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Dietary program and physical activity impact on biochemical markers in patients with type 2 diabetes: A systematic review

Eduarda Barreira[a,*], André Novo[a,b], Josiana A. Vaz[a,c], Ana M.G. Pereira[a]

[a] *Health School, Polytechnic Institute of Bragança, Bragança, Portugal*
[b] *CINTESIS-Research Center on Health Technologies and Services, Porto, Portugal*
[c] *CIMO-Mountain Research Centre, Polytechnic Institute of Bragança, Campus de Santa Apolónia, Bragança, Portugal*

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Abstract
Objectives: Evaluate the effectiveness of the implementation of independently or combined dietary and physical activity programs on the blood glucose values and lipid profile in patients with type 2 diabetes, including participants aged 60 years and over.
Design: Systematic review.
Data source: PubMed/Medline database, with language restrictions. Papers published between 2010 and 2016 were included.
Study selection: A total of 30 randomised controlled trials were included that focused on physical activity and dietary interventions in patients with type 2 diabetes mellitus and include participants aged 60 years and over.
Results: The selected articles have shown that the implementation of physical activity programs (aerobic, resistance, flexibility and combined exercises), and programs based on a higher intake of vegetables, grains, legumes, fruits, unsaturated fatty acids, as well as consumption of foods with low glycaemic index, calorie restriction, intake of probiotics, vitamin D supplementation and educational sessions about diabetes improves blood glucose levels, as well as the lipid profile, in patients with type 2 diabetes.
Conclusions: Physical activity and dietary programs are fundamental in the treatment and metabolic control of type 2 diabetes mellitus.

* Corresponding author.
E-mail address: edubarreira4@hotmail.com (E. Barreira).

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PALABRAS CLAVE
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Dislipidemia

Programa de dietas e impacto de la actividad física sobre marcadores bioquímicos en pacientes con diabetes tipo 2: una revisión sistemática

Resumen
Objetivos: Evaluar la efectividad de la implementación de programas de actividad física y dietética independientemente o combinados en los valores de glucosa en sangre y perfil lipídico en pacientes con diabetes tipo 2, incluyendo participantes de 60 años y más.
Diseño: Revisión sistemática.
Fuentes de datos: PubMed/Medline, con restricciones de idioma. Se incluyeron artículos publicados entre 2010 y 2016.
Selección de estudios: Se incluyeron 30 estudios controlados aleatorios, centrados en la actividad física e intervenciones dietéticas en pacientes con diabetes tipo 2 que incluían sujetos de 60 años y más.
Resultados: Los artículos seleccionados han demostrado que la implementación de programas de actividad física (ejercicios aeróbicos, resistencia, flexibilidad y ejercicios combinados) y programas basados en una mayor ingesta de vegetales, granos, legumbres, frutas, ácidos grasos insaturados, el consumo de alimentos con bajo índice glucémico, restricción calórica, ingesta de probióticos, suplementos de vitamina D y sesiones educativas sobre la diabetes mejoran los niveles glucémicos, así como el perfil lipídico en pacientes con diabetes tipo 2.
Conclusiones: Los programas de actividad física y dietéticos son fundamentales en el tratamiento y control metabólico de la diabetes mellitus tipo 2.

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia with disturbance of carbohydrates, protein and fat metabolism. Results of insufficient secretion of insulin by pancreatic cells and/or an incomplete action of produced insulin, to which are related a serial of macrovascular and microvascular complications that affect quality of life.[1–7] It is a chronic disorder with major expansion worldwide. It is estimated that the number of diabetes sufferers increase rapidly in the coming decades due to the population ageing, poor diet, lack of physical activity and obesity.[8–10] Worldwide, in 2015, it is estimated that there were 415 million people with diabetes, and this number is expected to reach 642 million by 2040. In the same year, this disease was responsible for 5 million deaths. The World Health Organization projects diabetes as the 7th leading cause of death in 2030.[9,11] Clinical manifestation of different variants of the disease, type 2 diabetes has been suffering a major increase worldwide representing 90–95% of all cases of diabetes mellitus.[1,9] Its prevalence increases with age,[9,12–16] and is directly related to bad eating habits, abdominal and visceral obesity, sedentary lifestyles.[1,7,9,16–19] People with diabetes have an increased risk to have cardiovascular disease than non-diabetics, which can be 2–4 times greater.[6,16,20–22] Dyslipidemia and insulin resistance are risk factors for cardiovascular disease dyslipidemia and insulin resistance are risk factors for cardiovascular disease.[16,21,23–28] This disease is a major cause of morbidity and reduced life expectancy in patients with diabetes.[29,30] It is estimated that at least 68% of diabetic patients over 65 years old die from heart disease and 16% due to stroke.[31]

A balanced and healthy diet is an essential component for the prevention and selfcontrol of type 2 diabetes. It contributes to a harmonious growth and development, also reflected in the patterns of acquired diseases, that is, it has a profound impact on the individual's health in all its dimensions (social, physical and mental). For this, the diet must respect the nutritional recommendations, namely hours and quality of meals.[32–34] The nutrition intervention emphasizing the promotion of healthy eating has been shown to be an important point in diabetes mellitus treatment since promotes a better glycemic control and lipid profile. Diets rich in whole grains, fruits, vegetables, nuts, whit a moderate alcohol intake, a lower intake of red meat, processed refined foods, sweets, dairy products with high fat and soft drinks have been correlated with a reduced risk of diabetes, better glycemic control and lipid profile in patients with diabetes.[1,35–41] Physical activity can be described as any body movement that which requires muscular use and more energy expenditure than at rest.[42] Is widely recommended as an essential non-pharmacological therapeutic strategy to the prevention and metabolic control of type 2 diabetes.[1,9,41]

International organizations recommend a weekly accumulation of a minimum of 150 min of aerobic moderate exercise (50–70% the maximum heart rate), 75 min of vigorous intensity, or a combination of both types, distributed over a minimum of 3 days per week, with no more than 2 consecutive days without exercise.[1,43]

The objective of this systematic review is evaluate the effectiveness of the implementation of independently or combined dietary and physical activity programs on the blood glucose values and lipid profile in patients with type 2 diabetes, including participants aged 60 and more years.

