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April 23, 2019

Systematic Review and Meta-Analysis of Very Low Carb Diets vs. Other Recommended Diets for Type-2 Diabetes Management

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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of Master of Public Health in Hubert Department of Global Health, 2019

Abstract

Systematic Review and Meta-Analysis of Very Low Carb Diets vs. Other Recommended Diets for Type-2 Diabetes Management

By

Ahmad Albediny

Objective

This study aims to examine the effect of very low carb diets compared to other recommended diets in the Glycated hemoglobin (HbA1c) outcome in patients with Type 2 diabetes by conducting a systematic review and meta-analysis of available RCTs.

Methods

We searched PubMed, Web of Science and the Cochrane Central Register of Controlled Trials. Only randomized controlled trials (RCTs) were included, which compared very low carb diets with other kinds of diets in diabetes type-2 patients. Meta-analysis using the fixed-effects model were conducted for the HbA1c outcome.

Results

A total of 11 studies involving 752 patients (368 in the low carb intervention group) were included in this analysis. Quantitative meta-analysis shows significant decrease in the HbA1c of type 2 patients after following very low carb for three and six months ((ES: 0.42; 95% CI: 0.19, -0.65 ; $P = 0.00$) (ES: 0.45; 95% CI: 0.27,-0.63 ; $P = 0.00$), respectively).

Conclusion

Very low carb diet is superior to other recommended kinds of diets in controlling HbA1c for patients with type 2 Diabetes mullites.

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Systematic Review and Meta-Analysis of Very Low Carb Diets vs. Other Recommended Diets for Type-2 Diabetes Management

Introduction

Although Diabetes mellitus is a manageable disease, it is still a critical public health issue worldwide with an estimated 1 in every 11 adults suffering from diabetes mellitus globally (90% T2DM) [12]. Type 2 diabetes mellitus complications are usually accompanied by high mortality and morbidity rate as they cause cardiovascular, kidney and neurological complications. Overweight and obesity are the leading risk factor in developing diabetes mellitus. Diet plays a significant role in managing type 2 diabetes. However, there is no optimal diet and patients have to adjust their diet towards their individual preferences [7]. American Diabetes Association is recommending three types of diets in order for diabetic patients to lose weight, these include: Low-carb, Low-fat, or a Mediterranean diet. It is also recommended that diabetic patients should count their carb intake and it has to be at least 150g/day [13].

Recent researches show that very low carb diets have a superior effect among other kinds of diets in glycemic control [7]. There are many concepts regarding exogenous carbohydrate in current nutrition literature that are important to consider, these include: glycemic index/load, fiber contents. Exogenous carbohydrate is the only source for muscle energy, glycogen, and energy for the brain. Although the current nutrition literature has started to look at these different factors, there remains a need to investigate more in depth their effect on the development of diabetes.

New studies are showing that hyperinsulinemia (excess insulin in the blood), a precursor to type-two diabetes and a major finding in prediabetes and metabolic syndrome, is the root cause of most of the ill effects of those conditions which illustrates some of the toxic effects of carbs. Furthering this view, several studies have shown that alcohol has similar toxic effects of fructose on the liver causing what is known as the nonalcoholic fatty liver disease.

Examining carbs as low glycemic vs. high glycemic, shows the rate of blood glucose increase after a meal. While they both have adverse health effects on the body, the only difference between the two, is the rate at which blood glucose levels become elevated. Many argue as well that we need carbs for survival which is inaccurate because it is a nonessential nutrient meaning the body can function normally without any external consumption. Given the similarities in the adverse health effects and metabolism of sugar and alcohol on the body, these should be considered together as their own macronutrient category.

There is also the addictive nature of carbs that have been shown in several studies and in what is known as the low carb diet community as the keto flu. This is a two week or longer withdrawal symptoms that starts when someone cuts carbs out of their diet that feels very much like the actual flu with severe cravings for sugars, body aches, and fatigue. In light of these findings and its potential to reverse type 2 diabetes, more attention and research into the low carb way of living is warranted. We are conducting this meta-analysis to add more evidence to the scientific knowledge base on this subject matter and highlight some of the key challenges facing the successful implementation of this method for type 2 diabetes management.

Objective

This study aims to examine the effect of very low carb diets compared to other recommended diets in the Glycated hemoglobin (HbA1c) outcome in patients with Type 2 diabetes by conducting a systematic review and meta-analysis of available RCTs.

