WHICH IS THE MOST EFFECTIVE MODE, INTENSITY, FREQUENCY AND TIME OF EXERCISE IN IMPROVING GLUCOSE AND INSULIN LEVELS ON NON-DIABETIC ADULTS AT RISK OF TYPE 2 DIABETES?

¿Cuál es el modo, intensidad, frecuencia y tiempo de ejercicio más eficaces para mejorar los niveles de glucosa e insulina en adultos no diabéticos con riesgo de diabetes tipo 2?

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RESUMEN

Introducción: La diabetes tipo 2 y pre-diabetes son condiciones que han incrementado su prevalencia en los últimos años. Individuos con uno o más factores de riesgo modificables (pre-diabetes, sobrepeso, falta de actividad física) son más propensos a desarrollar diabetes tipo 2. El ejercicio juega un papel crucial en la reducción de estos factores de riesgo, si bien la manera más efectiva, la intensidad, la frecuencia y el tiempo de ejercicio siguen sin estar claros. Objetivo: Esta revisión sistemática pretende determinar la frecuencia más efectiva, la intensidad y el tipo de ejercicio adecuados para incrementar los niveles de glucosa e insulina en adultos no diabéticos con riesgo de diabetes tipo 2. Método: Búsqueda doctrinal de estudios aleatorios realizada en Pubmed, PEDro, Science Direct, OT Seeker y Hooked on Evidence (hasta mayo de 2015) con diferentes palabras claves aisladas o combinadas ("tolerancia alterada a la glucosa", "prediabetes", "prevención de diabetes tipo 2", "actividad física", "ejercicio aeróbico" y "ejercicio de resistencia"). La calidad metodológica de esos estudios se evaluó mediante el uso de la escala de PEDro. También se utilizó la guía de The Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Resultados: La búsqueda culminó en seis artículos. Su calidad varió en una puntuación de entre 5/10 y 6/10 conforme a la escala PEDro. Cuatro de ellos incluyen un grupo de control sin intervención de ejercicio, el resto solo compararon grupos de ejercicio. Salvo un artículo que comparaba ejercicios de aguante y resistencia y otro que comparaba ejercicio aeróbico con ejercicio aeróbico más ejercicio de resistencia, el resto de artículos comparaban programas de ejercicio aeróbico con diferentes intensidades y volúmenes. Conclusiones: Debido a las diferencias metodológicas entre los distintos estudios, no resulta posible responder con precisión a la pregunta principal. Sin embargo, resulta evidente que el ejercicio aeróbico y de resistencia son beneficiosos para el incremento de resistencia y sensibilidad a la insulina.

Palabras claves: Tipo de diabetes, tiempo de ejercicio, intensidad.

ABSTRACT

Introduction: Type 2 diabetes and pre-diabetes are conditions that have increased their prevalence in recent years. Individuals with one or more modifiable risk factors (pre-diabetic, overweight, physical inactivity) are more likely to develop type 2 diabetes. Exercise plays a crucial role in reducing these risk factors although the most effective mode, intensity, frequency and time of exercise remains unclear. Objective: This systematic review seeks to know the most effective frequency, intensity, time and type of exercise to improve glucose and insulin levels in non-diabetic adults at risk of type 2 diabetes. Methods: Literature search of randomised controlled trials was conducted in Pubmed, PEDro, Science Direct, OT Seeker and Hooked on Evidence (until May 2015) with different keywords alone and in combination ("impaired glucose tolerance", "prediabetes", "type 2 diabetes prevention", "physical activity", "aerobic exercise" and "resistance exercise"). The methodological quality of the studies was assessed using PEDro scale. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was used. Results: The screening culminated in six articles. The quality ranged from 5/10 and 6/10 in the PEDro scale. Four of them include a control group with no exercise intervention, others only compared exercise groups. Except one article comparing endurance and resistance exercises, and one that compared aerobic exercise with aerobic plus resistance exercise, the remaining articles compared aerobic exercise programs with different intensities and volumes. Conclusions: Due to methodological differences between the studies it's not possible to answer accurately to the guiding question. However, it is evident that aerobic and resistance exercise are beneficial in improving insulin resistance and sensitivity.

Key words: Type diabetes, time of exercise, intensity.

INTRODUCTION

Diabetes is considered a worldwide epidemic with high human, social and economic costs. According to the World Health Organization (WHO), it is expected that between 2000 and 2030 the number of people with type 2 diabetes will increase from 170 million to 500 million people [(1)]. European data for 2011 pointed to 52 million people with

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diabetes aged 20-79 years, with an increased forecast for 64 million in 2030 and the consequent increase in the cost of health care [2].

The prevalence of this condition assumes particular importance in worldwide healthcare but it is not inevitable. There are several risk factors that can be divided into two categories: non-modifiable and modifiable risk factors. Among the major modifiable risk factors are considered overweight/obesity, sedentary lifestyle/physical inactivity, metabolic syndrome, disturbances in the intra-uterine development, impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and diet [3 - 4]. Several systematic reviews and meta-analysis centered on lifestyle interventions (concerning physical activity) in patients with type 2 diabetes have been carried out [5 - 11]. Despite the diversity of this interventions, all the authors agree in the importance of exercise for the improvement of glycemic control and insulin resistance.

