of patients in each trial ranged from 24 to 174. The length of follow-up varied from 3 to 24 months. All 9 studies provided the complete data on HbA1c and triglycerides levels. Five studies [10,18–21] reported the effect of LCD on fasting glucose, and 8 studies [10,12,18,20–24] reported
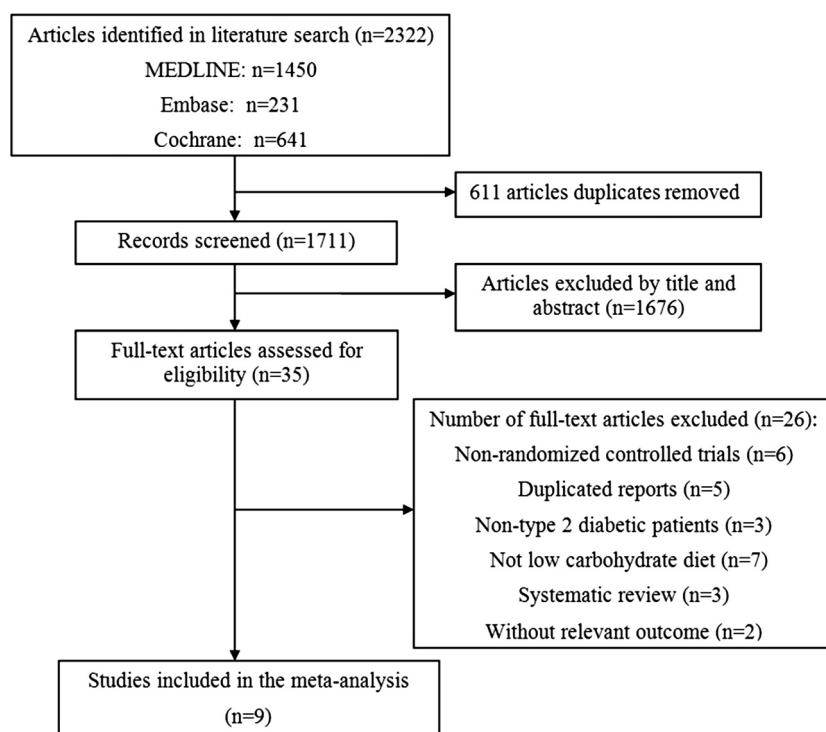

Fig. 1 – Flow diagram of literature searching and selection.

Table 1 – Characteristics of included studies in meta-analysis.

First author	Year	Country	Number of Participants (L/C)[†]	Intervention measures		Length of follow-up	Quality scores
				Treatmet group	Control group		
Tay [18]	2014	Australia	58/57	14% Carbohydrate	53% Carbohydrate	12 Weeks	4
Davis [12]	2011	USA	55/50	5% Carbohydrate	55% Carbohydrate	12 Months	3
Guldbrand [22]	2012	Sweden	30/31	20% Carbohydrate	60% Carbohydrate	24 Months	4
Iqbal [19]	2009	USA	70/74	<30 g Of carbohydrate daily	Unclear	24 Months	2
Daly [24]	2005	UK	51/51	<70 g Of carbohydrate daily	Unclear	3 Months	5
Saslow [20]	2014	USA	16/18	20–50 g Of carbohydrate daily	45–50% Carbohydrate	3 Months	5
Goldstein [21]	2011	Israel	26/26	20–25 g Of carbohydrate daily	Unclear	6 months	2
Westman [10]	2008	USA	48/49	<20 g of carbohydrate daily	55% Carbohydrate	24 Weeks	4
Yamada [23]	2014	Japan	12/12	Carbohydrates: 70–130 g/day	50–60% Carbohydrates	6 Months	2

[†] L: low carbohydrate diet group; C: control group.

the weight loss of patients. Six studies [10,12,18,19,21,22] investigated the outcomes of total cholesterol, and 7 studies [10,12,18–20,22,23] investigated LDL-c. All studies except one investigated the HDL-c levels [10,12,18–23].