Methodology

A) Search Strategy and Study Selection

This study was conducted with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. IRB review was not required (a note of exemption was received from Emory University). Searching published articles in PubMed, the Web of Science, and Cochrane Central Register of Controlled Trials was done with no date restrictions. The search was limited to human subjects and studies only published in English. Only randomized control trials studies were included. Studies were selected to meet these inclusion criteria: 1) Type 2 Diabetic patients and 2) the intervention to be assessed was the low carb diet with less than 50g/day. Only studies comparing low carb diets with any other types of diets, were included with the follow up of at least three months. Studies had HbA1C as a primary or secondary outcome. Articles in different languages and subjects less than 18 years of age were excluded. Reports or descriptive studies were also excluded.

Search terms and synonyms identified by Medical Subject Heading (MeSH) were used to find relevant articles in PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials databases:

1- "Diabetes" OR "diabetes mellitus"

2- "ketogenic diet" OR "low carbohydrate diet" OR "Atkins diet"

B) Data Extraction and Quality Assessment

Relevant data were extracted and summarized from eligible studies: author name, publication year, country, intervention and control measures, participants and length of follow up.

The quality assessment of included studies was performed by the Jadad Scale/Oxford Quality Scoring System in which, the randomization present, randomization method, blinding present, blinding method and appropriate long-term follow up on all patients were evaluated. Each study received a score from 0 to 5, and a score of 3 or more was considered to be of high quality (Table 1).

STUDY	RANDOMIZATION PRESENT(1 PT)	APPROPRIATE RANDOMIZATION UTILIZED(1 PT)	BLINDING PRESENT (1 PT)	APPROPRIATE BLINDING METHOD UTILIZED (1 PT)	APPROPRIATE LONG-TERM FOLLOW-UP ON ALL PATIENTS (1 PT)	SCORE TOTAL (5 PTS POSSIBLE)
Samaha, F F 2003 [1]	1	1	0	0	1	3/5
Westman, E 2008 [2]	1	1	1	0	0	3/5
Davis,N 2009 [3]	1	1	0	0	1	3/5
Iqbal,N 2010 [4]	1	1	0	0	1	3/5
Mayer, S B 2014 [5]	1	1	0	0	0	2/5
Tay, J 2014 [6] and follow up at 2015 [8]	1	1	1	1	1	5/5
Saslow, LR 2014 and followup at 2017 [7] [10]	1	1	1	1	1	5/5
Goday, A 2016 [9]	1	1	0	0	1	3/5
Saslow, LR 2017 [11]	1	1	0	0	1	3/5

Table 1 : Quality assessment of included studies by Jadad Scale Scoring, 2019

C) Statistical Quantitative Analysis

In order to examine the effect of the intervention of a very low carb diet (less than 50g carb/ day) and its association with the HbA1c, we ran a meta-analysis after grouping the studies according to

the follow-up length, three months, six months and 12 or more months. Meta-analysis and heterogeneity were tested after calculating the difference mean effect between the groups and the standard error (SE). Heterogeneity was identified if the I-square was equal to or more than 30 %. A fixed effect model was used as the results were all homogenous. Publication bias was assessed by funnel plot and Egger's regression test. Stata 15 was used for all of these analysis.

Results

A) Study Selection

Electronic searches conducted in PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials yielded 435 potential studies in the literature search, of which 108 were duplicate articles. After screening by title and abstract, we excluded 244 studies because they did not meet the inclusion criteria. Full-text screening of the remaining 83 resulted in 64 exclusions for not meeting the eligibility criteria. Another eight studies were excluded during the data extraction because of either no HbA1c measures or non-diabetic population. Therefore, 11 studies were included in the final analyses (Figure 1).
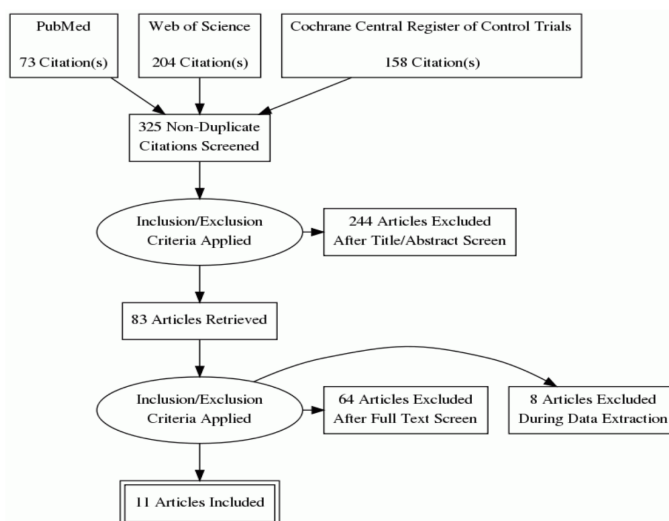

