

## Revisión

# Effect of weight loss on metabolic control in people with type 2 diabetes mellitus: systematic review

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### Abstract

**Objective:** The aim of this systematic review was to examine randomized clinical trials (RCT) regarding long-term effects of weight loss (WL) on biological markers in people with type 2 diabetes mellitus (T2DM).

**Methods:** We searched for articles published in English and Spanish recorded in the databases of Pubmed and Cochrane, and the journal collections platforms of Ebsco and Scielo between January 1, 2000 and January 1, 2010. Inclusion criteria included RCT with follow-up  $\geq$  12 months.

**Results:** A total of 842 articles were identified, 95 of them contained information on the effect of WL on biological markers. Twenty studies fulfilled the inclusion criteria. WL percentage ranged from 0.8 to 20%. A reduction of A1C was observed in nine studies, blood glucose in seven, of total cholesterol and LDL in four, systolic and diastolic blood pressure in three, and the use of hypoglycemic drugs in four; an increase of HDL was observed in seven studies. Remission of T2DM was reported in only one study, which included surgical treatment. The quality of the studies ranged from very low to high; however, the study with the longest follow-up that did not involve surgical treatment, was 52 months.

**Conclusion:** The evidence of the beneficial effect of WL on biological markers on long-term studies in people with T2DM is inconclusive. These results warrant longer and better designed studies.

(Nutr Hosp. 2011;26:1242-1249)

DOI:10.3305/nh.2011.26.6.5244

Key words: *Weight loss. Diabetes. Systematic review. Metabolic control.*

### EFFECTO DE LA PÉRDIDA DE PESO EN EL CONTROL METABÓLICO DE PERSONAS CON DIABETES MELLITUS TIPO 2: REVISIÓN SISTEMÁTICA

### Resumen

**Objetivo:** El propósito de esta revisión sistemática es evaluar ensayos clínicos aleatorios (ECA) acerca de los efectos a largo plazo de la pérdida de peso en los marcadores biológicos en personas con diabetes mellitus tipo 2 (DM2).

**Métodos:** Se buscaron estudios publicados en Inglés o Español registrados en la base de datos de Pubmed y Cochrane, y en las plataformas de acceso a colecciones de revistas Scielo y EBSCO, del 1° de Enero de 2000 al 1° de Enero de 2010. Los criterios de inclusión fueron ECA con un seguimiento  $\geq$  a 12 meses.

**Resultados:** Se identificó un total de 842 artículos, de los cuales 95 trataban del efecto de la pérdida de peso en los marcadores biológicos. Veinte estudios cumplieron con todos los criterios de inclusión. La pérdida de peso osciló entre 0,8 y 20%. Se observó una reducción de la A1C en nueve estudios, de glucosa sanguínea en siete, colesterol total y LDL en cuatro, presión arterial sistólica y diastólica en tres y el uso de medicamentos hipoglucemiantes en cuatro; y un incremento en los niveles de HDL en siete estudios. La remisión de la DM2 se reportó únicamente en un estudio y era de tratamiento quirúrgico. La calidad de los estudios osciló de muy bajo a alto; sin embargo el estudio con mayor seguimiento que no era de tratamiento quirúrgico fue de 52 meses.

**Conclusión:** La evidencia de que la pérdida de peso tiene un efecto benéfico en los marcadores biológicos en personas con DM2 a largo plazo no es concluyente. Estos resultados muestran la necesidad de más estudios bien diseñados y a largo plazo.

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DOI:10.3305/nh.2011.26.6.5244

Palabras clave: *Pérdida de peso. Diabetes. Revisión sistemática. Control metabólico.*

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Recibido: 17-II-2011.  
1.ª Revisión: 9-III-2011.  
Aceptado: 14-III-2011.