3.3. Study quality

Among the included studies, 5 trials [10,18,20,22,24] were considered as high the quality study (a modified Jadad score $\geq$4). All studies in which participants received LCD were not blinded. As these trials were dietary intervention study, they were not possible for the researchers and patients to be blinded to group allocation.

3.4. Effect of LCD on weight loss

The primacy outcome was the mean change in weight loss, which is shown in Fig. 2. Pooled results of 9 eligible studies revealed that LCD decreased the weight of patients with diabetes. But compared with the control group, the weight loss of LCD group was not significant difference (WMD: −0.94; 95% CI: −1.92, 0.05; P = 0.06). The statistical heterogeneity

was not identified (I^2 = 35.5%, P = 0.14). Therefore, we used the fixed-effects model for analysis.

3.5. Effect of LCD on FPG and HbA1c

The pooled result demonstrated no effect of LCD on the change of FPG concentration of patients with diabetes (WMD: −0.05; 95% CI: −0.58,0.47; P = 0.84) (Fig. 3A). Fig. 3B also shows the association between the LCD and reduction of HbA1c level. meta-analysis indicated that HbA1c level was significantly decreased in the LCD group compared with the control group (WMD: −0.44; 95% CI: −0.61,−0.26; P = 0.00). No significant heterogeneity was found in each test (FPG: I^2 = 0%, P = 0.50; HbA1c: I^2 = 19.6%, P = 0.26).

3.6. Effect of LCD on blood lipid concentrations

The pooled results of blood lipid concentrations are shown in Fig. 4. meta-analysis showed that LCD connected with a reduced concentration of TG in patients with diabetes (WMD: −0.33; 95% CI: −0.45, −0.21; P = 0.00) (Fig. 4B). The test for heterogeneity was no statistical significance (I^2=0%,
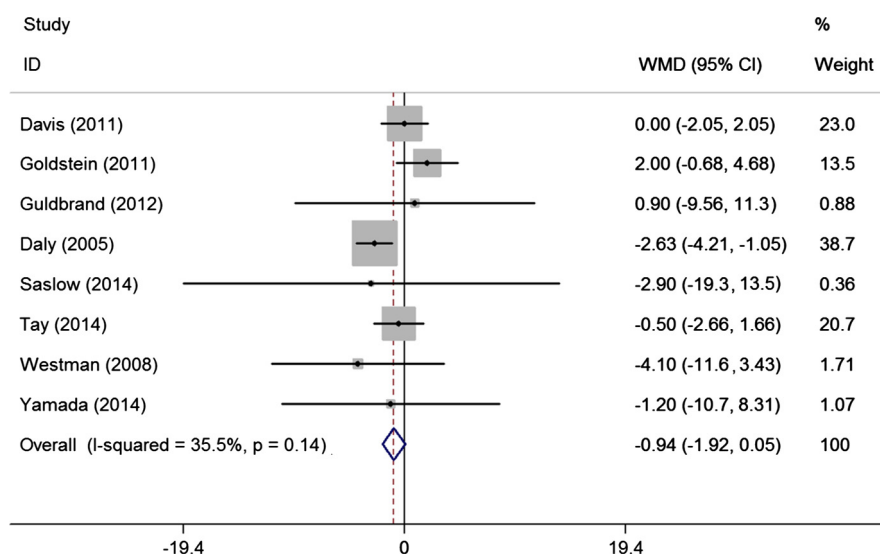