Figure 1: Selection process for Systematic Review and Meta Analysis of a low carb (Keto Diet) vs. High Carb diet for Type-2 diabetes management, 2019

B) Studies Characteristics

The total participants of the included studies were 752 cases, with 368 participants assigned to the very low carb diet intervention. The length of follow-up varied from 3 to 24 months. All 11 studies provided complete data on HbA1c (Table 2).

Author, Year	Country	Intervention measures		Number of Participants (I/C)*	Length of Follow up	Quality Assessment
		Intervention Group	Control Group(s)			
Samaha, F F 2003 [1]	USA	35 g carb/day	low fat calorie restricted	64/68	6 months	High
Westman, E 2008 [2]	USA	20g carb/day	low glycemic reduced calorie diet	38/46	24 weeks	High
Davis,N 2009 [3]	USA	20–25 g carb /day	low-fat diet modeled after Diabetes Prevention Program	55/50	12 months	High
Iqbal,N 2010 [54	USA	30g carb/ day	low fat reduced calorie diet	70/74	24 months	High
Mayer, S B 2014 [5]	USA	20 g carb / day	Restricted calories low fat diet + Orlistat	22/24	48 weeks	Low
Tay, J 2014 [6] and follow up at 2015 [8]	Australia	<50g carb/ day	High carb diet	46/47	24 weeks	High
Saslow, LR 2014 and followup at 2017 [7] [10]	USA	≤50 g carb/day	MCCR Diet**	16/18	3 months, 12 months	High
Goday, A 2016 [9]	Spain	<50g carb /day	low-calorie diet based on the American Diabetes Association guidelines	45/44	4 months	High
Saslow, LR 2017 [11]	USA	Very Low-Carbohydrate Ketogenic Diet 20–50 g of carb/day	American Diabetes Associations' "Create Your Plate" Diet	12/13	32 weeks	High

**Medium carbohydrate, low fat, calorie-restricted, carbohydrate counting diet (MCCR) consistent with guidelines from the American Diabetes Association *I = Intervention C= Control

Table 2. Characteristics of included studies in the meta analysis, 2019

C) Quality Assessment

Among the 11 included studies, 10 studies [1] [2] [3] [4] [6] [7] [8] [9] [10] [11] were considered as high-quality studies (by the Jadad Scale/Oxford Quality Scoring System ≥3) and only one study was of low quality [5].