Given the high aging rate and the prevalence of type 2 diabetes of the population, we choose to conduct an analysis of several publications on this topic.

Methods

Data sources

A comprehensive search was performed in the international scientific database:

PubMed/Medline, using the descriptors ''Diabetes AND ((food habits) OR BMI OR obesity OR (physical activity) OR exercise OR glucose OR HbA1c OR (total cholesterol) OR HDL OR LDL OR VLDL OR triglycerides OR apoA OR apoB OR apoC OR apoD OR apoE)''.

Study selection, selection criteria and quality assessment

The research and study selection was performed independently by two reviewers. If there were uncertainty regarding eligibility, their inclusion or not was jointly decided by the four reviewers. Were considered eligible for the purposes of this review only randomized clinical trials comparing physical activity or dietary interventions with control group in type 2 diabetes, that include participants with 60 and more years, published between 2010 and 2015, available in full text, with evaluation of the proposed intervention and published in Portuguese, Spanish, English or French. Were excluded studies that did not recruit elderly patients with type 2 diabetes, opinion articles, and with no final assessment of the proposed intervention. The following PICO (Population, Intervention, Comparator, Outcome) methodology was used: Population: patients with type 2 diabetes, age $\geq$60 years; Implementation/Indicator: Dietary program and physical activity; Comparator: control program; Outcome: Impact on the blood glucose values and lipid profile in patients with type 2 diabetes.

The included articles were assessed for the risk of bias using the recommendations for judging the risk of bias, provided in Chapter 8 of the Cochrane Handbook,[44] since the selected studies were randomized. Such studies are very prone to bias due to the arbitrariness of researchers in sample selection, assessment of the variables analyzed and difficulty in control of external variables that can influence the results.[45]

The evaluation consists of two parts, where the risk of bias is assessed in seven areas: Random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The first makes an analysis to what is described in that study and analyzed in order to be able to classify the risk of bias. In the second part is made the classification of the risk of bias in one of three categories: low risk of bias, high risk of bias or uncertain risk of bias, for each of the analyzed domains.[44] The general description and an overall assessment of risk of bias of the included trials in this review are shown in Table 1 and Figure 1

In Table 2 , are reported the general description of the included trials in this review per intervention and continent. In this table, taking into account the type of intervention, the articles were grouped in six categories: physical activity; dietary program; physical activity and dietary program; educational sessions; educational sessions whit physical activity; and educational sessions, physical activity and dietary program. Each study has the year and place of development, number of participants, description of the intervention, its duration and the principal results

Results and discussion

In the initial search were identified 230.825 studies through the PubMed/Medline database, of which 224.146 studies were excluded due to lack of relevancy and 6.679 were selected. Of these publications, 6.581 were excluded and 98 were initially selected based on title and abstract. Of these publications, 68 articles we excluded after full text reading; in the end 30 met the inclusion criteria and were considered for this systematic review. The flowchart for the selection of trials is shown in Figure 2.

Results of several studies confirm that physical exercise is a key tool in glycemic control and lipid profile in type 2 diabetic patients. The practice of physical activity programs is correlated with better glycemic control and lipid profile since it decreases glycated hemoglobin levels (HbA1c),[17,46–52] fasting glucose[17,46,48,50,52,53] and postprandial levels,[48] insulin resistance[48,50,52,53] and fasting plasma insulin levels.[50,52–54] It is also observed a decrease in TG,[17,48,50,52,55] TC,[17,46,48,50–52] LDL,[17,46,50,52] Apo B 48[55] an increase in HDL-cholesterol.[17,46,48,50,51]

Regarding the mode of exercise, it was found in three studies[47,54,55] that combined exercise, compared to individual aerobic or resistance exercise, has better benefits to people with diabetes. The intensity of the exercise influences the lipid profile because a moderate to low aerobic exercise does not reduce TG.[50]

In two studies[48,52] it was found that aerobic resistance and flexibility exercise decreases HDL cholesterol. The fasting glucose increased in one study.[54]

In summary, with respect to changes caused by exercise in the different continents where the various studies were conducted it is demonstrated reduction of HbA1c, glucose, insulin, TG, TC, LDL cholesterol, Apo B 48, lower insulin resistance and HDL cholesterol increase. According with studies performed by Nojima et al.,[56] Kasumov et al.,[57] De Filippis et al.,[58] Lazarevic et al.[59] and Hordern et al.,[60] where it has also found that physical exercise is essential in the metabolic control of type 2 diabetes. The implementation of educational sessions that address the practice of physical activity and healthy eating were addressed in three of the studies analyzed. It can be seen that educational sessions that address the importance of physical activity and an healthy diet in diabetes control, in conjunction with aerobic exercise of moderate intensity, correlates with lower HbA1c,[61–63] glucose,[61,62] TC, LDL cholesterol, TG and increased HDL cholesterol.[62,63] Similar results were observed in a systematic review with meta-analysis performed by Steinsbekk et al. where the self-management education promotes better control of type 2 diabetes.[64]

