

Revisión

# Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks

L. M. Castañeda-González<sup>1</sup>, M. Bacardí Gascón<sup>2</sup> and A. Jiménez Cruz<sup>2</sup>

<sup>1</sup>Doctorate student. Universidad Autónoma de Baja California. Facultad de Medicina y Psicología. Posgrado en Nutrición. Tijuana. México. <sup>2</sup>Professor. Medical and Psychology School. Universidad Autónoma de Baja California. Facultad de Medicina y Psicología. Tijuana. México.

Abstract

**Introduction:** Low carbohydrate diets (LCD) have shown beneficial effects on short-term weight reduction programs for obese individuals without diabetes, but the long-term evidence of efficacy on individuals with type 2 diabetes is not conclusive.

**Objective:** To evaluate, the effectiveness of 12 or more weeks of LCD compared to Low Fat Diet (LFD), Usual Care Diet (UCD) or Low Glycemic Index Diet (LGID) on weight reduction and A1C on type 2 diabetes individuals.

**Methods:** A systematic review was conducted on randomized trials registered in PubMed, Cochrane and EBSCOhost from January 1<sup>st</sup> 2000 to January 1<sup>st</sup> 2010 including those with an intervention program with LCD in type 2 diabetes subjects and a follow-up  $\geq$  12 weeks. Available data on study design; carbohydrate composition of diet; duration of diet; and the outcomes of weight, lipid levels (total, low density lipoprotein and high-density lipoprotein cholesterol, and triglycerides), hemoglobin A1C percent and/or fasting glucose were extracted.

**Results:** Five studies showed greater weight reduction with LCD, of which four demonstrated no significant difference. The longest trial intervention studies did not show a difference in weight change. Only two studies showed greater reduction of A1C with LCD, including the longest intervention trial with a low carbohydrate Mediterranean diet.

**Conclusions:** This review shows that there are no consistent differences in weight and A1C changes over the long-term treatment with LCD and LFD, UCD or LGID.

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Key words: Low carbohydrate diets. Low fat diets. Type 2 diabetes. Weight. A1C. Lipids.

## EFFECTOS DE LAS DIETAS BAJAS EN CARBOHIDRATOS SOBRE EL PESO Y EL CONTROL GLICÉMICO EN INDIVIDUOS CON DIABETES TIPO 2: REVISIÓN SISTEMÁTICA DE ESTUDIOS ALEATORIZADOS DE MÁS DE 12 SEMANAS

Resumen

**Introducción:** Las dietas bajas en carbohidratos han demostrado, a corto plazo, efectos benéficos sobre la pérdida de peso en individuos obesos sin diabetes, sin embargo la evidencia sobre su efectividad a largo plazo en individuos con diabetes tipo 2 no es concluyente.

**Objetivo:** Evaluar el efecto de dietas bajas en carbohidratos (DBC) en intervenciones mayores a 12 semanas comparadas con dietas bajas en grasas (DBG), dietas de cuidado común (DCC) o dietas con bajo índice glicémico (DBIG), sobre la pérdida de peso y la hemoglobina glucosilada (A1C) en individuos con diabetes tipo 2.

**Métodos:** Se realizó una revisión sistemática de estudios aleatorizados publicados en PubMed, Cochrane y EBSCOhost del 1<sup>o</sup> de Enero del 2000 al 1<sup>o</sup> de Enero del 2010. Se extrajeron datos sobre el diseño del estudio, la composición de carbohidratos de la dieta, la duración de la dieta y resultados de cambios en peso, en porcentaje de A1C, glucosa en ayuno y lípidos sanguíneos.

**Resultados:** Cinco estudios mostraron mayor reducción de peso con DBC, de los cuales cuatro no demostraron diferencia estadística. El estudio de mayor tiempo de intervención no mostró diferencia en la pérdida de peso. Únicamente dos estudios mostraron mayor reducción en el porcentaje de A1C con DBC, incluyendo el estudio de mayor tiempo de intervención.