Lifestyle interventions are crucial for the management of type 2 diabetes even if this condition can only be controlled, it has no cure. For this reason primary prevention is becoming particularly important in populations at risk, such as pre-diabetics. There is no consensus in the definition of pre-diabetes, but IFG and/or IGT are the two risk factors commonly used to identify people with pre-diabetes [12]. However the values considered for the definition of IFG and IGT are not consensual between countries. Usually IFG is defined as fasting glucose between 100-125mg/dl (5,6-6,9mmol/L). IGT is present when blood glucose values are between 140-199mg/dL (7,8-11,0mmol/L) two hours after ingestion of 75g of glucose diluted in 300cc of water (oral glucose tolerance test - OGTT). According to the American Diabetes Association values between 5.7% and 6.4% of glycated haemoglobin (HbA1c) may also be used to identify pre-diabetes. Note that subjects with IFG are 4.6 more likely to develop type 2 diabetes and IGT subjects are 6.3 more likely. If both conditions are present (IFG and IGT) this probability increases to 12.1 [12 - 13].

The prevalence of type 2 diabetes is particularly high in overweight individuals. According to recent studies, obese individuals are 42.1 more likely to develop type 2 diabetes (follow-up of 5 years) compared to subjects with normal weight [12]. Especially in pre-diabetic condition, physical inactivity is considered a main risk factor [14].

Therefore, an individual with one or more of these modifiable risk factors can be considered as someone with greater likelihood of developing type 2 diabetes [9, 15].

In general, the most relevant studies focused on lifestyle changes in individuals at risk of developing type 2 diabetes are consensual regarding the benefits of physical exercise [16 - 20]. However, since that physical activity is not usually considered independently of other variables, such as weight loss, diet or pharmacological therapy, it becomes difficult to quantify the contribution of exercise alone in improving the diabetes risk factors (primarily glucose and insulin regulation)[14, 18, 21, 22]. Concerning this purpose, recent study designs investigated the effects of exercise as an independent variable in individuals diagnosed with type 2 diabetes [7, 23] and non-diabetics [24, 25]. Mainly the definition of the most effective frequency, intensity, time and type of exercise (FITT) in improving diabetes risk factors or complications still remains questionable, despite the latest recommendations [13]. Randomized controlled trials (RCT), primarily investigating aerobic and resistance training in diabetic patients, are not conclusive in response to FITT, although underline the benefit of exercise compared to physical inactivity [26 - 29].

The aim of this systematic review is to assess the most effective frequency, intensity, time and type of exercise to improve glucose and insulin levels in non-diabetic adults at risk of developing type 2 diabetes.

METHODS

Study design

This systematic review was developed using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for randomised trials[30].

Search Strategy

Identification of studies

The literature search was performed by four reviewers between 27 April and 11 May 2015 and included the following databases: PubMed, PEDro, Science Direct, OT Seeker and Hooked on Evidence. The following keywords alone and in combination were used: 'impaired glucose tolerance', 'prediabetes', 'type 2 diabetes prevention', 'physical activity', 'aerobic exercise' and 'resistance exercise'. Additionally secondary research was conducted within the reference lists of all articles considered of interest (including systematic reviews on the topic) to retrieve relevant publications that were not identified in the computerised database search.

Eligibility criteria included full-text RCT published in English until May 2015 found in peer-reviewed journals. Population needed to involve non-diabetic human adults (≥18 years) at risk of developing type 2 diabetes (mainly pre-diabetics). The intervention should include an exercise program (aerobic or resistance exercise) that had to be compared with a control group – other exercise program (aerobic, resistance or combined exercise) or no exercise. The following outcome measures had to be used for inclusion: fasting glucose and insulin blood levels, insulin sensitivity and insulin resistance. Pre- and post-intervention means and standard deviations for experimental and control groups had to be present. There was no restriction in the follow-up period for the outcome measurement.

Study selection

The studies selection was conducted in two phases. The first consisted in the evaluation of the article titles found (independently by the four reviewers). Each article was considered to the next stage if the title identified terms of the PICO (participants, intervention, comparison, and outcome). The second phase consisted in reviewing abstracts of the articles considered with potential interest. In case there was insufficient information from the abstract to allow the eligibility, articles were divided into two groups of reviewers (two elements in each group) for full-text reading independently. Any disagreement was resolved by consensus.

Quality assessment of studies

The methodological quality of individual studies was assessed using the PEDro scale. This scale uses 11 criteria to evaluate the risk of bias of RCT. Three reviewers independently assessed the quality of the selected studies. Each reviewer assigned one point to the criterion satisfied. Potential maximum value is 10 points because the first criterion doesn't account for the score. In case of disagreement, the issue was resolved by consensus discussion with a 4th reviewer.

Summary measures

The interventions were evaluated by calculating mean differences, effect size (Cohen's d value) and 95% confidence interval. The flow of participants through the study was also recorded (withdrawal rate).

It has not been possible to conduct a full meta-analyses because of the varying methods with which each outcome had been measured.