Table 1 Risk of bias for each study included in the analysis.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gavin et al. (2010)[55]	+	?	?	?	+	+	+
Okada et al. (2010)[46]	?	?	?	?	+	+	+
Church et al. (2010)[47]	+	?	+	+	+	+	+
Wong et al. (2010)[65]	?	+	+	+	+	+	+
De Greef et al. (2011)[61]	+	+	+	?	+	+	+
Ariza Copado et al. (2011)[62]	?	?	+	?	+	+	+
Jorge et al. (2011)[48]	?	?	?	?	+	+	+
Larose et al. (2011)[49]	?	?	?	?	+	+	+
Ferrer-García et al. (2011)[17]	?	?	?	?	+	+	+
Cohen and Johnston (2011)[37]	?	?	?	?	+	+	+
Sharma et al. (2011)[73]	?	+	+	?	+	+	+
Kahleova et al. (2011)[67]	?	?	?	?	+	+	+
Andrews et al. (2011)[69]	+	+	+	+	+	+	+
Balducci et al. (2012)[50]	+	+	+	+	+	+	+
Balducci et al. (2012)[51]	?	?	?	?	+	+	+
Swift et al. (2012)[54]	?	?	−	+	+	+	+
Soric (et al. 2012)[75]	?	?	+	+	+	+	+
Breslavsky et al. (2013)[78]	?	?	?	+	+	+	+
Strobel et al. (2014)[76]	?	?	+	+	+	+	+
Kampmann et al. (2014)[77]	?	?	+	+	+	+	+
Ryu et al. (2014)[79]	+	+	+	+	+	+	+
Yuan et al. (2014)[63]	?	+	?	?	+	+	+
Asemi et al. (2014)[93]	?	?	+	+	+	+	+
Li et al. (2014)[72]	?	?	−	−	+	+	+
Stenvers et al. (2014)[70]	+	+	?	?	+	+	+
Vinetti et al. (2015)[52]	?	?	?	?	+	+	+

Table 1 (*Continued*)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Motahari-Tabari et al. (2015)[53]	+	?	?	?	+	+	+
Ostadrahimi et al. (2015)[94]	+	?	+	+	+	+	+
Hove et al. (2015)[95]	+	+	+	+	+	+	+
Tonucci et al. (2015)[96]	+	+	+	+	+	+	+

+ : low risk of bias; − : high risk of bias; ? : unclear risk of bias.

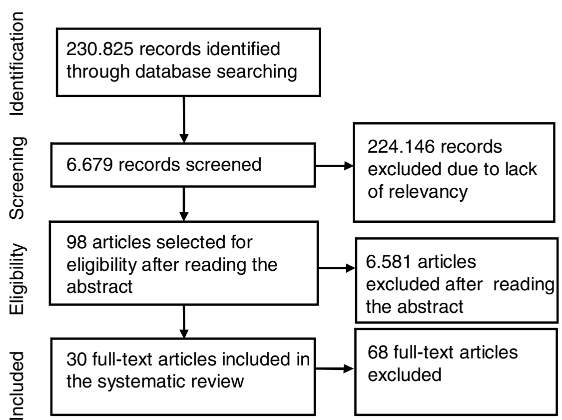

Figure 1 Percentage of risk of bias for each study included in the analysis.

A healthy and balanced nutrition is an essential component for the prevention and selfmanagement of type 2 diabetes.[1] A correct intake of the various food components, namely avoiding the excessive consumption of saturated fat and carbohydrates are important for obtaining a good glycemic and lipid control. A dietary program with emphasis on greater consumption of polyunsaturated fatty acids is correlated with lower levels of fasting glucose, TG, TC and LDL cholesterol.[65] This is in agreement with the results of the study of Lee et al.[66]

The intake of almonds reduces fasting blood glucose, HbA1c and increases fasting insulin. Regarding the lipid profile, there is an increase of TC and HDL cholesterol and a reduction of TG.[37]

The increased consumption of grains, fruit and vegetables alone (vegetarian diet) or in combination with supervised aerobic exercise correlates with decrease of HbA1c, glucose and fasting insulin, TG, TC and LDL. HDL cholesterol also decreases.[67] Given these results, the vegetarian diets may be beneficial for people with type 2 diabetes, as they induce glycemic and lipid control. However, we consider that is needed to be cautious in this matter as is also needed to carry out further studies in this field.

According to the study of Takahashi et al., the consumption of vegetables is correlated with improved control of HbA1c and TG levels in elderly type 2 diabetes.[68] Modifying the amount of macronutrients may improve glycemic and lipid control in patients with type 2 diabetes. Low-calorie, low-fat and low-GI diets correlate with lower levels of HbA1c, fasting glucose and insulin, insulin resistance, TC, LDL and HDL cholesterol. TG had a slightly increase. When this type of diet is combined with physical activity, the results obtained are similar.[69] When uncontrolled type 2 diabetes ingest a low glycemic index liquid breakfast, rich in polyunsaturated fatty acids, fiber and fructose, reduces fasting glucose, TC, LDL, HDL cholesterol and increase the fasting insulin.[70] Since participants had uncontrolled DM2, replacement of breakfast alone as well as the intervention period may not have been sufficient to provide long term glycemic control. Thus, further investigations should be conducted in this population over a longer period of time, replacing not only breakfast but other meals. The consumption of low glycemic foods at breakfast decreased the HbA1c, glycated serum protein and insulin. There was an increase of glucose, insulin resistance, TG, TC, LDL, HDL cholesterol, Apo A1 and Apo B.[71] Results of the systematic review and meta-analysis of Ajala et al.[72] they demonstrated that low-carbohydrate, low glycemic index, Mediterranean, and high-protein diets are effective in controlling the glycemic and lipid profile and should be part of the management of type 2 diabetes.

The effectiveness of the consumption of chromium, vitamin D and probiotics supplements were also studied in some articles selected for this revision.[73–82] The chromium supplementation for 3 months provides a reduction in HbA1c. And has also beneficial effects on dyslipidemia, since decrease TC, LDL cholesterol, VLDL cholesterol and TG levels, and increase HDL cholesterol.[73] The same is verified in a systematic review with meta-analysis performed by Suksomboon et al.[83]

Five of the studies analyzed the effectiveness of vitamin D supplementation in patients with type 2 diabetes.[74–78] The consumption of these supplements decrease the HbA1c,[74–76] glucose, insulin resistance[75] and increased insulin secretion.[76] Glucose increased in 3 studies,[76–78] such as HbA1c and insulin resistance.[77,78] Given this, it can be

Table 2 General description of the included trials in this review per intervention and continent.