Fig. 2 – Forest plot for the effect of low carbohydrate diet on weight loss.
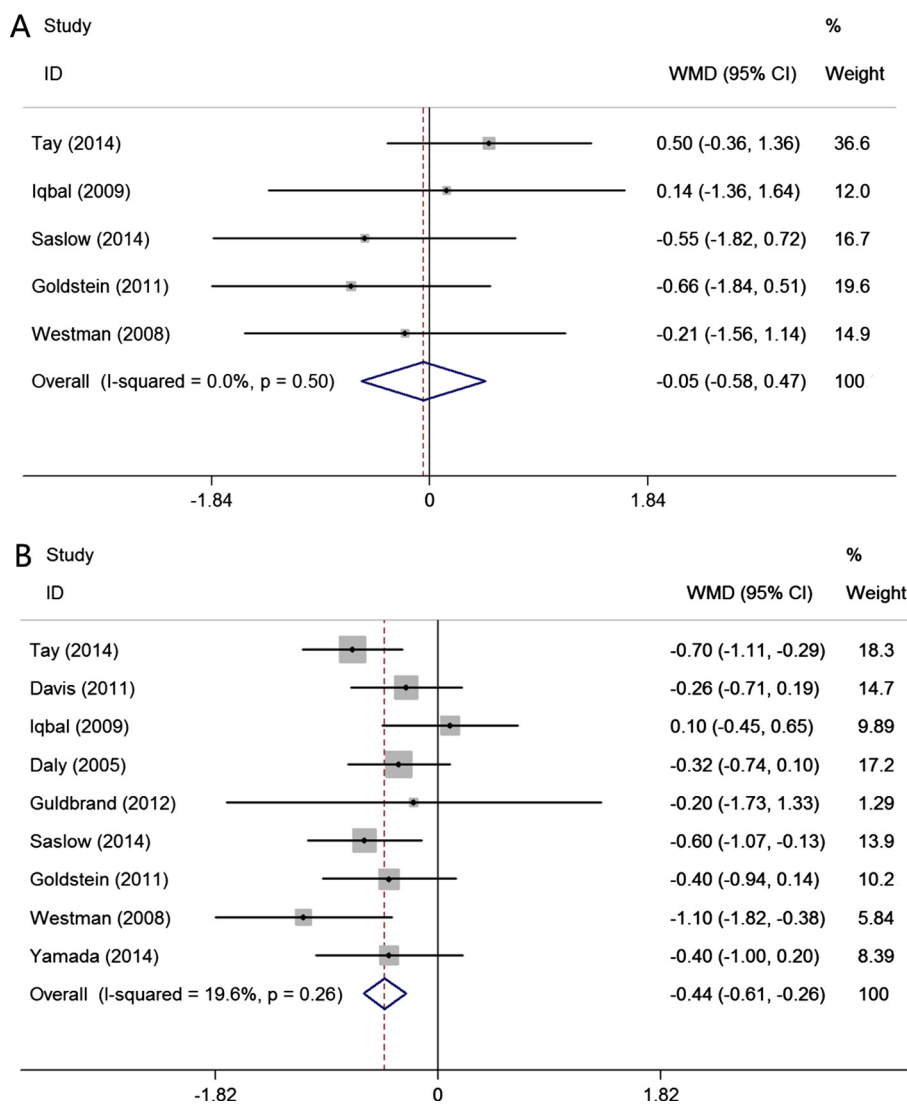
Fig. 3 – Forest plot for the effect of low carbohydrate diet on FPG (A) and HbA1c (B).

$P = 0.72$). The mean difference in HDL-c between the LCD and control group were estimated as 0.07 (95% CI: 0.03, 0.11; $P = 0.00$) (Fig. 4C). The result indicated that LCD significantly improved the level of HDL-c. There was no significant heterogeneity among the included studies ($I^2 = 40.6\%$, $P = 0.108$). Six studies reported TC, which were not significantly different between the groups (WMD: 0.06; 95% CI: −0.08, 0.21; $P = 0.33$) (Fig. 4A). The pooled of 7 studies also did not show any significant difference about LDL-c in two groups (WMD: 0.04; 95% CI: −0.08, 0.16; $P = 0.53$) (Fig. 4D). Meanwhile, meta-analysis on TC and LDL-c indicated no statistical heterogeneity was found (TC: $I^2 = 0\%$, $P = 0.63$; LDL-c: $I^2 = 0\%$, $P = 0.97$), and fixed-effects model was used.