D) Quantitative Analysis Results

The pooled results show significant association between low carb diet and HbA1c reduction in the levels of 3 months (ES: 0.42; 95% CI: 0.19,−0.65 ; P = 0.00) (Figure 2) and 6 months (ES: 0.45; 95% CI: 0.27,−0.63 ; P = 0.00) (Figure 3) compared to the control groups . However, at 12 months, there was no significant effect on the intervention group compared to the control group (ES: 0.134; 95% CI: -0.09, 0.358; P = 0.24) (Figure 4). There was no heterogeneity observed among the 3- and 6-months subgroups, but insignificant heterogeneity (23%) was observed in the 12 months subgroup.

```
            Study     |    ES    [95% Conf. Interval]    % Weight
--------------------+------------------------------------------------
Westman 2008 [2]    |   0.800    -0.616    2.216           2.62
Davis 2009 [3]      |   0.380    -0.111    0.871          21.79
Goday 2016 [9]      |   0.500    -0.051    1.051          17.31
Saslow 2017 [11]    |   0.400     0.100    0.700          58.29
--------------------+------------------------------------------------
I-V pooled ES       |   0.423     0.194    0.652         100.00
--------------------+------------------------------------------------

  Heterogeneity chi-squared =    0.40 (d.f. = 3) p = 0.940
  I-squared (variation in ES attributable to heterogeneity) =    0.0%

  Test of ES=0 : z=   3.62 p = 0.000
```
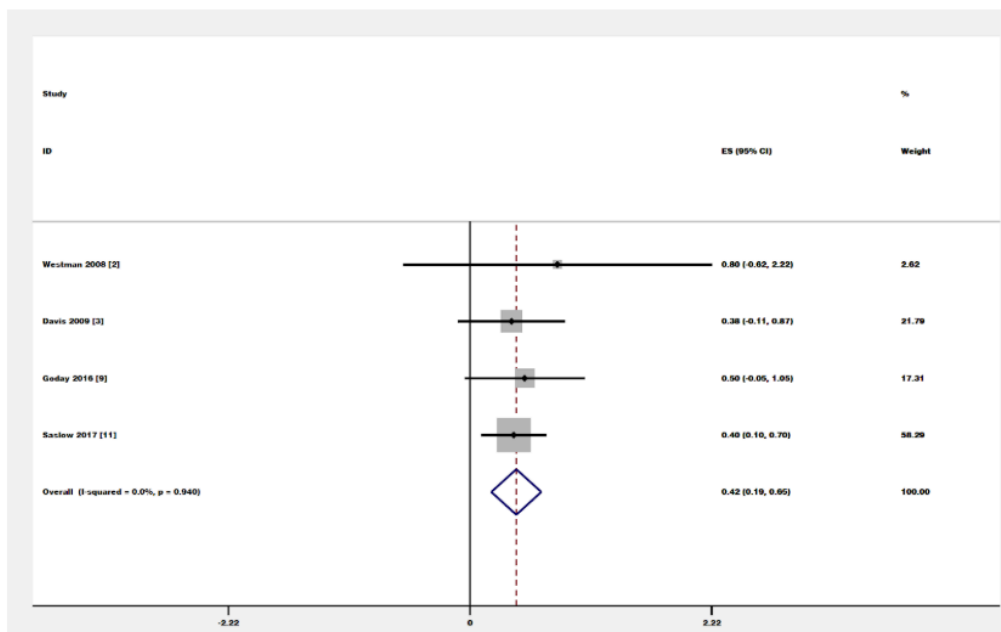

Figure 2: Forest plot for the effect of low carbohydrate diet on HbA1c at 3 months.

```
. . metan diff6 diffsse6 , label (namevar=study)

            Study      |    ES    [95% Conf. Interval]    % Weight
--------------------+------------------------------------------------
Samaha 2003 [1]     |  0.600    -0.269    1.469           4.35
Westman 2008 [2]    |  1.000    -0.548    2.548           1.37
Davis 2009 [3]      |  0.140    -0.250    0.530          21.58
Iqbal 2010 [4]      |  0.400    -0.160    0.960          10.49
Saslow 2014 [7]     |  0.400    -0.186    0.986           9.56
Tay 2014 [6]        |  0.700     0.249    1.151          16.16
Saslow 2017 [11]    |  0.500     0.200    0.800          36.49
--------------------+------------------------------------------------
I-V pooled ES       |  0.446     0.265    0.627         100.00
--------------------+------------------------------------------------

  Heterogeneity chi-squared =   4.37 (d.f. = 6) p = 0.627
  I-squared (variation in ES attributable to heterogeneity) =   0.0%

  Test of ES=0 : z=  4.82 p = 0.000
```
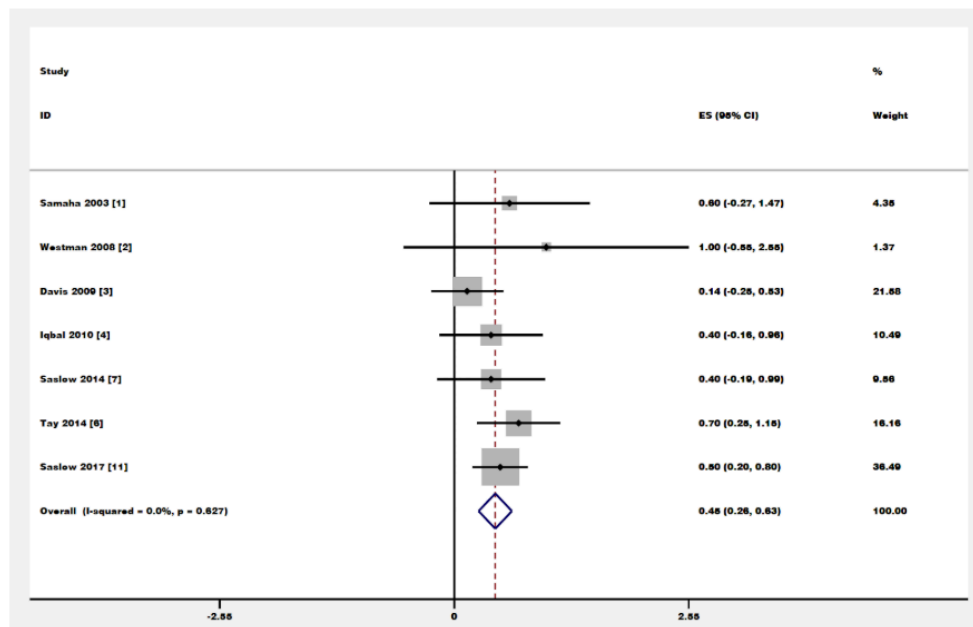