Physical activity: American continent					
Author Reference	Year, Country	Group, number of patients	Description of intervention	Length of program	Results
Gavin et al.[55]	2010, Canada	Aerobic training group, 60	Aerobic training supervised, three times per week on a treadmill or cycle ergometer.	6 months	Triglycerides (TG) were reduced in resistance combined and aerobic exercise group, $p = 0.02/0.001/p > 0.05$. Apo B48 decreased in resistance and combined exercise group, $p < 0.05/p > 0.05$. In the aerobic exercise group increased, $p > 0.05$.
		Resistance exercise, 64	2–3 sets the resistance exercise supervised on weight machines, 2–3 days per week		
		Combined exercise, 64	Full aerobic plus the full resistance program.		
		Control, 63	Revert to their level of activity at baseline and to maintain this level		
Church et al.[47]	2010, USA	Aerobic exercise, 72	Aerobic exercise supervised at 50%–80% of maximum oxygen consumption with an energy expenditure of 12 kcal/kg per week	9 months	Compared with the control group, the HbA1c decrease 0.34% in the combined exercise group, 0.16% in resistance exercise group, and 0.24% in aerobic exercise group, $p = 0.03/032/0.14$. In diabetes patients with HbA1c ≥ 7 and compared with the control group, the combined exercise reduces HbA1c 0.53%, the aerobic exercise 0.50%, and 0.33% the resistance exercise, $p = 0.008/0.01/0.10$.
		Resistance exercise, 73	Resistance exercise supervised 3 days per week		
		Combination exercise, 76	2 resistance training sessions per week and aerobic exercise supervised with energy expenditure of 10 kcal/kg per week		
		Control, 41	Stretching and relaxation classes supervised. And was asked to maintain current activity during the study period		
Jorge et al.[48]	2011, Brazil	Aerobic, 12	60 min of aerobic exercise (cycling) 3 days per week	12 weeks	It has been found in 4 groups a reduction of fasting and postprandial glucose, $p < 0.05$. The HbA1c and insulin resistance decreased in the aerobic, resistance and combined exercise group and increased in the control group, $p > 0.05$. It was found in 4 groups decrease the TC and TG, $p < 0.05$. The HDL cholesterol had a decreased in the aerobic, resistance and control group, $p < 0.05$.
		Resistance, 12	60 min of resistance exercise supervised 3 days per week		
		Combined, 12	Aerobic and resistance exercise interchanged at the same intensity and half the volume of the aerobic and resistance group		
		Control, 12	Stretching exercises designed to provide participative involvement but not to elicit changes in muscle strength or cardiovascular fitness		

Table 2 *Continued*

Physical activity: American continent

Author Reference	Year, Country	Group, number of patients	Description of intervention	Length of program	Results
Larose et al.[49]	2011, Canada	Aerobic, 60	45 min of aerobic exercise supervised (treadmill or cycle ergometer) 3 days per week	6 months	Aerobic exercise and resistance reduced HbA1c (0.51/0.38%, $p = 0.007/0.037$) compared with the control group. In the group that practiced exercise combined the reduction was 0.46%, $p = 0.014$ compared to the group that practiced aerobic exercise and 0.59%, $p = 0.001$ compared to the group that performed resistance exercise.
		Resistance, 64	45 min of resistance exercise supervised on weight machines, 2–3 days per week		
		Combined, 64	Aerobic and resistance exercise supervised		
		Control, 63	Subsequent to the run-in phase, were asked to revert to their level of activity at baseline and to maintain this level for the remainder of the study		
Swift et al.[54]	2012, USA	Aerobic exercise, 50	Aerobic training supervised by study staff in exercise training laboratory.	9 months	There was a reduction in HbA1c from the group practiced combined exercise (0.34%, $p < 0.05$) compared with the control group (+0.24%). In the group aerobic exercise and resistance is also reduced (0.15/0.16%, $p > 0.05$). The increased fasting glucose in the 4 groups (aerobic exercise: 2.96 mg/dl; resistance: 4.76 mg/dl; combined: 0.46 mg/dl; control: 7.54 mg/dl) and fasting insulin decreased (aerobic exercise: 1.53 pmol/l resistance: 1.89 pmol/l; combined: 2.05 pmol/l; Control: 3.61 pmol/l, $p > 0.05$).
		Resistance exercise, 58	Resistance training supervised in exercise training laboratory 3 days per week		
		Combination exercise, 59	Combination of resistance and aerobic training in exercise training laboratory.		
		Control, 37	Stretching and relaxation classes and was asked to maintain their current activity during the study period.		

Physical activity: Asiatic continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Okada et al.[46]	2010, Japan	Exercise, 21	Aerobic and resistance exercise program from 3 to 5 days per week, supervised by physiotherapist.	3 months	The HbA1c was decreased in the exercise and control group, $p < 0.01$. Fasting blood glucose levels in plasma in the exercise group increased and decreased in the control group, $p > 0.05$. There was a decreased in both group the TC, $p > 0.05$, LDL cholesterol (exercise: $p < 0.01$; control: $p < 0.05$) and TG, $p > 0.05$. The HDL cholesterol increased (exercise: $p < 0.01$; control: $p < 0.05$)
		Control, 17	Without exercise training		

Table 2 *Continued*

Physical activity: Asiatic continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Motahari-Tabari et al.[53]	2015, Iran	Exercise, 27 Control, 26	Aerobic exercise 3 times a week Without exercise training	8 weeks	The fasting glucose was reduced in the exercise group and increased in the control group, $p = 0.06$. These changes were not statistically significant between groups, $p = 0.06$. Plasma insulin was reduced in both groups throughout the study $p = 0.002$. These changes were statistically significant between groups, $p = 0.007$. Insulin resistance was lower in the exercise group compared with the control group. These changes were statistically significant throughout the study and between groups, $p = 0.004/0.007$

Physical activity: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Ferrer-García et al.[17]	2011, Spain	Intervention, 44 Control, 40	45 min of combined physical exercise program (aerobic and anaerobic exercises) from 3 to 5 days per week, and conventional treatment for diabetes Conventional treatment for diabetes	24 weeks	HbA1c decreased in the experimental and control group, $p < 0.05$. The fasting glucose decreased in the intervention group, $p = 0.002$, and increased in the control group, $p = 0.10$. In the experimental group TG, TC and LDL decreased and HDL increased after 6 months ($p = 0.138/0.046/0.217/0.226$). In the control group TC, LDL and HDL were reduced and increased TG ($p = 0.624/0.220/0.460/0.032$).