**Conclusiones:** Esta revisión muestra la falta de consistencia en las diferencias sobre los cambios en el peso y la A1C en intervenciones con seguimiento mayor de 12 semanas con DBC comparadas con DBG, DCC o DBIG.

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Palabras clave: Dietas bajas en carbohidratos. Dietas bajas en grasas. Diabetes tipo 2. Peso. A1C. Lípidos.

**Correspondence:** Arturo Jiménez Cruz.  
Unidad Universitaria.  
Calzada Tecnológico 14418. Mesa de Otay.  
22390 Tijuana. B. C. México  
E-mail: ajimenez@uabc.edu.mx

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## Introduction

As the prevalence of chronic diseases associated with obesity persists in high levels, methods to accomplish long-term or permanent metabolic control remains unclear.<sup>1,2,3,4</sup> The American Diabetes Association recommends that diabetes treatment should include lifestyle changes, such as a low fat, low carbohydrate and a reduced calorie diet, in order to reduce cardiovascular risk factors and increase insulin sensitivity.<sup>5,6</sup>

Low carbohydrate diets have shown beneficial effects on short-term weight reduction programs on obese individuals without diabetes, but the evidence over the long-term efficacy and safety on individuals with type 2 diabetes is not conclusive.<sup>7,8</sup>

The lack of a standard definition of low carbohydrate diets is associated with the effect variation of different carbohydrate amounts over metabolic markers.<sup>9</sup> The American Diabetes Association designates low carbohydrate diets as less than 130 g/d of a nominal 2,000 kcal diet considering a reasonable cutoff for the definition of a low carbohydrate diet; a 26% to 45% of the total caloric intake, as the range for moderate-carbohydrate diet; and intake of less than 30 g/d, as noted above should be referred to as a very low carbohydrate ketogenic diet (VLCKD).<sup>10</sup> However, the American Diabetes Association also recommends reducing carbohydrate intake to no less than 130 g/day.<sup>11</sup> The rationale to this is the requirement of glucose as the source of energy for the brain and the central nervous system, and the need for the water-soluble vitamins, minerals, and dietary fiber provided by foods with carbohydrates.<sup>12,13</sup> However, some authors have proposed the reduction of carbohydrates to < 130 g/day.<sup>14,15</sup> Reduced carbohydrate diets limit both the energy and glucose available to the body, resulting in the increased use of fat oxidation to supply energy needs and ultimately leading to weight loss.<sup>15</sup>

A meta-analysis, conducted on studies using restricted-carbohydrate diets in subjects with type 2 diabetes, reported that glycated hemoglobin (A1C), fasting glucose, and some lipid fractions improved with lower carbohydrate content diets. However, the carbohydrate content criteria was limited to 45% of the total calories from the diet, studies were conducted only in the USA and Canada, and published up to 2006; additionally, they only included two studies with a follow-up longer than 12 weeks. A more recent meta-analysis on randomized trials showed no difference between low-fat diets high in carbohydrates and high-fat low carbohydrate diets on values of A1C, fasting plasma glucose, and total and low density lipoprotein (LDL)-cholesterol.<sup>17</sup> The carbohydrate content criterion was limited to 40% of the total calories from the diet and included studies published up to 2004. However, no studies with a follow-up greater than 12 weeks were included. Therefore, the objective of the present study is to evaluate the effect of low carbohydrate diets on weight reduction, glycemic control, and glycated hemoglobin and

lipid levels in type 2 diabetes individuals with an intervention period equal to or greater than 12 weeks.

## Methods

### *Search strategy and identification of studies*

An electronic search was conducted on articles registered in PUBMED, COCHRANE and EBCOhost, published in English with the following search data: (“2000/01/01”: “2010/01/01”) AND (“diabetes mellitus” AND “carbohydrate-restricted diet”), to identify all randomized controlled trials that evaluated low carbohydrate diets. Also, search reference lists of identified publications for citations of additional relevant articles were reviewed.