RESULTS

Selection of studies

One hundred and sixteen titles were identified through database and reference list searches. After the removal of

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two duplicate articles and abstract screening the search was reduced to seventeen articles of potential interest. Further review of full-text led to the exclusion of other eleven studies, related to inappropriate study design and other methodological features. Six articles (31 - 36) were included in this systematic review (332 participants). Figure 1 shows the process of study selection with reasons for exclusion. Table 1 describes the population, intervention, comparison, outcome measures and length of follow-up of the six reviewed articles. One study included only male participants (32) and another only female (33). The number of participants ranged from 10 (34) to 154 (31). Four studies included a control group with no exercise intervention (31, 32, 35, 36), however in the study conducted by Hansen et al (35) the control group was subsequently performed with an exercise program. Two other studies only compared groups with exercise, where each group served as their own control (33 - 34). The majority compared aerobic exercise programs with different intensities and volumes (31 - 34). The exceptions were the studies of Liu et al (36) and Hansen et al (35). The first compared aerobic exercise with aerobic combined with resistance exercise, and the second compared maximal and endurance resistance training.

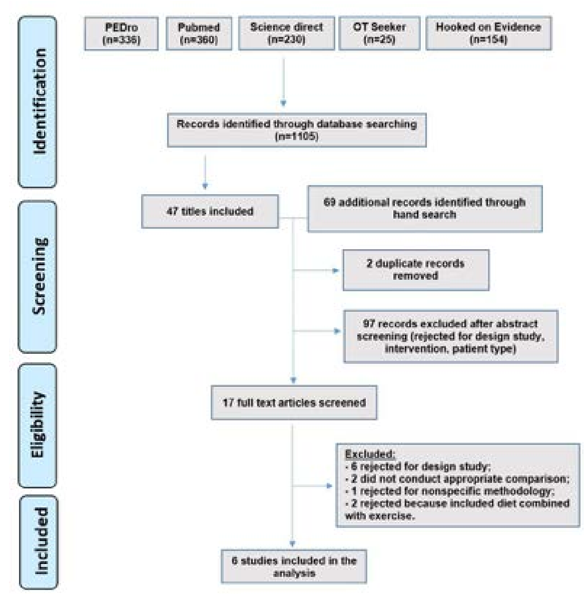

Figure 1. Flow diagram for study inclusion.

Table 1. Description of studies included in the review.

Study	Participants	Intervention	Comparison	Length of follow-up	Outcome measures
Houmard et al (31)	Sedentary and overweight subjects Control group: N=40 (M=23; F=17) Age: 51,4 ± 1,2 years Group 1: N=41 (M=24; F=17) Age: 53,1 ± 0,9 years Group 2: N=30 (M=15; F=15) Age: 52,6 ± 1,3 years Group 3: N=43 (M=23; F=20) Age: 51,4 ± 0,9 years	Group 1 – low volume/moderate intensity 1200 Kcal/week; 40-55% VO2max; Frequency: 3,3 ± 0,1 sessions/week; Duration: 51,5 ± 1,1 min/session; Week duration: 171 ± 5,9 min/week Group 2 – low volume/high intensity 1200 Kcal/semana; 65-80% VO2max; Frequency: 2,9 ± 0,1 sessions/week; Duration: 39,1 ± 1,1 min/session; Week duration: 114,4 ± 5 min/week Group 3 – high volume/high intensity 2000 Kcal/semana; 65-80% VO2max; Frequency: 3,6 ± 0,1 sessions/week; Duration: 47,9 ± 1,6 min/session; Week duration: 167 ± 6,9 min/week Exercise mode: walking or jogging in cycle ergometer, treadmill and elliptical	Control group Without exercise	6 Months	SI (Insulin sensitivity); Fasting insulin; Fasting glucose;

O'Donovan et al [32]	Sedentary men; Age: 30-45 years Control group: N=13 Group 1: N=10 Group 2: N=13	Group 1 – Moderate intensity exercise 400Kcal/session; 60% VO2max; 3 sessions/week Group 2 – High intensity exercise 400Kcal/session; 80% VO2max; 3 sessions/week	Control Group Without exercise	6 Months	Fasting insulin; Fasting glucose; Insulin sensitivity; Insulin resistance (HOMA-IR)
DiPietro et al [33]	Elderly female; Sedentary/inactive; 52% classified as IGT Mean age: 73±10 years Control group: N=7 Group 1: N=9 Group 2: N=9	Group 1 – High intensity exercise 80% VO2max; Mean heart rate: 123 beats/min Group 2 – Moderate intensity exercise 65% VO2max; Mean heart rate: 104 beats/min Protocol for both groups: 300Kcal/ session; 4 sessions/week; Training mode: 15-20 min of treadmill plus 5 min of mini-trampolines, rowing ergometers or step aerobics (maintaining target heart rate)	Control group Placebo low intensity exercise 50% VO2max; Mean heart rate: 81 beats/min Protocol: stretching and strengthening exercises using Thera-bands, Thera-balls and balance boards; 4 sessions/week; 45 min/session	9 Months	Fasting glucose; Fasting insulin; M value 10 mU; M value a 40 mU; M40/I, µU/ml
Hansen et al [35]	Overweight; Sedentary/inactive; Classified as IGT; N=18 (M=4; F=14); Age: 33-69 years Group 1: N=9 Group 2: N=7	Group 1 – Maximal resistance training (MRT) 8 exercises involving the whole body; 60-85% of 1RM (3-4 repetitions); 5 bouts (≈ 20 repetitions) in the set; Without breaks between bouts; 3 days/week Group 2 – Endurance resistance training (ERT) 8 exercises involving the whole body; 45-65% of 1RM; 3 bouts at 12-13 repetitions for ≈ 45 repetitions); break between bouts 30-60 seconds	Group 2 (control) Note: Initially group 2 was the control for group 1. After 4 months, group 2 subsequently performed 4 months of ERT, acting as their own control (pre-training baseline values).	4 months (intervention in group 1) + 4 months (intervention in group 2)	Fasting glucose; OGTT2h; Insulin blood levels; Insulin resistance and sensitivity estimation
Liu et al [36]	Pre-diabetic adults (classified as IGT) Mean age: 49,8±4,8 years Control group: N=17 Group 1: N=17 Group 2: N=16	Group 1 – Walking exercise Intensity: 60-70% HRmax (maximum heart rate); 4 sessions/week; 60 min/session (including 5 min warming-up, 50 min walking exercise and 5 min relaxation). Group 2 – Walking + resistance exercise (20 min + 30 min) Resistance training included upper arm, chest, waist, abdominal and leg exercises; 2-3 bouts of 15-20 repetitions.	Control group Without exercise	6 Months	Fasting glucose; OGTT2h; Fasting insulin; Insulin resistance (HOMA-IR)