Table 2 *Continued*

Physical activity: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Balducci et al.[50]	2012, Italy	Exercise moderate-to-high intensity (HI), 152 Exercise low-to-moderate intensity (LI), 136 Control, 303	Aerobic and resistance exercise supervised the moderate to high intensity 2 days per week and recommendations on both types of exercise every 3 months Aerobic and resistance exercise supervised the low to moderate intensity 2 days per week and recommendations on both types of exercise every 3 months Exercise counseling	12 months	There were lower HbA1c, fasting blood glucose, plasma insulin, insulin resistance in the LI group ($p = 0.005/0.030/0.009$) and the HI group ($p < 0.001/=0.003/=0.03/=0.003$). In the LI group, TG and HDL cholesterol increased ($p = 0.010/<0.001$), the TC and LDL cholesterol decreased ($p < 0.001$). In the HI group, there was a decrease of TG, TC and LDL, the HDL cholesterol increased ($p = 0.51/<0.001/<0.001/<0.001$).
Balducci et al.[51]	2012, Italy	Exercise group, 36 Control group, 34	75 min day of aerobic and resistance exercise supervised twice weekly. All participants received structured exercise counseling, encouraging any type of leisure-time physical activity Structured exercise counseling, encouraging any type of leisure-time physical activity	12 months	In the exercise group there were lower HbA1c, TC, and LDL cholesterol ($p < 0.001/=0.20/=0.04$). TG and HDL cholesterol increased ($p = 0.80/0.25$). In the control group HbA1c, TC, HDL and LDL cholesterol decreased ($p = 0.16/0.74/0.18/0.75$) and increased TG ($p = 0.035$).
Vinetti et al.[52]	2015, Italy	Intervention, 10	Aerobic, resistance and flexibility exercise supervised by personal trainers and hospital-based setting	12 months	The fasting plasma glucose decreased in intervention/control groups ($p = 0.32/0.26$). HbA1c decreased in the experimental group and increased in the control group ($p = 0.08/0.25$,these changes were not statistically significant between groups, $p = 0.75/0.05$). The same is observed with the fasting insulin ($p = 0.01/0.42$, these alterations were statistically significant between groups, $p = 0.02$), insulin resistance ($p = 0.02/p < 0.05$), TC ($p = 0.03/0.52$, these changes were not statistically significant between groups, $p = 0.05$), LDL cholesterol ($p = 0.04/>0.05$) and

Table 2 *Continued*

Physical activity: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
		Control, 10	Standard medical care only		TG ($p=0.11/0.33$. These changes were statistically significant between groups, $p=0.06$). HDL cholesterol decreased in the 2 groups ($p=0.79/0.20$). This reduction was not statistically significant between the groups $p=0.29$.

Dietary program: American continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Cohen and Johnston.[37]	2011, USA	Almond, 7 Control, 6	28 g almond ingestion 5 day/week 2 cheese sticks ingestion 5 day/week	12 weeks	The consumption of almond decreased the HbA1c, $p=0.045$, glucose concentration, $p=0.305$ and TG, $p>0.05$. The fasting insulin increased in groups 2, $p=0.610$. The TC and LDL increased consumption almond group and decreased in the control group, $p>0.05$.
Soric et al.[75]	2012, USA	Vitamin D, 19 Vitamin C (control), 18	2000 IU vitamin D3 (cholecalciferol) daily by mouth 500 mg vitamin C daily by mouth.	12 weeks	The HbA1c decreased in Vitamin D group and increased in control group, $p=0.16$. In the subgroup analysis, diabetic patients with baseline HbA1c > 9% who had received vitamin D, have a largest decline in HbA1c (−1.4%, $p=0.013$) compared to those with values between 8 and 8.9% (+0.3, $p=0.90$) and between 7 and 7.9% (+0.1%, $p=0.50$).
Toinucci et al.[96]	2015, Brazil	Probiotic, 23	120 g/daily of fermented milk fermented milk containing *Lactobacillus acidophilus La-5* and *Bifidobacterium animalis subsp lactis BB-12*	6 weeks	HbA1c decreased in the probiotic group and increased in the placebo group, $p=0.06/0.82$. These changes were statistically significant between groups $p=0.02$. The fasting glucose increased in 2 groups $p=0.14/0.65$,

Table 2 *Continued*

Dietary program: American continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
		Placebo, 22	Conventional fermented milk.		no statistically significant differences between groups, $p = 0.48$. The same is observed with insulin resistance, $p = 0.41/0.7$; between groups: $p = 0.77$, and TG, $p = 0.16/0.08$, between groups: $p = 0.62$. Insulin decreased in the 2 groups, $p = 0.73/0.95$, no statistically significant differences between groups, $p = 0.72$. The TC, LDL and HDL cholesterol were reduced in the probiotic $p = 0.52$; $p = 0.31$; $p = 0.50$, and increased in the placebo group, $p = 0.01$, $p = 0.004$; $p = 0.59$. These changes were statistically significant differences between groups for the TC/LDL values, $p = 0.04/0.03$, but not HDL cholesterol, $p = 0.38$.