## Introduction

A worldwide increase in overweight (OW) and obesity (OB) has taken place in the past two decades, which has become a public health problem.<sup>1,2</sup> Genetic, environmental, biochemical, neurological, physiological, cultural, and socio-economic factors play important roles in the development of OB.<sup>3,4</sup> Along with the rise of OB, there is an important increase in the incidence of type 2 diabetes (T2DM).<sup>2,3</sup> The World Health Organization (WHO) reports that more than 220 million people worldwide have diabetes and that in 2005 an estimated 1.1 million people died from diabetes, an estimation that will be doubled by 2030.<sup>5</sup> It has been estimated that up to 75% of the risk of T2DM is attributable to OB.<sup>6</sup> Eighty-six percent of people with T2DM are OW or OB, and 52% are obese.<sup>7</sup> People with OW or OB are at a higher risk of developing T2DM; on the other hand weight loss has been associated to a decrease in risk.<sup>8-14</sup> Several weight reduction strategies have been used to improve the metabolic control of diabetes, including lifestyle interventions,<sup>10-12</sup> drugs,<sup>15-18</sup> and surgical treatment<sup>19,20</sup> which have shown to be effective as a primary prevention and/or as a strategy to delay the onset of T2DM. The benefits of weight reduction in people with T2DM are not thoroughly documented. Weight lost has resulted in the reduction of use of hypoglycemic drugs<sup>21-24</sup> and/or remission of diabetes.<sup>25</sup> In the review conducted by Aucott (2008), the influences of weight loss on long-term diabetes outcomes were assessed.<sup>3</sup> The author concluded that intentional weight loss reduces the risk of T2DM by lifestyle interventions, drugs or surgical treatment, including in some cases remission of the disease. This study also showed that in order to obtain significant reductions on blood glucose, greater and sustained weight loss is required. Although literature reviews and meta-analyses were included in this study, the results included people with and without T2DM and most of the studies were cohorts. Few randomized clinical trials were evaluated and most of them had less than 12 months of follow-up.<sup>26-28</sup> Since diabetes is a chronic disease and its implications on other health problems are discovered in the long-term, the conduction of longer follow-up studies is warranted<sup>29-30</sup>.

The present paper examines the long-term effects ( $\geq 12$  months) of randomized clinical trials (RCT) of weight loss intervention on people with diabetes.

## Methods

The search was conducted in the databases of Pubmed and Cochrane, and the journal collection platforms of Ebsco and Scielo. The studies were searched using the following Mesh descriptors: (“2000/01/01”: “2010/06/01”) AND (“Diabetes Mellitus, Type 2” AND “obesity” AND “overweight”

AND “weight loss” AND “body weight changes”). The MesH descriptors were used to search in Pubmed, Cochrane and Ebsco, and their equivalent in Spanish in Scielo.

Inclusion criteria were the following: randomized clinical trials (RCT), papers written in English, conducted on T2DM people, with at least 12 months of follow-up, which recorded weight changes (BMI or kg), metabolic parameters (A1C, blood glucose, total cholesterol, LDL, HDL, Triglycerides, SBP, DBP) and the use of hypoglycemic drugs (Figure 1). From the initial search, several studies were removed due to the inclusion of people without diagnoses of T2DM (747), lack of BMI or weight data (7) and those with a follow-up less than 12 months.

Given the heterogeneity in study design, a meta-analysis was not appropriate; however, we conducted a systematic review of the available studies. Each study was evaluated according to the number of subjects, age (median), percentage of retention, type of intervention, duration of intervention or follow-up (months), initial and final BMI, percentage of weight change and effects on metabolic parameters.

The quality of the randomized clinical trials was assessed using the GRADE scale.<sup>31,32</sup> The design of the study, methodological strengths and weakness, and significance of the findings were used to characterize the quality of the evidence of any given study. According to this scale, randomized clinical trials could receive the number four as a maximum score. One point was subtracted when the following occurred: a) significant baseline differences between intervention groups (weight, BMI, age, prevalence of OW or OB), b) percentage of retention  $\leq 70\%$ , c) no intention- to -treat analysis, d) uncertainty of directness (questionable validity of instruments/techniques), e) sparse data, f) high probability of reporting bias (sample, population characteristics), g) internal inconsistency (data, values). Two points were subtracted when the study showed: a) very serious design limitations (sample, population characteristics), b) serious uncertainty of directness (validity of instruments). One point was added when: a) the study possessed strong association without plausible confounders, consistent, and direct evidence, b) all plausible confounders would have diminished the effect size. Each study was assessed independently with the criteria recommended by GRADE and mentioned above, by two of the authors (MSG, AJC). When there was no consistency a consensus was reached with the aid of a third author (MBG) using the same criteria for evaluation in quality of the studies.