### *Trial selection*

For the purposes of this study, trials required to use a randomized controlled design comparing the effects of a restricted carbohydrate diet (defined as a diet allowing a maximum intake of 130 g of carbohydrates per day with any other type of diet), expressed in grams or estimated from the percentage of the total calorie intake. We based our definition of restricted carbohydrate on grams of total calories rather than percentage of carbohydrate, in order to provide a uniform standard of comparison. Also, trials required to include 18 years and older individuals with type 2 diabetes and to have a long term follow-up (at least 4 months or 12 weeks). Trials in individuals with type 1 diabetes were excluded. Also, studies involving pharmacological treatments for weight reduction and interventions in hospitalized individuals were not considered. Trials with both single arm and cross-over interventions were excluded. Due to the reported effects of fiber on lowering glycemia and lipid profiles regardless of the Carbohydrate/Fiber ratio, trials that involved variations in contents and quality of carbohydrates such as increase of fiber of the diet or substitution by whole grains, were omitted. Among the studies identified we included those studies that compared a restricted-carbohydrate diet to a nonrestricted-carbohydrate diet in participants with type 2 diabetes and reported one or more of the outcome measures of interest.

Due to the heterogeneity of study characteristics and impact indicators, undertaking a meta-analysis was not appropriate. The analysis was focused on a narrative description of the data.

### *Data extraction and outcome measures*

Extracted data included features of the study design, the number of individuals, the age, the intervention time, and the characteristics of each diet, such as