Dietary program: Asian continent

Author reference	Year, Country	Group, number of patients	Description of intervention	Length of program	Results
Wong et al.[65]	2010, China	Fish oil, 49 Control, 48	Fish-oil (4 g/day) supplements Olive-oil, with equivalent calories of fish-oil supplements	12 weeks	The consumption of fish oil reduced the serum TG, $p < 0.01$, TC, $p = 0.08$, LDL cholesterol, $p = 0.53$, HDL cholesterol, $p = 0.65$ and fasting glucose, $p = 0.08$.
Sharma et al.[73]	2011, India	Experimental, 20 Control, 20	9 g brewer's yeast (42 μg chromium) daily. 3 capsules after breakfast, lunch and dinner with either milk or water Received yeast devoid of chromium	3 months	There was a reduction in the experimental group/control in the HbA1c, $p < 0.001/<0.01$, TC, $p < 0.02/<0.08$, LDL cholesterol, $p < 0.001/<0.04$ and VLDL cholesterol, $p < 0.04/<0.02$. The TG decreased in the experimental group and increased in the control group, $p < 0.05/<0.09$. HDL cholesterol increased in the experimental group, and decreased in the control group, $p < 0.5/<0.06$.

Table 2 *Continued*

Dietary program: Asian continent					
Author reference	Year, Country	Group, number of patients	Description of intervention	Length of program	Results
Breslavsky et al.[78]	2013, Israel	Group 1, 24 Group 2 (control), 23	Oral daily supplementation with vitamin D (1000 U/day) Placebo capsules	12 months	In group 1, fasting glucose, HbA1c, insulin, and insulin resistance increased, $p > 0.05$. The same was found with TC, HDL and LDL cholesterol, $p > 0.05$. Only the TG decreased, $p > 0.05$. In group 2 only registered lower HbA1c, $p > 0.05$. The fasting glucose, insulin, insulin resistance, TC, HDL cholesterol, LDL cholesterol and TG increased, $p > 0.05$.
Ryu et al.[79]	2014, Korea	Vitamin D, 40 Placebo, 41	Cholecalciferol 2000 IU/day and calcium 200 mg/day Calcium 200 mg/day	24 weeks	HbA1c, insulin resistance and TG increased in the vitamin D group and decreased in placebo group, $p = 0.280/0.981/0.682$. The fasting blood glucose increased 3.2 ± 27.5 mg/dl in vitamin D group and 28.2 ± 3.9 mg/dl in the placebo group, $p = 0.891$. The CT, LDL and HDL cholesterol increased in the vitamin D group and in the placebo group, $p = 0.248/0.092/0.998$.
Asemi et al.[93]	2014, Iran	Synbiotic food, 31 Control food, 31	27×10^7 UFC *L. sporogenes* and 1.08 g inulin each day. Same substance without probiotic bacteria and insulin	6 weeks	The consumption of probiotic compared with the control resulted in a decrease in serum insulin levels, $p = 0.03$. The fasting plasma glucose also decreased in the probiotic group and increased in the control group. The same is observed with insulin resistance. The serum levels of TG, TC and LDL cholesterol increased in 2 groups. The HDL cholesterol increased in the group that consumed probiotic, and decreased in the control group. All these changes were not statistically significant, $p > 0.05$.

Table 2 *Continued*

Dietary program: Asian continent					
Author reference	Year, Country	Group, number of patients	Description of intervention	Length of program	Results
Li et al.[72]	2014, China	Breakfast replacement, 36 Control, 18	75 g of the low glycemic index multi-nutrient supplement (provides 346 kcal energy) in place of breakfast Healthy breakfast	12 weeks	In breakfast replacement group showed a decrease in HbA1c, glycated protein in the serum, $p < 0.01$ and insulin, $p > 0.05$. The fasting glucose and insulin resistance increase, $p > 0.05$. In the control group there was an increase in fasting blood glucose, HbA1c, insulin resistance, $p < 0.05$ and insulin, $p > 0.05$. Glycated serum protein decreased, $p < 0.05$. In the breakfast replacement group TG, TC, HDL cholesterol, Apo A1 and Apo B increased, $p > 0.05$. In the control group there was a decrease of TG, TC and LDL cholesterol, $p < 0.05$) and increased HDL-cholesterol, Apo A1, $p > 0.05$ and Apo B, $p < 0.005$.
Ostadrahimi et al.[94]	2015, Iran	Intervention, 30 Placebo, 30	600 ml fermented milk (kefir) containing probiotics twice a day (in lunch and dinner) 600 ml conventional fermented milk (dough) twice a day (in lunch and dinner)	8 weeks	There was a decrease in serum glucose in both groups (intervention: $p = 0.05$; placebo: $p > 0.05$, this decrease was statistically significant between groups, $p = 0.03$. HbA1c decreased in the intervention group and increased placebo group, $p = 0.001/p > 0.05$, these changes were statistically significant between groups, $p = 0.02$. The TC, LDL cholesterol and TG levels decreased in both, $p > 0.05$. The HDL cholesterol decreased in the intervention group and increased in the placebo group, $p > 0.05$.

Table 2 *Continued*

Dietary program: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Strobel et al.[76]	2014, Germany	Verum, 40 Placebo, 40	20 drops vigantol oil once a week, corresponding to a daily dose of 1904 IU/day Placebo oil consisting of medium chain triglycerides	6 months	The fasting glucose and HbA1c decreased in the 2 groups (verum, $p = 0.282/0.245$; control: $p = 0.85/0.064$). Insulin increased in the 2 groups, $p = 0.492/0.013$. The decreased insulin resistance in verum group and increasing in the control group, $p = 0.954/0.030$. The HbA1c value was lowest at baseline and after intervention in diabetic patients with levels of 25-hydroxy-vitamin D > 20 ng/ml, $p = 0.008/0.009$.
Kampmann et al.[77]	2014, Denmark	Vitamin D, 7 Placebo, 8	Colecalciferol (280 μg daily for 2 weeks, 140 μg daily for 10 weeks) Identical placebo tablets	12 week	HbA1c decreased in vitamin D group, and placebo group, $p = 0.79/0.07$. Glucose increased in 2 groups, $p = 0.78/0.73$; none of these changes was statistically significant between groups, $p = 0.13/0.89$. Insulin in serum increased in the vitamin D group and decreased in the placebo group, $p = 0.087/0.95$, and insulin secretion increased in the 2 groups, $p = 0.22/0.25$. None of these changes was statistically significant between groups, $p = 0.28/0.34$. The TC ($p = 0.90/0.61$) and LDL ($p = 1.00/0.16$) increased in vitamin D and placebo group, and HDL decreased in the 2 groups, $p = 0.65/0.92$. None of these changes was statistically significant between groups, $p = 0.71/0.28/0.78$.
Stenvers et al.[70]	2014, Nederlands	Low glycaemic response (GR), 9	103 ml of Glucerna SR	3 months	In the low glycaemic response group there was a decrease in fasting glucose, TC, LDL and HDL cholesterol. Fasting insulin increase, and HbA1c was maintained. In the control group increased fasting glucose, HbA1c, fasting insulin,