## Results

Our search resulted in 842 articles; 95 of them contained information on the effect of weight loss in metabolic parameters in people with T2DM (fig. 1). Twenty published studies (table I) fulfilled the inclusion crite-

**Table I**  
Randomized clinical trials on the effect of weight loss in people with type 2 diabetes

Authors Country (year)	N	Age media (range)	Intervention	Follow-up (months)	RET (%)	Initial BMI (media)	Final BMI (media)	WC (%)	Effects in T2D	Grade scale
<i>Pharmacologic therapy</i>										
Kelley et al. USA (2002) <sup>32</sup>	550	57.9	a) Orlistat 120 mg + reduced-calorie diet b) Placebo	12	97 ITT	a) 35.8 b) 35.6	a) NA b) NA	a) ↓ 3.8 b) ↓ 1.2	There was a significant difference in weight loss between groups Greater ↓ of BG, A1C, TC, LDL, LDL/HDL ratio and hypoglycemic drug use in Orlistat group	4
Hanfelfeld et al. Germany (2002) <sup>33</sup>	492	55.7	a) Orlistat 360 mg/day b) Placebo	12	75 ITT	a) 34.5 b) 33.7	a) NA b) NA	a) ↓ 5.4 b) ↓ 3.6	There was a significant difference in weight loss between groups Greater ↑ HDL in placebo group	4
Miles et al. USA (2002) <sup>33</sup>	516	53.1	a) Orlistat 360 mg/day b) Placebo	12	98 ITT	a) 35.6 b) 35.2	a) NA b) NA	a) ↓ 4.6 b) ↓ 1.7	There was a significant difference in weight loss between groups Greater ↓ in use of metformin and hypoglycemic drugs, A1C, TC, LDL, LDL/HDL ratio and systolic BP in Orlistat groups	4
McNulty et al. UK (2003) <sup>34</sup>	195	49	a) Sibutramine 15 mg/day b) Sibutramine 20 mg/day c) Placebo	12	99 ITT	a) 36.3 b) 37.5 c) 36.2	a) 34.3 b) 34.6 c) 36.1	a) ↓ 5.3* b) ↓ 7.7* c) ↓ 0.2	There was a significant difference in weight loss between groups ↑ systolic and diastolic BP in Sibutramine (15 mg/day) group ↑ pulse in both treatment groups	4
Redmon et al. USA (2003) <sup>36</sup>	61	53.5	a) Standard therapy b) Combination therapy (low-calorie diet + sibutramine 10 mg/day + meal replacement and snack bar)	12	97 ITT	a) 38.6 b) 37.8	a) 38.3 b) 35.2	a) ↓ 0.8 b) ↓ 6.4	There was a significant difference in weight loss between groups ↓ A1C in combination therapy group	2
Kaukua et al. Finland (2004) <sup>35</sup>	236	53.5	a) Sibutramine 15 mg/day b) Placebo	12	98 ITT	a) 35.7 b) 35.6	a) NA b) NA	a) ↓ 7.3 b) ↓ 2.4	There was a significant difference in weight loss between groups Greater ↓ of diastolic BP in Sibutramine group	3
Berne et al. Sweden (2005) <sup>35</sup>	221	59.1	a) Orlistat 120 mg b) Placebo	12	100 ITT	a) 32.6 b) 32.9	a) NA b) NA	a) ↓ 5.0* b) ↓ 1.8*	There was a significant difference in weight loss between groups Greater ↓ of A1C, BG, TC in Orlistat group Greater ↑ HDL in Orlistat group	4
Scheen et al. USA (2007) <sup>37</sup>	1,045	55.6	a) Rimonabant 5 mg/day b) Rimonabant 20 mg/day c) Placebo	12	100 ITT	a) 34.4 b) 34.1 c) 34.2	a) NA b) NA c) NA	a) ↓ 2.3 b) ↓ 5.5 c) ↓ 1.4	There was a significant difference in weight loss between groups Greater ↓ A1C and systolic BP in both Rimonabant groups Greater ↓ TGL and BG, and greater ↑ HDL in Rimonabant 20 mg group	4
<i>Surgical therapy</i>										
Dixon et al. Australia (2008) <sup>38</sup>	60	(20-60)	a) Conventional-Therapy Program b) Surgical Program	24	92	a) 37.2 b) 37.0	NA	a) ↓ 1.4 b) ↓ 20.0**	There was a significant difference in weight loss between groups 76% and 15% of surgical and conventional program respectively had remission of T2D Greater ↓ BG, A1C and use of hypoglycemic drugs in surgical group	2