Subgroup analyses according to length of follow-up showed that short term effect of LCD intervention on weight loss was greater than long term (Fig. 5). The LCD intervention significantly decreased body weight in the subgroup which lasted less than 12 months (WMD: −1.18; 95% CI: −2.32, −0.04; $P = 0.04$). But no significant effect on weight loss was observed in the longer term group (WMD: −0.24; 95% CI: −2.18, 1.7; $P = 0.81$).

3.7.   Publication bias

Visual inspection of funnel plots and Egger test suggests no evidence of publication bias for the LCD on FPG ($P = 0.28$), HbA1c ($P = 0.98$), TC ($P = 0.78$), TG ($P = 0.75$), HDL-c ($P = 0.57$), LDL-c ($P = 0.37$), and weight loss ($P = 0.80$).

4.   Discussion

Our meta-analysis is the first one to evaluate the efficacy of LCD for type 2 diabetes management. Nine RCTs with 734 participants were included in our current research. The finding from this meta-analysis suggested that LCD intervention had a positive effect on HbA1c, TG, and HDL-c concentrations. There was no significant efficacy of LCD in improving TC and LDL-c concentrations. The result also indicated that LCD intervention reduced the body weight of patients, but it did not achieve statistical significance. However, the subgroup analyses indicated that LCD was effective for weight loss in the shorter term.
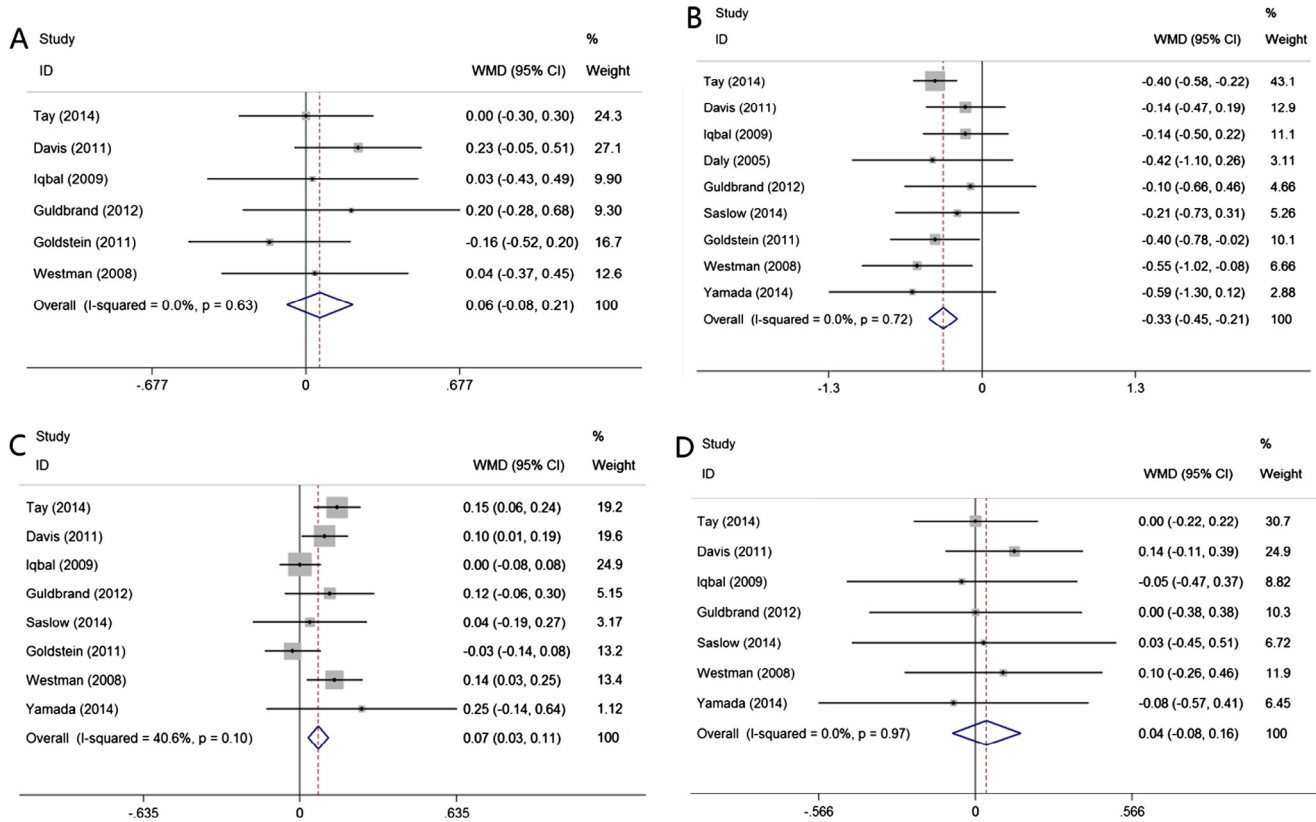
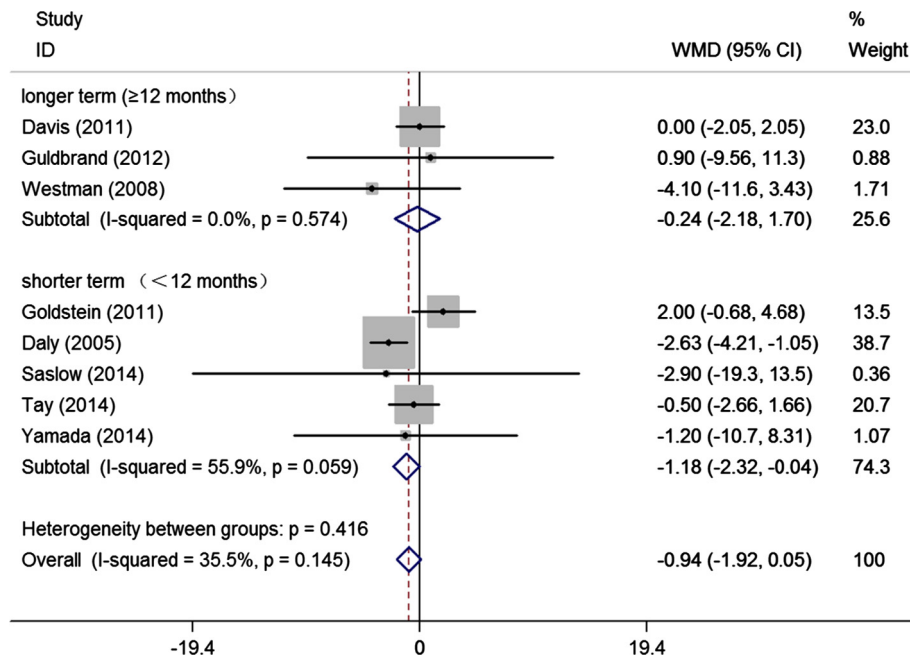Fig. 4 – Forest plot for the effect of low carbohydrate diet on TC (A), TG (B), HDL-c (C), and LDL-c (D).