Figure 3: Forest plot for the effect of low carbohydrate diet on HbA1c at 6 months

```
. . metan diff12 diffsse12 , label (namevar=study)

              Study    |    ES      [95% Conf. Interval]    % Weight
---------------------+---------------------------------------------
Davis 2009 [3]        |   0.260    -0.190     0.710          24.79
Iqbal 2010 [4]        |  -0.200    -0.760     0.360          16.02
Mayer 2014 [5]        |   0.800     0.010     1.590           8.04
Saslow 2014 [10]      |   0.300    -0.336     0.936          12.40
Tay 2015 [8]          |   0.000    -0.360     0.360          38.74
---------------------+---------------------------------------------
I-V pooled ES         |   0.134    -0.090     0.358         100.00
---------------------+---------------------------------------------

  Heterogeneity chi-squared =    5.19 (d.f. = 4) p = 0.268
  I-squared (variation in ES attributable to heterogeneity) =  23.0%

  Test of ES=0 : z=   1.17 p = 0.241
```
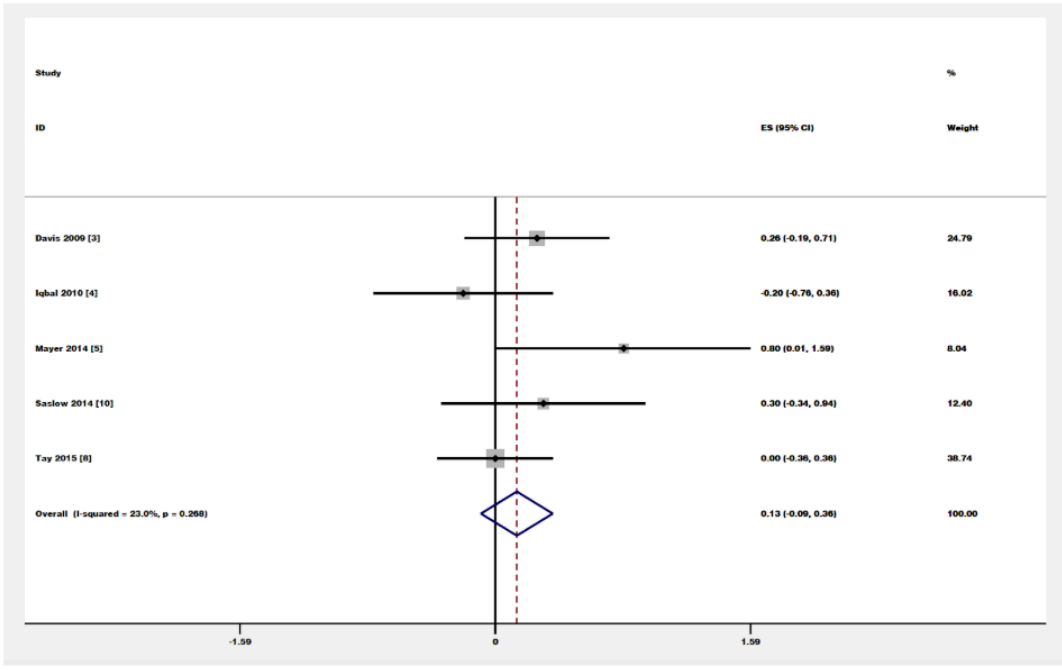