DiPietro et al [34].	Older subjects; BMI < 35kg/m2; Sedentary/inactive; Impaired fasting glucose; N=10 Mean age: 69 ± 6 years	Group 1 – Three 15-min bouts of moderate postmeal walking Group 2 – 45 min sustained morning walking (10h30 AM) Group 3 – 45 min sustained afternoon walking (4h30 PM) Each of the 3 study protocols were spaced 4 weeks apart and comprised a 48h stay in a whole-room calorimeter, with the first day serving as the control and the second as the exercise day. Exercise was performed in a treadmill walking at an intensity of 3 METs.	Pre-intervention baseline values (first day of the study)	48 hours (2 days)	AUC24 24h 103 AUCdinner 3h 103 AUClunch 3h 103 (continuous glucose monitoring)

Table 2. PEDro quality assessment of individual trials.

Article	PEDro scale classification											
	1	2	3	4	5	6	7	8	9	10	11	Score
Houmard et al [31].	+	+	-	+	-	-	-	-	+	+	+	5/10
O'Donovan et al [32].	+	+	-	+	-	-	-	-	+	+	+	5/10
DiPietro et al [33].	+	+	-	+	-	-	-	+	+	+	+	6/10
DiPietro et al [34].	+	+	-	+	-	-	-	+	+	+	+	6/10
Hansen et al [35].	+	+	-	+	-	-	-	+	+	+	+	6/10
Liu et al [36].	+	+	-	+	-	-	-	-	+	+	+	5/10

+, met criteria; -, criteria not met; 1, eligibility criteria were specified; 2, participants were randomly allocated to groups; 3, allocation was concealed; 4, groups were similar at baseline regarding most important prognostic indicators; 5, blinding of all participants; 6, blinding of therapists who administered the therapy; 7, blinding of all assessors who measured at least one key outcome; 8, measures of at least one key outcome were obtained from more than 85% of the participants; 9, all participants for whom outcome measures were available received the treatment or control condition as allocated; 10, results of between-group statistical comparisons are reported for at least one key outcome; 11, study provides both point measures and measures of variability for at least one key outcome.
PEDro, Physiotherapy Evidence Database

Quality of studies

The quality assessment for each study with PEDro scale is presented in Table 2. When assessing the quality of the studies, items 3, 5 and 6 were those that sustained more disagreement between the reviewers, although it was resolved by consensus.

Three articles attained a score of 5 of 10 total points [31, 32, 36] and the three others achieved a score of 6 [33 - 35]. Low/moderate quality of the articles is related to the item 8 (withdrawals during follow-up) and the criteria 3, 5, 6 and 7 (allocation concealment and blind assessment). These criteria were not clearly exposed by the authors. Nevertheless, the nature of the studies made it difficult for the blinded exercise intervention. All the studies had similar groups at baseline for the primary outcome, although the small sample sizes in general.

Concerning length of follow-up, in five studies it ranged from 4 to 9 months. Only one study [34] had a shorter follow-up of 2 days, which creates a risk of bias in data comparison. With the exception of DiPietro et al [34], all the authors reported dropouts during the follow-up period.

O'Donovan et al [32], Houmard et al [31] and Liu et al [36] had the highest withdrawal rate in their trials: 44%, 32% and 18%, respectively (Table 3).

Table 3. Number of dropouts by group (n) and withdrawal rate (%) in each study.