**Table I (continuation)**  
Randomized clinical trials on the effect of weight loss in people with type 2 diabetes

Authors Country (year)	N	Age media (range)	Intervention	Follow-up (months)	RET (%)	Initial BMI (media)	Final BMI (media)	WC (%)	Effects in T2D	Grade scale
<i>Lifestyle intervention</i>										
Brinkworth et al. Australia (2004) <sup>37</sup>	66	61.8	a) Low-protein diet b) High-protein diet	12	58	a) 33.3 b) 33.6	a) NA b) NA	a) ↓ 2.4* b) ↓ 3.9*	Greater ↓ of diastolic BP in high-protein diet	1
Li et al. USA (2005) <sup>34</sup>	104	55.5	a) Soy-based-meal replacement b) Individualized diet plan	12	74	a) 32.8 b) 33.7	a) 31.4 b) 32.9	a) ↓ 4.6* b) ↓ 2.3*	Greater ↓ of hypoglycemic drugs in meal replacement group	3
As et al. Norway (2005) <sup>34</sup>	38	57 (47-67)	a) Lifestyle intervention programme b) Lifestyle intervention programme + insulin c) Insulin	12	74	a) 29.8 b) 31.1 c) 30.0	a) 28.9 b) 32.4 c) 29.6	a) ↓ 1.7 b) ↑ 3.0 c) ↓ 2.5	NS	2
West et al. USA (2007) <sup>38</sup>	217	53	a) Individual sessions of motivational interviewing + weight control program b) Attention control + weight control program	18	93	a) 36.5 b) 36.5	a) NA b) NA	a) ↓ 3.6 b) ↓ 1.8	At 18 months there was a significant difference in weight loss between groups, but not difference was found in A1C	2
Cheskin et al. USA (2008) <sup>38</sup>	119	55.0	a) Standard diet b) Portion-controlled diet	12	28	a) 35.0 b) 35.7	a) 33.3 b) 33.8	a) ↓ 2.3 b) ↓ 4.4*	↑ HDL in portion-controlled diet ↓ BG and systolic BP in portion-controlled diet	3
Davies et al. UK (2008) <sup>39</sup>	824	59.5	a) Structured education programme b) Conventional care	12	68	a) 32.3 b) 32.4	a) NA b) NA	a) ↓ 3.3* b) ↓ 2.0*	NS	1
Ma et al. USA (2008) <sup>44</sup>	40	53.5	a) Low-GI diet b) ADA diet	12	48	a) 35.6 b) 36.0	a) NA b) NA	a) ↓ 1.3 b) ↓ 0.8	↓ A1C, TC in both groups Greater ↓ of LDL in the low-GI group Low-GI group had much lower likelihood of switching to a new drug or increasing dosage of hypoglycemic drugs	0
Esposito et al. Italy (2009) <sup>41</sup>	283	(30-75)	a) Low-carbohydrate MED diet b) Low-fat diet	48	76	a) 29.7 b) 29.5	a) 28.5 b) 28.6	a) ↓ 4.4 b) ↓ 0.7	Greater ↓ BG, A1C and LDL, and ↑ HDL in MED diet group	4
Barnard et al. USA (2009) <sup>35</sup>	99	55.7 (27-82)	a) Vegan diet b) Conventional diet	18	88	a) 33.9 b) 35.9	a) 32.3 b) 34.8	a) ↓ 4.4 kg b) ↓ 3.0 kg	NS	4
Brehm et al. USA (2009) <sup>36</sup>	124	56.5 (38-75)	a) High-MUFA diet b) High-CHO diet	12	77	35.9	a) 34.6 b) 34.5	a) ↓ 3.9** b) ↓ 3.7**	↑ HDL, ↓ A1C, BG, diastolic BP, insulin concentration and insulin resistance in both groups	3
Davi et al. USA (2009) <sup>40</sup>	105	53.5	a) Low-CHO diet b) Low-fat diet	12	81	a) 35.0 b) 37.0	a) NA b) NA	a) ↓ 3.3* b) ↓ 3.1*	↑ HDL in low-CHO group	2