Figure 4:Forest plot for the effect of low carbohydrate diet on HbA1c at 12 months

F) Publication Bias Results

By inspection of funnel plots and Egger's regression tests, there was no evidence of publication
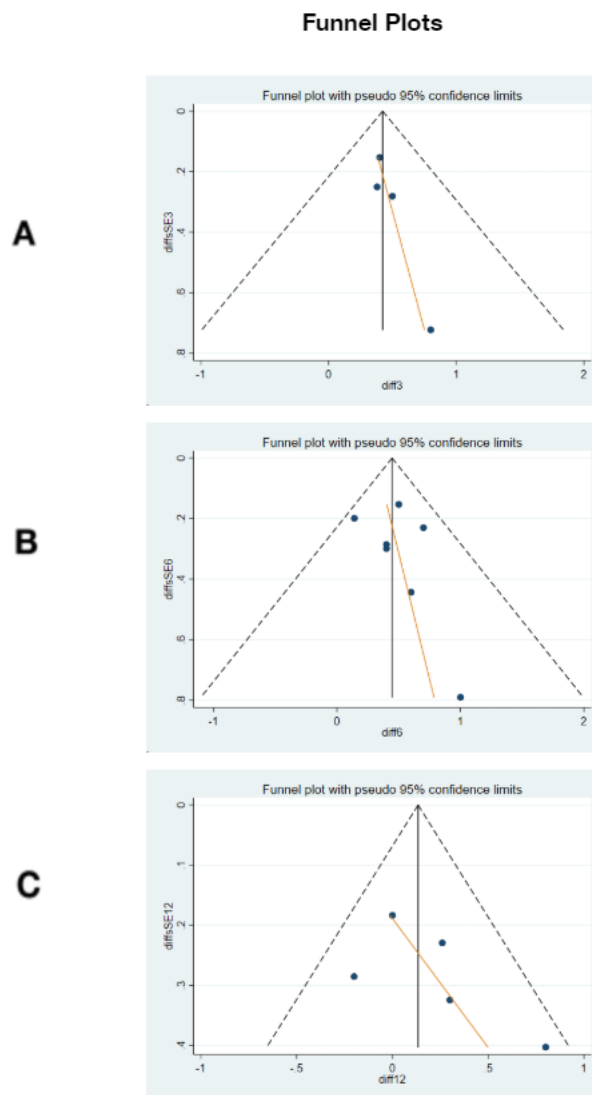
bias on HbA1c levels.

Funnel Plots

Figure 4: Funnel Plots and Eager's regression line for a low carbohydrate diet on HbA1c
   A) 3 months
   B) 6 months
   C) 12 months

Discussion

This review of 11 RCTs is the first meta-analysis to compare the effect of strict low carb diet with other kinds of diets to manage the blood glucose (HbA1c) in type 2 diabetes mellitus patients. Our finding suggests that a strict low carb diet with less than 50 gram /day (4 to 10% of daily energy) can benefit type 2 diabetic patients in managing their HbA1c level. After subgroup analysis of the LCD duration, we found that the glycated hemoglobin significantly decreased after three and six months of the intervention. However, this finding seems to fade with time as by the 12-month time period, there was no significant change. This could be affected by dropout rate and diet adherence difficulties.

The main strength of the present meta-analysis is our selection criteria that only included randomized control trials with strict carb diet intervention (just 5 to 10% energy driven from carbs) were included. Among the 11 trials included, 10 trials were of high-quality studies. Also, the absence of the heterogeneity in our findings and the absence of publication bias further strengthen the findings from this study. However, our study investigated the HbA1c outcome only and did not investigate other clinical conditions such as weight.

 A previous meta-analysis of nine trials among type 2 diabetic patients has reported that low-carbohydrate diets resulted in a significant decrease of HbA1c in the intervention group compared to the control group [14]. Another meta-analysis of 36 RCTs and CCTs also found that patients with type 2 diabetes can benefits from low carb diets in decreasing their HbA1c in the short and medium term, but this effect tends to fall after one year of the intervention [15]. These results are consistent with our meta-analysis results.

Implications of the findings

Patients with type 2 diabetes are recommended to follow the very low carb diet to control their blood glucose as it is superior to other recommended kinds of diets. We encourage health stakeholders and ministries of health to apply a policy that encourage these patients to follow these types of very low carb diets.

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