Fig. 5 – Subgroup analyses of the effect of low carbohydrate diet on weight loss in different study duration.

In overweight and obese patients with diabetes, modest weight loss is considered effective to improve insulin resistance [11]. A recent meta-analysis had shown that a very low carbohydrate ketogenic diet (VLCKD) achieves greater reductions in body weight for overweight and obese patients [25]. But we failed to observe a significant association between the LCD intervention and weight loss. The finding might be explained by several reasons. Firstly, instead of including

the overweight and obese patients in the previous meta-analysis, our research only included the patients with diabetes who received the LCD. Secondly, in our meta-analysis, the mean changes from baseline of body weight at longer term were extracted. But an obvious weight regain was observed in the LCD group after 6 months intervention in several studies [12,21]. Therefore, the weight regain might directly affect the association between the LCD and weight loss. Finally, recently research shows that an isocaloric low carbohydrate ketogenic diet was accompanied by a small increase in energy expenditure, and the influence had waned over time. Furthermore, a slowing of fat loss was observed in this study, and the primary cause for weight loss of participants might be the loss of water [26].

In the present meta-analysis, although no significant association between the LCD and FPG was found, but FPG was affected by many uncertainties. The result indicated that LCD exerted a beneficial effect on HbA1c, which represented the secular variation of blood glucose level. The possible explanation for the positive finding might be attributed to the improvements in glucose metabolism and insulin sensitivity. The low carbohydrate diet also produced a greater reduction in insulin dose, and that the reduction of insulin might promote weight loss. In addition, the LCD might directly affect hepatic glucose output and glucose utilization through the production of ketone bodies [27,28].

The beneficial effects on TG and HDL-c were consistent with several previous studies [18,29,30], and the levels of these two indicators reflected the important risk of coronary heart disease [31]. The former research considered that the VLCKD would have no benefit for non-obese diabetes patients, because weight loss might be the main reason for anti-diabetic [32]. In our meta-analysis, the weight range of enrolled patients was not be limited, and some normal patients were also included in several studies [22,23]. Therefore, our results suggested that the benefit of LCD might be independent of weight loss. A similar conclusion was also confirmed in a study of normal weight men [33]. A short term VLCKD was thought to improve TG and HDL-c without change in body weight. Our study did not identify that the LCD was more effective in decreasing both TC and LDL-c concentrations compared normal or high carbohydrate diet. This might be due to the increased intake of cholesterol and diet saturated fat [34]. Traditionally, a high intake of saturated fat associated with increased risk for cardiovascular disease. Furthermore, the significant increase of LDL-c concentration was usually considered a primary indicator of cardiovascular risk [4]. According to the results of this meta-analysis, there was no evidence that LCD had any adverse effect on LDL-c and TC.

The present meta-analysis is the first study to focus on type 2 diabetes mellitus patients. Only RCTs were included in our meta-analysis in order to reduce the confounding bias. The tests for heterogeneity were not significantly. Moreover, we did not find any evidence of publication bias. However, this meta-analysis had several limitations. Firstly, the quality scores of included studies varied from low to high, and only 5 studies were considered as high quality. One of the primary reasons was that these studies were unlikely to use blinding and concealment of allocation. Secondly, although patients had all received LCD in this meta-analysis, it was different that carbohydrate intake ranged from 5% to 20% of daily energy from carbohydrates. The carbohydrate content may directly lead to high heterogeneity and affect the summarized results.

Considering the current situation in the application of LCD, we believe that several questions need to be solved in the future. Among the included studies of this meta-analysis, the length of intervention time ranged from 3 to 24 months. Some studies indicated that the short term effects of LCD on weight loss tend to be greater compared long term effects [12,21]. Similar, the weight regain was shown in previous studies. Foster et al. demonstrated that 6 months low carbohydrate Atkins diet intervention caused obvious weight loss in obese patients. But there was not significantly different in weight loss at 12 months [31]. The reasons might be attributed to dietary compliance or a metabolic response of the body [35]. The current theory holds that body weight management needs a continuous improvement program. Therefore, long term compliance of carbohydrate restriction dietary is a key issue for weight loss. Future studies should improve the dietary compliance and focus on the long-term efficacy of LCD.

5.   Conclusion

In conclusion, LCD intervention showed a beneficial effect on improving HbA1c level compared with the high or normal carbohydrate dietary, suggesting LCD might be effective for type 2 diabetes management. The result also suggested that LCD may be beneficial to cardiovascular risk factors, according to summaries of data of TG and HDL-c concentrations. But, there was no evidence to show that LCD was effective for reducing TC and LDL-c concentrations. Although no significant association was found between the LCD and weight loss throughout the duration of intervention, the subgroup analyses indicated short term effect was obvious. In the future, further researches on the long term effect of LCD on type 2 diabetes management in non-obese patients may be needed.

Conflicts of interest

None declared.

Funding source

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