N = number of subjects; RET % = retention percentage; BMI = body mass index; WC = weight change; T2D = type 2 diabetes; M = male; F = female; MED = Mediterranean style; NA = not available; BG = blood glucose; A1C = ; TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; BP = blood pressure; MUFA = monounsaturated fat; CHO = carbohydrate; DSE = Diabetes Support and Education; GI = glycemic index; ADA = American Diabetes Association; ITT = Intention-to-treat.  
\*p < 0.05.  
\*\*p < 0.001.

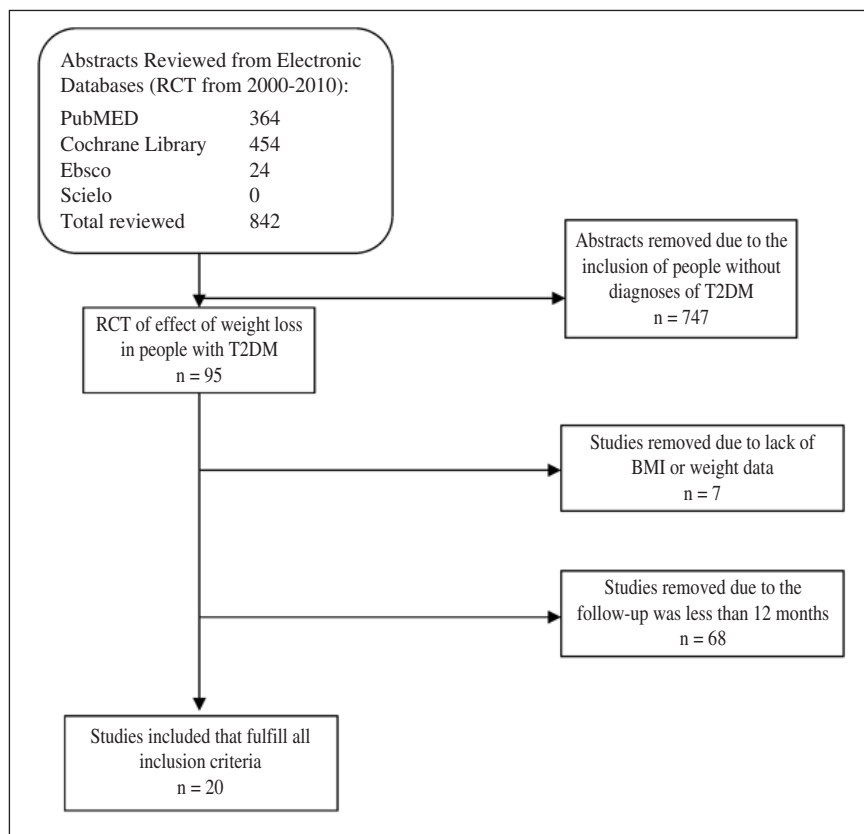


Fig. 1.—Flow diagram of the article selection in the systematic review of literature.