Study	Sample size (n)		Number of dropouts			Withdrawal rate (%)
	Initial	Final	Control group (N)	Experimental group (N)	Total (N)	
Houmard et al[31]	228	154	8	Group 1=26 Group 2=11 Group 3=29	74	32%
O'Donovan et al[32]	64	36	7	Group 1=12 Group 2=9	28	44%
DiPietro et al[33]	27*	25	-	-	2*	7,4%
Hansen et al[35]	18	16	-	2	2	11%
Liu et al[36]	61	50	4	Group 1=3 Group 2=4	11	18%
DiPietro et al[34]	10	10	-	-	-	-

RESULTS

Aerobic exercise

To test the effect of exercise on insulin action, Houmard et al [31] compared three exercise programs of different intensities and volumes with a control group (without exercise). The fasting insulin increased significantly in the control group and decreased in the exercise groups low-volume/moderate-intensity and high-volume/high-intensity. There were no significant changes in fasting plasma glucose over time. The insulin sensitivity index (SI) decreased over time in the control group, while in the three exercise groups increased significantly. According to the authors, the magnitude of the changes in insulin sensitivity (before and after exercise) was -4 ± 7% decline in the control group, 37,6 ± 8.9% increase in the low-volume/high-intensity group, 82,7 ± 15.3% increase in the high-volume/high-intensity group and 88 ± 18.7% increase in the low-volume/moderate-intensity group. Adherence to the prescribed exercise was significantly lower in the high-volume/high-intensity group (80% ± 2.5).

O'Donovan et al [32] investigated the effect of exercise intensity on insulin resistance, comparing a moderate-intensity and a high-intensity exercise groups with a control group (without exercise), for the same volume (400Kcal/session). A statistically significant reduction of insulin concentration, an increase in insulin sensitivity and a decrease in insulin resistance were found in both exercise groups. No differences were detected between the two exercise groups.

DiPietro et al [33] compared two aerobic exercise groups of different intensities (moderate and high), for the same volume (300Kcal/session), with a low-intensity (stretching exercises) control group. With regard to fasting glucose and insulin, no significant differences before and after any exercise training condition was found. However, the M value 40 (glucose utilization rate (M) at the higher insulin dose (40mU) – indicator of insulin sensitivity in the muscle) increased in all groups and were observed without changes in body composition and VO2peak. Nevertheless, this improvement was statistically significant only in the high-intensity exercise group (21%), compared with moderate-intensity (16%) and control (8%) groups.

A different study conducted by DiPietro et al [34] aimed to investigate the effectiveness of 15 minutes postmeal walking (3 times daily), compared to a 45 minutes continuous daily walking (executed in the morning or afternoon), in elderly 24-h glycemic control. Each of the three exercise protocols lasted 2 days (first day served as control) and was

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performed on a treadmill at a moderate intensity (3 MET). Both sustained morning walking and 15 minutes postmeal walking significantly improved 24-h glycemic control compared with the control day. Furthermore, 15 minutes postmeal walking were significantly more effective than the continuous daily walking in reducing glucose levels 3 hours after dinner, as expressed by the area under the glucose response curve (AUC) according to exercise condition.

Resistance exercise

Hansen et al [35] meant to compare the effects of a maximal resistance training (MRT) and an endurance resistance training (ERT) on the improvement of insulin sensitivity and glucose tolerance in overweight individuals at risk of type 2 diabetes. The MRT led to a significant reduction of 2h-glucose blood levels (oral glucose tolerance test – OGTT2h), whereas the ERT led to a significant reduction in insulin levels. After estimation of insulin sensitivity and insulin resistance (IR), by the Homeostatic Model Assessment method (HOMA-IR), it was found that MRT conducted to a significant reduction of insulin resistance and ERT resulted on a significant increase in insulin sensitivity and decrease in insulin resistance. These data suggest that the two types of exercise decrease insulin resistance, with additional positive effects prompted by ERT.

In the last study reviewed, conducted by Liu et al[36], the authors compared a walking exercise group (moderate intensity) and a walking plus resistance exercise group with no exercise (control group) in pre-diabetic subjects. For both exercise groups there were significant differences (before and after exercise) in OGTT2h, fasting insulin and insulin resistance (HOMA-IR) when compared with the control group. Nevertheless, no significant differences in fasting glucose were found. The exercise protocols significantly decreased OGTT2h, fasting insulin and insulin resistance, but not the fasting glucose. No significant differences were found between the two exercise groups.
In tables 4 to 9 are presented the mean differences, 95% confidence intervals and the effect sizes between groups for each study outcome measured.

Table 4. Mean differences, 95% confidence interval and effect size in the outcomes of Houmard et al [31].

Study groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
Low-volume/moderate-intensity vs Control group (no exercise)	SI (mU/l/min)	-1,4	[-1,5;-1,3]	-4,66667	<0,05
	Fasting insulin (µU/ml)	0,6	[0,3;0,9]	0,85714	-
	Fasting glucose (mg/dl)	0,6	[-0,2;1,4]	0,375	-
Low-volume/high-intensity vs Control group	SI (mU/l/min)	-1,5	[-1,7;-1,3]	-5	<0,05
	Fasting insulin (µU/ml)	1,3	[0,9;1,7]	1,85714	-
	Fasting glucose (mg/dl)	0,2	[-0,6;1]	0,125	-
High-volume/high-intensity vs Control group	SI (mU/l/min)	-1,8	[-1,9;-1,7]	-6	<0,05
	Fasting insulin (µU/ml)	0,7	[0,4;1]	1	-
	Fasting glucose (mg/dl)	-0,7	[-1,4;0]	-0,4375	-
Low-volume/moderate-intensity vs Low-volume/high-intensity	SI (mU/l/min)	0,10	[-0,1;0,3]	0,25	<0,05
	Fasting insulin (µU/ml)	-0,7	[-1;-0,4]	-1,16667	-
	Fasting glucose (mg/dl)	0,4	[-0,5;1,3]	0,22222	-
Low-volume/moderate-intensity vs High-volume/high-intensity	SI (mU/l/min)	0,4	[0,2;0,6]	0,8	>0,05
	Fasting insulin (µU/ml)	-0,1	[-0,4;0,2]	-0,14286	-
	Fasting glucose (mg/dl)	1,3	[0,5;2,1]	0,76471	-