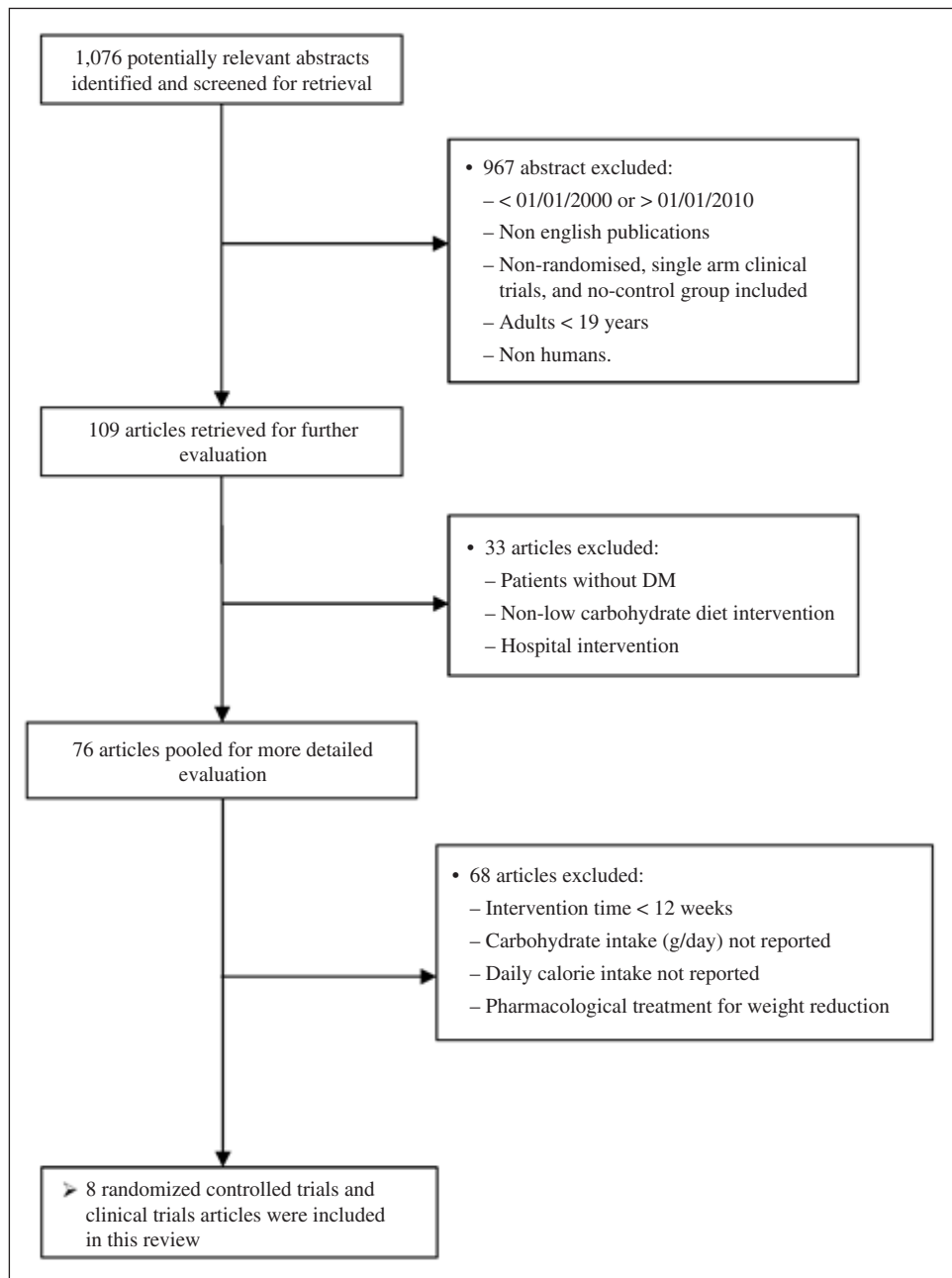


Fig. 1.—Flowchart of selection of studies for inclusion in the review.

macronutrient composition (g). When the total carbohydrate composition of the diet was not reported in grams, the carbohydrate percentage of the diet was converted to total grams. Also, outcome measures were extracted for change in weight and the following metabolic markers: A1C, total cholesterol, High Density lipoprotein (HDL)-cholesterol, LDL-cholesterol and triglycerides levels (fig. 1).

#### Quality assessment

The quality of quasi-experimental and experimental trials was assessed using the GRADE scale.<sup>18</sup> Accord-

ing to these criteria, randomized trials have the highest grade of evidence (score of 4). One point was subtracted if: a) baseline differences occurred between groups (weight, BMI, age, overweight and obesity prevalence), b) attrition rate > 30%, c) no intention to treat analysis was evident, d) there was uncertainty about directness, e) imprecise or sparse data existed, f) a high probability of reporting bias was possible, g) important inconsistencies existed. Two points were subtracted if there were: a) very serious limitations to the quality of the study, and b) major uncertainties about directness. One point was added when there was: a) strong evidence of association, b) evidence of a dose response gradient, and c) all plausible confounders

**Table I**  
Comparative clinical trials of low carbohydrate diets in type 2 diabetes

Author	(n)	Age (range)	IT (months)	Intervention (diets)	CHO'S g/day	Weight difference (kg)	Afc difference	Observations	Grade scale
Samaha et al., 2003 <sup>19</sup>	52	>18	6	a) LCD b) LFD	≤ 30	NA	-0.6 ± 1.2 -0.0 ± 1.0	- Greater reduction on serum glucose levels in LCD (p = 0.01)	4
Nielsen et al., 2006 <sup>20</sup>	31	>18	6	a) LCD b) LFD	75-95	-11.4 ± 4.0** -1.8 ± 3.8	-1.4 ± 1.2 -0.6 ± 1.4	- No difference between group variables was reported	2 No ITT No RMR
Daly et al., 2006 <sup>21</sup>	102	>18	3	a) LCD b) LFD	70	-3.5 ± 0.63*** -0.92 ± 0.40	-0.55 ± 0.17 -0.23 ± 0.13	- No significant difference between groups on lipid variables.	3 No ITT
McLaughlin et al., 2007 <sup>22</sup>	29	>18	4	a) LCD b) UCD	75	-5.9 ± 3.5 -7.0 ± 4.7	NA	- No difference between group variables was reported	2 ID No RMR
Dyson et al., 2007 <sup>23</sup>	13	>18	3	a) LCD b) HED	≤ 40	-8.0** -0.8	-0.4 -0.2	- Increase on HDL and LDL on LCD (p = 0.05)	4
Westman et al., 2008 <sup>24</sup>	97	18-65	4	a) LCD b) LGID	≤ 20	-11.1** -6.9	-1.5** -0.5	- Greater reduction of A1C, fasting glucose, trig. and BMI in LCD. - Greater increase of HDL in LCD (p = 0.05)	3 No ITT No RMR REP
Davis et al., 2009 <sup>25</sup>	105	>18	12	a) LCD b) LFD	20-25	-3.1 ± 4.8 -3.1 ± 5.8	-0.02 ± 0.9 0.24 ± 1.4	- Greater increase of HDL in LCD (p = 0.002)	3 No ITT
Esposito et al., 2009 <sup>26</sup>	215	30-75	48	a) LCMD b) LFD	< 50	-3.8 -3.2	-0.9** -0.5	- Greater reduction of A1c, HOMA, TC and insulin on LCMD - Greater increase of HDL on LCMD	4