Table 2 *Continued*

Dietary program: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
		Control, 11	Free-choice breakfast		LDL and HDL cholesterol, and decreased TC. None of these changes was statistically significant, $p > 0.05$.
Hove et al.[95]	2015, Denmark	Cardi04 yogurt, 23 Placebo, 18	300 ml milk fermented with *L. helveticus* (Cardi04 yogurt) 300 ml artificially acidified milk (placebo yogurt)	12 weeks	HbA1c increased in the Cardi04 yogurt group and placebo group, $p = 0.740$. Compared to placebo group, the plasma glucose and insulin resistance decreased in the Cardi04 yogurt group, $p = 0.525/0.022$. The C-peptide, insulin, CT and LDL cholesterol increased, $p = 0.616/0.628/0.835/0.851$. HDL cholesterol and proinsulin decreased, $p = 0.092/0.035$. The TG showed the same value. In the control group, TC, LDL, HDL, TG and proinsulin increased. The C-peptide and insulin decreased, $p < 0.05$.

Physical activity and dietary program: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Kahleova et al.[67]	2011, Czech Republic	Experimental, 37 Control, 37	12 weeks of vegetarian diet. The second 12 weeks of the diet were combined with aerobic exercise. 12 weeks of conventional diabetic diet. The second 12 weeks of the diet were combined with aerobic exercise	24 weeks	The HbA1c and fasting glucose were reduced in the experimental group to 3/6 months, $p < 0.001$. In control group HbA1c decreased to 3/6 months, $p < 0.001/p = 0, 370$. The fasting plasma glucose decreased to 3/6 months, $p < 0.01/p = 0.420$. The fasting plasma insulin decreased at 3/6 months in the experimental group, $p < 0.05/0.001$ and experimental group, $p = 0.780$. In experimental group to 3/6 months decreased the TC, TG, LDL and HDL cholesterol, $p = 0.730/p = 0.120/p < 0.05/p = 0.070$. In the control group at 3 months increased TC and decreased at 6 months, $p = 0.730$. HDL cholesterol increased, $p = 0.70/p < 0.05$, LDL cholesterol was reduced, $p = 0.050$ and increased TG, $p = 0.12$.

Table 2 *Continued*

Physical activity and dietary program: European continent					
Andrews et al.[69]	2011, England	Dietary Intervention, 248 Dietary intervention and physical activity, 246 Control, 99	Intensive diet intervention to lose 5–10% of their initial bodyweight and to maintain this loss throughout the study. Plus dietary consultation every 3 months with monthly nurse support. Intensive diet intervention plus a pedometer-based physical activity program. Initial dietary consultation and follow-up every 6 months	12 moths	Compared with the control group, HbA1c decreased in dietary intervention group and physical activity and dietary intervention group, $p = 0.005/0.027$. The same is observed with glucose, $p < 0.0001/p = 0.01$, and fasting insulin, $p = 0.001/0.022$. Insulin resistance decreased in the diet intervention group and dietary intervention and physical activity, $p = 0.0001/0.011$. The insulin secretion decreased in the dietary intervention group diet and dietary intervention and physical activity group, $p > 0.05$. The TC decreased in the dietary intervention group and dietary intervention and physical activity, $p > 0.05$. The LDL and HDL cholesterol decreased in the dietary intervention group and increased in dietary intervention and physical activity group. TG increased in the dietary group and decreased in dietary intervention and physical activity group, $p > 0.05$.

Educational sessions: European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
De Greef et al.[61]	2011, Belgium	Individual consultation, 22 Group counseling, 21 Control, 24	Physical activity individual counseling by a general practitioner Physical activity group counseling by a general practitioner General care from their general practitioner	12 weeks	The participants of individual, counseling/group and control group had a decrease in HbA1c value, $p \leq 0.05$. The fasting glucose also decreased, $p < 0.05$, and increased in the control group, $p > 0.05$. The TC increased in the 3 groups, $p > 0.05$.

Table 2 *Continued*

Educational sessions and physical activity European continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Ariza Copado et al.[62]	2011, Spain	1: diabetes education, 27	Educational sessions with basic content on diabetes mellitus	6 months	Compared with the control group, HbA1c decreased in 3 groups (Group 1: −1.00; Group 2: −1.93, Group 3: −1.56%). The same is true of glucose (−1.00, −1.45, −1.48 mg/dl), TC (−1.08; 1.48; −1.20 mg/dl), LDL (−1.44, 1.82, 1, 27 mg/dl), TG (−1.08; −1.04; −1.04 mg/dl). HDL cholesterol increased in the 3 groups (+1.00, +1.17, +1.11).
		2: diabetes education and physical, exercise, 28	Educational sessions with basic content on diabetes mellitus and 3–4 sections/week of aerobic exercise of moderate intensity with a duration of 60–90 min each.		
		3: physical exercise, 26	3–4 sections/week of aerobic exercise of moderate intensity with duration of 60–90 min each.		
		4: control, 27	It was followed in normal diabetes consultations.		