Low-volume/high-intensity vs High-volume/high-intensity	SI (mU/l/min)	0,3	[0,1;0,5]	0,6	<0,05
	Fasting insulin (µU/ml)	0,6	[0,3;0,9]	0,85714	-
	Fasting glucose (mg/dl)	0,9	[0,1;1,7]	0,52941	-

Table 5. Mean differences, 95% confidence interval and effect size in the outcomes of O'Donovan et a [32].

Study Groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
Moderate-intensity vs Control group	Fasting insulin (mU/l)	2,67	[-2,0;7,3]	0,50473	0,048
	Fasting glucose (mmol/l)	0,21	[-0,3;0,8]	0,33871	0,11
	Insulin sensitivity	-1,03	[-2,0;0,0]	-0,9115	0,02
	Insulin resistance	0,80	[-0,5;2,1]	0,53333	0,03
High-intensity vs Control group	Fasting insulin (mU/l)	2,50	[-1,9;6,9]	0,47259	0,048
	Fasting glucose (mmol/l)	0,19	[-0,3;0,7]	0,30645	0,11
	Insulin sensitivity	-0,91	[-1,9;0,0]	-0,80531	0,02
	Insulin resistance	0,70	[-0,5;1,9]	0,46667	0,03
Moderate-intensity vs High-intensity	Fasting insulin (mU/l)	0,17	[-2,8;3,1]	0,05075	0,46
	Fasting glucose (mmol/l)	0,02	[-0,3;0,3]	0,0625	0,46
	Insulin sensitivity	-0,12	[-1,3;1,1]	-0,08759	0,42
	Insulin resistance	0,10	[-0,6;0,8]	0,125	0,49

Table 6. Mean differences, 95% confidence interval and effect size in the outcomes of DiPietro et al [33].

Study Groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
Moderate-intensity vs Control group	Fasting glucose (mg/dL)	-4,10	[-7,5;-0,7]	-1,28125	>0,05
	Fasting insulin (µU/ml)	-3,7	[-7,9;0,5]	-0,925	>0,05
	M value 10 mU	0,8	[-1,4;3]	0,38462	>0,05
	M value a 40 mU	1	[-2,6;4,6]	0,29586	>0,05
	M40/I, µU/ml	0,01	0	0,33333	>0,05
High-intensity vs Control group	Fasting glucose (mg/dL)	-3,3	[-6,7;0,1]	-1,03125	>0,05
	Fasting insulin (µU/ml)	-2,9	[-7,1;1,3]	-0,725	>0,05
	M value 10 mU	0,3	[-1,9;2,5]	0,14423	>0,05
	M value a 40 mU	-0,9	[-4,5;2,7]	-0,26627	<0,02
	M40/I, µU/ml	-0,02	[-0,1;0]	-0,66667	<0,05
High-intensity vs Moderate-intensity	Fasting glucose (mg/dL)	0,8	[-6;7,6]	0,11765	>0,05
	Fasting insulin (µU/ml)	0,8	[-6,3;7,9]	0,11268	>0,05
	M value 10 mU	-0,5	[-2;1]	-0,3268	>0,05
	M value a 40 mU	-1,9	[-4,6;0,8]	-0,69597	>0,05
	M40/I, µU/ml	-0,03	[-0,1;0]	-1	<0,05

M value - glucose metabolism rate, with low or high dose of insulin;
M40 / I – M value to a plasma insulin concentration of 40 mU in the last 30 minutes of the test (insulin sensitivity).

Table 7. Mean differences, 95% confidence interval and effect size in the outcomes of DiPietro et al [34].

Study Groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
15 minutes postmeal walking vs Sustained morning walking (10:30 AM)	AUC24 (mg/dL) 24h 103	-1	[-21,9;19,9]	-0,04545	-
	AUCdinner (mg/dL) 3h 103	1	[-3,7;5,7]	0,2	<0,05
	AUClunch (mg/dL) 3h 103	1	[-2,8;4,8]	0,25	>0,05
15 minutes postmeal walking vs Sustained afternoon walking (4:30 PM)	AUC24 (mg/dL) 24h 103	11	[-11,8;33,8]	0,45833	-
	AUCdinner (mg/dL) 3h 103	2	[-2,7;6,7]	0,4	<0,05
	AUClunch (mg/dL) 3h 103	2	[-1,8;5,8]	0,5	>0,05
Sustained morning walking (10:30 AM) vs Sustained afternoon walking (4:30 PM)	AUC24 (mg/dL) 24h 103	12	[-10,8;34,8]	0,5	-
	AUCdinner (mg/dL) 3h 103	1	[-3,7;5,7]	0,2	-
	AUClunch (mg/dL) 3h 103	1	[-2,8;4,8]	0,25	-

Table 8. Mean differences, 95% confidence interval and effect size in the outcomes of Hansen et al [35].