N: Number of subjects; NA: Not Available; IT: Intervention Time; A1C: Glycosylated hemoglobin; Kg: Kilograms; CHOS (g): Grams of arbohydrates in diet; LCD: Low Carbohydrate Diet; LFD: Low Fat Diet; LGID: Low Glicemic Index Diet; LCMD: Low Carbohydrate Mediterranean Diet; TC: Total Cholesterol; HDL: High Density Lipoproteins; LDL: Low Density Lipoproteins; Trig: Triglycerides; UCD: Self-selected usual-care die; HED: Healthy Eating Diet; BMI: Body Mass Index; BF%: Percentage of body fat; \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001; AR: Attrition Rate; ITT: Intention To Treat; ID: Imprecise Data; NR: No Randomization method reported. REP: Reported Statistical Power.

would have reduced the effect. Two points were added when very strong evidence of association was found in the trial. Each article was independently analyzed by a researcher (LMC and MBG). Disagreements or inconsistencies on the analysis were resolved by consensus. Afterwards, a last analysis was carried out by a third investigator (AJC) resolving the remaining disagreements.<sup>18</sup>

## Results

### Description of studies

From the electronic searches, 1,076 abstracts were identified; 969 were excluded on the basis of initial limits (time range, randomized and single arm trials, English language, adults and humans). Of the 109 remaining articles, 101 were eliminated because they did not include type 2 diabetes subjects or a low carbohydrate diet, they included subjects that had undergone hospital interventions or pharmacological treatment for

weight reduction, they were single arm trials, the intervention time was less than 12 weeks or there was no report of glycemia, A1C, weight and lipid changes. Eight studies met the inclusion criteria and involved a total of 664 subjects older than 18 years. Five studies described the attrition rate,<sup>19,21,23,24</sup> five studies described methods of randomization,<sup>19,21,25,26</sup> and only two reported intention to treat, leading to a low quality score of the trial.<sup>19,26</sup> Additionally, only four studies reported statistical power analysis.<sup>19,22,24,26</sup> The number of subjects in each study ranged from 13 to 2014.<sup>19-26</sup> There was little consistency in the amount of carbohydrates included in the intervention arms of these studies, with the lowest intake being reported as 19 g day<sup>24,25</sup> and the highest as 95 g day.<sup>20</sup> The follow-up of these trials ranged from three<sup>21,23</sup> to 48 months.<sup>26</sup> Intervention diets included a low carbohydrate diet compared with either a low fat diet,<sup>19-21,25</sup> a usual care diet,<sup>22</sup> a healthy eating diet,<sup>23</sup> a low glycemic index diet<sup>24</sup> or a low carbohydrate Mediterranean diet.<sup>26</sup> Physical Activity changes were not specifically addressed in most of the trials evaluated (table I).