ria.<sup>22-25,33-48</sup> A summary description of all 20 studies included in this systematic review is presented in table I. The mean age of study participants was 55.6 years (20 to 82 years). Seven studies (35%) included participants with insulin therapy,<sup>22,25,34-37,40,44</sup> and fourteen studies (70%) used isocaloric diets in all participants.<sup>22-24,33,34,36-38,41-43,46-48</sup> Compliance to diets was evaluated by food records<sup>22,34-36,40-42,48</sup> and diet recalls,<sup>22,34,44</sup> while compliance to medications was evaluated by pill count.<sup>22,33,43,45</sup> No specific guidelines regarding physical activity (PA) modifications were provided in 45% of these studies.<sup>23,24,35,37-39,42,43,45</sup> Only one study (5%) established a specific PA program,<sup>34</sup> three studies (20%) assessed PA levels using diary records,<sup>41,44,48</sup> and one with pedometers;<sup>36</sup> six (30%) studies generally encouraged participants to increase PA.<sup>22,25,33,40,46,47</sup>

### Weight change

All studies included in this revision reported weight loss after the follow-up period. According to the weight reduction strategies, a greater mean reduction was reported using surgical treatment (-20% of body weight (BW)), followed by drug therapy (-2.3-7.7% of BW), and lifestyle interventions (-0.8-4.6% of BW). Greater mean weight reduction was reported using soy-based meal replacements (-4.6% of BW); however, the

follow-up of this study was up to 12 months.<sup>24</sup> Esposito et al., using a Mediterranean (MED) diet, reported a weight loss of 4.4% of BW after 48 months of follow-up,<sup>41</sup> and Barnard et al. reported weight loss after 18 months with a vegan diet.<sup>35</sup>

### Glycemic values

All studies included in this revision assessed the reduction of A1C, but only nine of them (45%) reported a significant reduction after the follow-up period. Of these studies, five were RCT with good quality and had the maximum punctuation using the GRADE scale, four of them used drug therapy,<sup>22,23,33,47</sup> and one used the MED-diet.<sup>41</sup> One of them<sup>42</sup> had zero points using the GRADE scale due to important methodological weaknesses such as differences between groups in baseline characteristics, insufficient samples, retention percentage < 70%, and a lack of intention-to-treat analysis. The rest of the studies also had insufficient samples.<sup>25,36,46</sup>

BG was assessed in only 16 studies (80%), seven of which (44%) reported a significant reduction. Four of the studies were evaluated and received four points using the GRADE scale, three of them used drug therapy<sup>22,33,47</sup> and one MED-diet.<sup>41</sup> The rest had insufficient samples or low retention rate.<sup>25,36,38</sup>



### *Lipid values*

The effect of weight loss on lipid values was assessed in 18 studies (90%). Four of them (20%) reported a significant reduction in total cholesterol, three of them used Orlistat to reduce body weight<sup>22,33,42</sup> and received four points using the GRADE scale; one study<sup>44</sup> used the low-GI diet or ADA-diet but had important methodological weaknesses. Also, four of them (20%) reported significant reduction in LDL, two used Orlistat (4 points with GRADE scale),<sup>22,23</sup> one the low-GI diet (0 points with GRADE scale)<sup>44</sup> and one the MED-diet (4 points with GRADE scale).<sup>41</sup> Seven studies (35%) reported an elevation of HDL, three using drugs,<sup>33,42,47</sup> one with a portion controlled diet,<sup>38</sup> one with the MED-diet,<sup>41</sup> one with the high-MUFA and high-CHO diet,<sup>36</sup> and one with low-CHO.<sup>40</sup>

### *Blood pressure*

Sixteen studies (80%) assessed blood pressure, of which only three (19%) reported a significant reduction in systolic BP<sup>23,38,47</sup> and three others in diastolic BP.<sup>36,37,43</sup> In one study using sibutramine (15 mg/day) a significant elevation of systolic, diastolic BP and pulse rate was reported.<sup>45</sup>

### *Hypoglycemic drugs use*

Nine studies (45%) assessed if there was a reduction in the use of hypoglycemic drugs. A significant reduction was observed in four (44%) of these studies. Two used Orlistat,<sup>22,23</sup> one used surgical treatment,<sup>25</sup> and one used soy-based meal replacement.<sup>24</sup>

### *Remission of T2DM*

Remission of T2DM was only reported in the study using surgical treatment as the weight control strategy.<sup>25</sup> The remission was observed in the surgical group (76%) and in the conventional treatment group (15%).