Study Groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
Group 1 (MRT) vs Group 2 (control)	Fasting glucose	0,00	[-0,6;0,6]	0	>0,05
	OGTT2h	-0,93	[-2,1;0,3]	-0,7686	0,044
	Insulin blood level	-3	[-35;29]	-0,09375	>0,05
Group 2 (ERT) vs Group 2 (control)	Fasting glucose	0,06	[-0,5;0,7]	0,10714	>0,05
	OGTT2h	-0,19	[-1,5;1,1]	-0,15702	>0,05
	Insulin blood level	17	[-16,9;50,9]	0,53125	0,023
Group 1 (MRT) vs Group 2 (ERT)	Fasting glucose	-0,06	[-0,6;0,4]	-0,125	-
	OGTT2h	-0,74	[-2,4;1,0]	-0,45963	-
	Insulin blood level	-20	[-40,2;0,2]	-1,05263	-

Table 9. Mean differences, 95% confidence interval and effect size in the outcomes of Hansen et al [35].

Study Groups	Outcome	Mean Differences	95% Confidence Interval	Effect Size	P value
Walking exercise vs Control group	Fasting glucose (mmol/l)	0,09	[-0,1;0,3]	0,35135	>0,05
	OGTT2h (mmol/l)	0,55	[0,1;1]	0,95122	<0,05
	Fasting insulin (mIU/l)	1,98	[-3,8;7,7]	0,25013	<0,05
	Insulin resistance	0,79	[-0,9;2,4]	0,34949	<0,05
Walking plus resistance exercise vs Control group	Fasting glucose (mmol/l)	0,08	[-0,1;0,3]	0,29344	>0,05
	OGTT2h (mmol/l)	0,7	[0,3;1,1]	1,21254	<0,05
	Fasting insulin (mIU/l)	2,03	[-3,8;7,9]	0,25709	<0,05
	Insulin resistance	0,8	[-0,9;2,5]	0,35616	<0,05
Walking exercise vs Walking plus resistance exercise	Fasting glucose (mmol/l)	0,01	[-0,4;0,4]	0,02913	>0,05
	OGTT2h (mmol/l)	-0,15	[-0,5;0,2]	-0,32397	>0,05
	Fasting insulin (mIU/l)	-0,05	[-5,2;5,1]	-0,00795	>0,05
	Insulin resistance	-0,02	[-1,5;1,5]	-0,00737	>0,05

DISCUSSION

Despite the methodological differences found in all studies reviewed, the effects of exercise were determinant on glycemic control, especially in insulin resistance and sensitivity where the beneficial results of aerobic exercise were more consistent.

Concerning prevention among adults at risk of type 2 diabetes, previous systematic reviews and meta-analyses were focused on combined exercise and diet interventions [37 - 39] and few have addressed exercise interventions alone on adults at high risk for type 2 diabetes [40]. Based on only two primary studies, Orozco et al [40] found that exercise did not significantly reduce diabetes incidence. On the other hand, two of the most recent systematic reviews, not including the same studies, showed the beneficial effects of exercise on insulin sensitivity improvement [10, 25]. One was centred on primary studies with different designs in healthy subjects [25]. The other, based on RCT, assessed the changes in insulin sensitivity in response to different exercise modalities (aerobic exercise, resistance training and combined) both in non-diabetic and diabetic subjects [10]. Mann et al [10] adds that there may be a dose-response relationship between the intensity and duration of exercise and the improvement in insulin sensitivity, where the progression towards higher intensity levels may enhance more benefits. Aerobic exercise is effective when performed either at a moderate or high intensity, prescribed according to the participant's ability and preferences for exercise. This authors also suggest that resistance training may be effective when performed at an intensity below 50% of 1RM, targeting glucose regulation in muscle. The combined training (aerobic and resistance exercise) might be the most effective strategy, although further research is needed in population subgroups [10, 25]. To maintain insulin sensitivity in healthy subjects it is recommended the inclusion of high intensity aerobic exercise (>75%VO2) three times a week, combined with resistance exercise (comprising all major muscles groups) at 70% of 1RM two times a week. For those with type 2 diabetes and limited mobility (such as elderly populations), aerobic and resistance exercise of low and moderate-intensity (40-80% heart rate reserve; 50-55% of 1RM), three times a week, are recommended [10].

Our review includes one of the same study from Mann et al [10], three from Conn et al [25] and two additional studies [34, 36]. The analysis of the results suggest that frequency and duration of aerobic exercise can be more important than intensity and that moderate intensity is as effective as high intensity performance in glycemic control (especially regarding the elderly). When integrating resistance exercise, additional effects can be achieved. These findings are in agreement with the latest recommendations for healthy and diabetic individuals [10, 13, 25, 41], despite the heterogeneity of samples, differences in exercise programs and outcome measures, in addition to the relatively low quality of studies according to PEDro scale. The longest follow-up ranged from 4 to 9 months and the shortest was 2 days, however in all of them metabolic benefits were found. Thus, according to the Cochrane Back Review Group our systematic review may show a moderate degree of evidence recommendation.

The following RCT on pre-diabetic subjects were not included for analysis in this review because they only compared one exercise group with other kinds of intervention, independently or in combination (diet, pharmacological or no intervention). However they are mentioned here because, despite the differences in exercise protocols, they also favour the incomes of physical activity alone on metabolic control, regardless the mode, intensity, volume and duration.