### *Weight change*

Table I provides a summary of outcome measures. In order to examine the carbohydrate intake as a potential mediator of weight changes differences between groups at the end of the intervention trials were considered. Results on weight changes were not consistent throughout the studies. A six-month study conducted in 31 individuals receiving a diet providing 75-95 g of carbohydrates as energy source reported the greatest weight reduction (11.4 kg compared to 1.8 kg) on the low fat diet group.<sup>20</sup> However, a 12-month randomized study involving 105 individuals comparing a low carbohydrate diet with a low fat diet showed the lowest weight reduction (3.1 kg). At the end of the study, no difference in weight change was found in both groups.<sup>25</sup> Only one study conducted by McLaughlin et al., (2007) and involving 29 individuals, who received 75 g of carbohydrates in their diet, showed that the highest weight reduction with the usual care diet.<sup>22</sup> Five studies showed greater weight reduction on low carbohydrate diets<sup>20,21,23,24,26</sup> and in four there were no significant differences between groups,<sup>20,21,23, 24</sup> including the study with the longest follow-up.<sup>26</sup>

### *Glycemic control and lipid values*

All studies reported significant A1C reduction with a hypocaloric, reduced carbohydrate diets in people with type 2 diabetes. A study conducted by Westman et al. (2008) showed the highest and most significant reduction of A1C levels on subjects under a LCD compared to a LGID (-1.5 vs. -0.5); however the between group difference adjusted to baseline values was not significant.<sup>24</sup> A study by Davis et al. (2009) on a 12-month intervention reported the least benefit on reduction of A1C levels using a LCD as diet of choice on DM2 individuals (-0.02 vs. -0.24).<sup>25</sup> However, overall effects of the intervention diets on A1C levels were inconsistent. Only two out of eight studies reported significant differences between groups.<sup>24,26</sup>

On the other hand, a three-month randomized study conducted by Dyson et al. (2007) on eighteen individuals, showed an increase of HDL and LDL on the LCD group.<sup>23</sup> No other differences on the lipid profile were reported.

Most of the studies did not examine and report the potential adverse effects of reduced carbohydrate diets over cardiovascular risks, renal function and other nutrient components such as calcium and vitamins.

### *Dietary intake and drugs assessment*

With low carbohydrate diets, decreases in insulin and hypoglycemic drugs requirements have been reported on previous trials.<sup>8,16</sup> However in our review, three out of eight studies reported results on drugs

requirements.<sup>19,21,26</sup> Samaha et al. (2005) assessed dietary intake and included a 6-month dietary counseling in individuals with type 2 diabetes. Results showed a decrease in mean fasting plasma glucose levels in the low carbohydrate diet group compared to the low fat diet group.<sup>19</sup> Also, a reduction on insulin and hypoglycemic medications was reported on seven individuals with low carbohydrate diet compared to one subject in the low fat diet group.<sup>19</sup> Likewise, Daly et al. (2006), on a 3-month dietary intervention reported that 85% of individuals in the low carbohydrate diet group reduced insulin requirements, compared to 22% in the low fat diet group.<sup>21</sup> However, Esposito et al (2009) found no difference on medication requirements on a 48 month intervention trial.<sup>26</sup>

### **Discussion**

This review evaluates the long-term effects of restricted carbohydrate diets (< 130 g) over weight, A1C and lipid profiles on individuals with type 2 diabetes. The review shows that, although four out of seven studies reported weight changes from baseline with low carbohydrate diet, the two studies with the longest follow-up (12 and 48 months) showed no statistical differences. These results are consistent with reviews conducted by Kirk et al. (2008) and Dyson et al. (2008), including interventions of less than 12 weeks. However, in this review it was included only studies with a follow-up greater than 12 weeks. The exclusion of interventions of a lower follow-up is due to the fact that the main purpose of the metabolic control of individuals with diabetes is to reduce the long-term diabetes implications. In this review, only half of the studies reported significant differences on long-term weight loss with low carbohydrate diets,<sup>19,21,23,24</sup> but only one had the highest quality score<sup>23</sup> and the longest follow-up was six months.<sup>19</sup> Therefore, in the two longest-term studies (more than six months) no difference on weight changes was reported.