Educational sessions, physical activity and dietary program: Asiatic continent

Author reference	Year, country	Group, number of patients	Description of intervention	Length of program	Results
Yuan et al.[63]	2014, Japan	Intervention, 44	8-week education on self-management of diabetes mellitus and subsequent 4 weeks of practice of the self-management guidelines	3-month	HbA1c levels decreased in the intervention group and increased in the control group, $p = 0.039/0.102$, the same was found with fasting glucose, $p = 0.238/0.427$ and TG, $p = 0.626/0.850$. In both groups there was a decrease in TC, $p = 0.034/<0.001$, LDL, $p = 0.005/<0.001$). The HDL cholesterol increased in intervention group and decreased in the control group, $p = 0.160/0.303$).
		Control, 44	Standard advice on medical nutrition therapy		

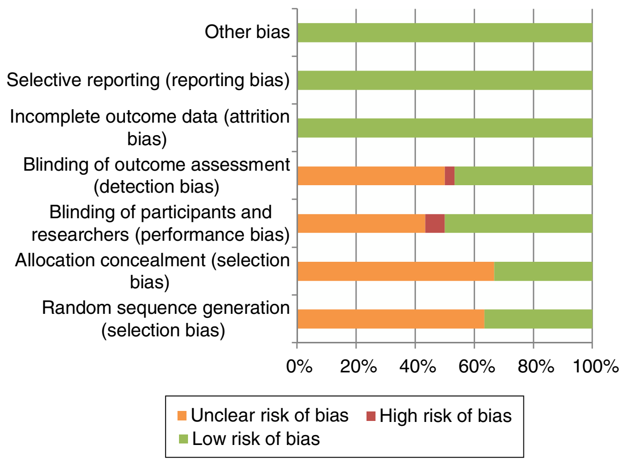

Figure 2 Flowchart depicting the study selection procedure.

seen that vitamin D supplementation provides a blood glucose control in the short and long term only in studies in the American and European continent. In Asia it was not found relation to benefits. This may be due to different lifestyles and eating habits of each region.

The lipid level results were not favorable because there was an increase in total cholesterol, LDL, HDL,[77,78] TG increased in one study[78] in another decreased.[77] This discrepancy may be due to the fact that vitamin D administered was not the same in all studies, as well as the duration of treatment, of serum levels of vitamin D of the participants could be different, researchers may not have taken into account the sun exposure of the participants in the studies. Some scientific evidence has suggested that vitamin D may play a causal role in the development of diabetes and its complications. Deficiency of this vitamin is associated with increased risk of cardiovascular disease, obesity, diabetes mellitus, dyslipidemia and hypertension. High serum vitamin D concentrations have a protective effect on glucose intolerance, insulin resistance and the risk of developing DM2. The use of supplements of this vitamin in glycemic control, insulin resistance and lipid profile is not yet clear, although some studies have shown beneficial effects.[84–96] Four studies have analyzed the influence of the consumption of probiotics in patients with type 2 diabetes.[79,82] It was found a decrease in glucose,[79–81] HbA1c,[80,82] insulin[79,82] and insulin resistance.[79,81] Glucose and insulin resistance only increased in one study,[82] as well as HbA1c.[81] The consumption of probiotics in studies conducted in Asia translates into control of the short and long term blood sugar. On the European continent there was only a blood glucose control of short term and on the American continent the control was long-term.

There was a decrease in TC, LDL and TG in two studies,[80,82] and increased in two other studies.[79,81]The HDL cholesterol increased only in one study[79] and decreased in the remaining.[80–82] It may also be noted that only the administration of probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium* provided lipid control. This discrepancy results may be due to five facts: the probiotic used, the amount administered, the time of administration, the duration of the treatment was not the same, as well as the continent where the studies were conducted (different dietary habits and lifestyles).

Since not all studies replicate positive results after taking vitamin D supplements and probiotics, the association between this supplementation and glycemic and lipid profile in type 2 diabetic elderly patients had a somewhat uncertain development. To provide more evidence is necessary to perform further studies to confirm the potentially beneficial relationship between supplementation with vitamin D and probiotics on glycemic and lipid profile in patients with type 2 diabetes.

Regarding the evaluation of the quality of the selected studies, as can be seen in the Figure 1, it was found that most of the articles feature uncertain selection bias because they do not describe in detail the method used to generate the random sequence and to hide this sequence; half of the articles do not describe what measures used to blind outcome assessors in relation to knowledge of the intervention provided to each participant and the results according to what has been proposed. With regard to attrition and reporting bias, all studies are at low risk since all describe the sample size at the beginning and at the end of the study. If any participant was deleted or abandoned the study that fact is referenced as well the reasons for that.

Our study shows, however, some limitations that should be considered when interpreting the results, such as the intensity and type of exercise and different diet plans may affect the outcome; different duration of the programs, and the population studied in the various articles are also heterogeneous. The exercise and usual practice of physical activity and eating habits may be over underestimated, lack of monitoring of patients after program to evaluate the persistence of potential long-term benefits and unclear risk of bias in the included studies.

Another of the limitations is the fact that pharmacological treatment for diabetes is not taken into account as well as the use of dietary supplements or other treatments, particularly to lose weight. All this makes it difficult to compare the studies and their results.

Although, some articles do not show favorable results regarding the implementation of dietary programs, and prevails a greater number of articles that highlights the importance of nutrition education, physical activity and healthy eating on glycemic control and lipid profile in patients with type 2 diabetes. We understand therefore that it is appropriate to continue to perform this type of intervention, since they have lower cost if compared with pharmacological treatments, but in a longer period of time in order to prove the long-term results.

Conclusions

Given the high prevalence of type 2 diabetes in the population, particularly in the elderly population, and considering that this pathology tends to increase with age, it becomes crucial to change behaviors in activities of daily living, promoting more active and healthy lifestyles throughout life. Physical activity, dietary programs and health education sessions regarding the importance of changing lifestyles according to scientifically valid information are revealed as complementary therapeutic strategies in treatment and metabolic control of type 2 diabetes.

Conflict of interest statement

The authors state that they have no conflicts of interest.

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