## **Discussion**

This revision indicates that the effect of WL on biological markers on long-term studies in people with T2DM is inconclusive. WL percentage ranged from 0.8 to 20%, reduction in A1C was observed in nine out of 20 studies, blood glucose in seven out of 16, total cholesterol and LDL in four out of 18, systolic and diastolic blood pressure in three out of 16 and the use of hypoglycemic drugs in four out of nine; an increase of HDL was observed in seven out of 18 studies. In addition, remission of T2DM was only reported in the study in which subjects underwent bariatric surgery. Most

studies had a follow-up of 12 months, four studies had a follow up  $\geq 12$  months, and the longest non surgical study had a follow-up of 48 months. One of the studies with the longest follow-up (24 months) reported weight loss, reduction in BG, A1C, and the use of hypoglycemic drugs after bariatric surgery, however, the sample size was insufficient to obtain 80% of statistical power, and no intention-to-treat analysis was used, which resulted in an evaluation score of 2. One of the studies with the follow-up of 18 months reported reductions in weight; however, the quality score of this study was 2 because neither intention-to-treat nor statistical power was reported. One of the longest studies (18 months) had the highest quality score (4) and reported no significant changes in any parameter. The study that included low carbohydrate Mediterranean diet also had the highest quality score and reported a reduction of BG, A1C and LDL and an increase of HDL, after 48 months of follow-up, with no difference in weight lost.

Previous reviews assessed the impact of weight loss in patients with T2DM, but the results included people with and without T2DM; they only assessed one type of intervention, and most of the studies were cohorts. Few RCT were evaluated and most of them had a follow-up of less than 12 months.<sup>3,18,49,50</sup> This study includes RCT with a follow-up  $\geq 12$  months in order to assess the long term sustainability of the effects on biological markers. The results observed in this study confirm that the metabolic control of people with diabetes is challenging at the long-term.

People with OW or OB have an increased risk of developing T2DM, and weight loss has been associated with a reduced risk.<sup>8-14</sup> Several large RCT have shown that weight loss might be an important management strategy for OW and OB persons with pre-diabetes, as it may delay or prevent the progression of clinically defined T2DM.<sup>10,51</sup> Consistently, some studies have shown that weight loss in obese people with T2DM can significantly improve glycemic control, and some subjects can discontinue insulin or oral therapy.<sup>49</sup> However, most studies assessed short-term improvements and long-term effects were less described.

The results of this study suggests that the treatment of OB and OW on people with T2DM should focus in encouraging lifestyle changes and improving biological markers, instead of establishing weight loss goals that are difficult to reach, as an intermediate objective to improve biological markers. However, these results warrant longer and better designed studies.

The strength of this study is the inclusion of studies of  $\geq 12$  months of follow-up, since diabetes is a chronic disease and its implications on other health problems are discovered in the long-term; therefore, the result are not overestimated by shorter-term intervention ( $< 6$  months). Unfortunately, several studies had to be excluded due to the inclusion of combined data from people with and without diabetes. The main limitation of the study is the lack of a meta-analysis due to the het-

erogeneity of the studies' design. In addition, the treatment strategy was mixed, ranging from diet management to stable and flexible doses of insulin or oral hypoglycemic agents. Further, most of the studies did not have specific guidelines regarding physical activity modifications and no objective reports of PA were recorded. The dropout rate in some studies was high, and most of the studies did not performed intention-to-treat analysis. Therefore, the evidence of the beneficial effect of WL on biological markers on long-term studies in people with T2DM is inconclusive.

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