Low carbohydrate diets have been associated to beneficial effects on triglycerides and HDL-cholesterol levels in non-diabetic individuals.<sup>27</sup> Several trials have demonstrated that even a modest loss of 5-10% of initial body weight may significantly improve glycemic control, hyperinsulinemia and other metabolic abnormalities.<sup>28-30</sup> Low carbohydrate diets are designed to limit energy intake and available glucose, consequently fat oxidation is increased to supply energy needs and ultimately lead to weight loss.<sup>15</sup> Previous meta-analysis have evaluated short term effects of restricted carbohydrate diets on type 2 diabetes subjects and reported positive effects on weight and A1C.<sup>8,16-17</sup> Weight reduction may be primarily caused by decreased caloric intake and energy efficiency.<sup>5-9</sup> Also, it has been suggested that high-starch, high-carbohydrate diet stimulates appetite and disturbs energy balance in patients with type 2 diabetes leading to the

rationale of the positive effects of low carbohydrate diets over glycemic control.<sup>30-32</sup> However, this review showed that the weight reduction was not consistent throughout the studies when a follow-up was greater than 12-weeks and it has not been reported to be consistently maintained when interventions are greater than 12 months.

Since A1C represents average blood glucose over a period of approximately one to three months, the time needed to observe true effects of the intervention was met by the inclusion of studies with a follow-up greater than 12 weeks. However, only two out of eight studies found a statistically significant reduction in A1C outcomes in the low carbohydrate diet compared to the low fat diet group.<sup>25,26</sup> Although one of them had a high quality score and the longest follow-up period,<sup>26</sup> no consistent difference on A1C was found.

Results of long-term effects on triglycerides and cholesterol are also not conclusive. In this review only one out of eight reported greater reductions on triglycerides on the low carbohydrate diet,<sup>24</sup> and three studies reported significant increase on HDL in the low carbohydrate diet group.<sup>24-26</sup> These results are consistent with a recent review that assessed the effect of weight loss on biological markers in individuals with type 2 diabetes.<sup>33</sup> Twenty randomized clinical trials with at least 12 months of follow-up were reviewed and no conclusive results were found.<sup>33</sup>

Despite the more homogenous content of carbohydrates (< 130 g day) of the low carbohydrate diet, the randomized controlled trials reviewed in this study indicated that the role of carbohydrate restricted diets over health in the long-term is yet to be investigated. The approaches to restriction of carbohydrate intake resulted in increases in other components of the diet; either fat or protein contents in diets, which in the long-term may be deleterious to the renal function of individuals with diabetes or to LDL or triglycerides increase. Also, there were no evaluations on the potential adverse effects over mineral and vitamin contents of the diets, since low carbohydrate diets may result in restricted intakes of fiber, fruits, vegetables and dairy products.

There are several limitations to this systematic review. Foremost is the small number of randomized studies available with  $\leq 130$  g/day carbohydrate intake of the diet and an intervention time greater than 12 weeks. Only two studies with an intervention greater than 12 months and no study with a follow-up greater than 48 months were found. Also, the inclusion of studies with a wide range of carbohydrate content may limit the conclusion on the least amount that would represent a positive impact on treatment in subjects with type 2 diabetes without deleterious effects. However, the strength of this review is the inclusion of studies with less than 130 g/day of carbohydrates, which reduces the high range of carbohydrate intake among the studies reported in other reviews. Also, this report includes results observed on interventions longer than 12 weeks.

Although low carbohydrate diets may appear to be effective over the short-term on weight loss in non diabetic individuals, our review indicates that differences on weight, A1C and lipid profiles changes over the long-term comparing a low carbohydrate diet with a low fat diet, a usual care diet or a low glycemic index diet were not consistent and conclusive. Therefore, further investigation on the long-term effects over cardiovascular outcomes and safety in subjects with type 2 diabetes is needed.

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