Pan et al [16] developed one of the first trials concerning lifestyle modification as a primary prevention for type 2 diabetes in pre-diabetic adults. With an initial sample of

577 individuals of both sexes and a six years follow-up, the withdrawal rate was low (530 individuals completed the study). Subjects were randomly assigned into a control group or one of three intervention groups: diet, exercise and diet plus exercise. In the exercise group the goal of the intervention was to increase recreational physical activity (adjusted for type, intensity and time), where individual recommendations were given. At the end of follow-up it was found that diabetes incidence was lower in the exercise group (41.1%, 95% CI [33.4-49.4]) compared with the control group (67.7%, 95% CI [59.8-75.2]), diet group (43.8%, 95% CI [35.5-52.3]) and diet plus exercise group (46%, 95% CI [37.3-54.7]). Regarding the risk of developing the disease, the largest reduction was observed in the exercise group (46%) compared with diet plus exercise group (42%) and diet group (31%). The authors concluded that diet effectiveness was similar to that from exercise and there was no additional benefits from both interventions combination.

The double-blinded RCT conducted by Malin et al (21) aimed to determine the effects of metformin and physical exercise, independently or combined, on insulin sensitivity in a sample of 32 pre-diabetic subjects. Subjects were randomly allocated into three intervention groups: metformin, exercise (with placebo) and exercise plus metformin. The exercise program consisted of combined aerobic plus resistance exercise. At the end of follow-up (12 weeks) all three interventions increased insulin sensitivity. This increase was 25-30% higher in the exercise group compared to the others, although the difference was not statistically significant. It was concluded that exercise increased insulin sensitivity and the addition of metformin to physical training did not emphasized that improvement. On the contrary, it may have affected the full effect of exercise.

Aerobic exercise

In the study of Houmard et al (31) the results of insulin sensitivity are clinically relevant, considering that significant mean differences, low range 95% confidence intervals and large effect sizes favours the experimental groups compared with the control group. Although the effect size is greater in high-volume/high-intensity group than in the low-volume/moderate-intensity group this difference was not significant. Fasting glucose levels were not clinically relevant (wide confidence intervals) with no significant differences. The decline in insulin action in the control group emphasizes that the lack of regular physical exercise, at least for 6 months, may result in a significant increase of insulin resistance. The study confirms that physical activity of at least moderate intensity increases insulin sensitivity, which is relevant for type 2 diabetes prevention. An aerobic exercise program with a duration of 170 minutes/week (frequency of 3-4 times per week), regardless of variations in intensity and volume, improved insulin sensitivity (low volume/moderate intensity and high volume/high intensity groups). These results were more substantial than the 115 minutes/week program (3 times a week), regardless of the volume and intensity (low volume/high intensity group).

The O'Donovan et al (32) research also exposes the positive effects of the two exercise intensities (moderate and high) in insulin action. Concerning fasting insulin and insulin resistance, although the mean differences were statistically significant with a moderate effect size, 95% confidence intervals were wide. For insulin sensitivity the results are considered clinically relevant for both exercise intensities since, in addition to the average difference being statistically significant, 95% confidence interval only includes negative values and the effect size is large. The small average difference between the two exercise groups is not significant. These results suggest that a training performed at 60% of maximum oxygen consumption (VO2max) (moderate intensity) is as effective as a training performed at 80% of VO2max (high intensity), when 400kcal are spent per session.

Contrary to the studies of Houmard et al (31) and O'Donovan et al [32], in the study of DiPietro et al [33] the benefits of aerobic exercise with different intensities on glycemic control were less robust. Even so, a greater improvement was observed on insulin sensitivity of women who performed high-intensity exercise compared to moderate or low-intensity exercise. Between moderate intensity and control groups the mean difference was almost zero and the effect size was small. Among the high-intensity and control groups the mean difference favoured the experimental group (significant difference), with a small 95% confidence interval and a moderate effect size. When comparing the two experimental groups, the mean difference favours high-intensity exercise (significant difference) with a small 95% confidence interval and a large effect size, which makes it clinically relevant. The other outcomes were not clinically relevant. The results suggest that long-term high-intensity exercise provides more lasting benefits in insulin action compared to low or moderate-intensity exercise.

In the DiPietro et al [34] investigation, with only 2 days of follow-up, the results indicate that a 15 minutes short daily walking after meals seems as effective as continuous morning walking in postprandial hyperglycaemia control, compared with continuous afternoon walking. Although the mean difference favours the postmeal walking, the effect size is small to moderate and the 95% confidence intervals suggest a wide dispersion of the data. Still, performing moderate aerobic exercise with shorter duration and higher daily frequency can be seen as a strategy to increase adherence to exercise programs in the elderly.

Resistance exercise

With regard to resistance exercise, Hansen et al [35] found a significant mean difference in OGTT2h, with a moderate effect size, when comparing MRT with no exercise. Although it favours MRT, the 95% confidence interval was wide. Comparing ERT with the baseline values of the group (control) the mean difference was significant for insulin levels with a moderate effect size, but also with a wide 95% confidence interval. Both exercises had almost no effect on fasting glucose. Clinically these results are of little relevance given the wide variation of the confidence intervals, even if MRT and ERT leads to a decrease in insulin resistance in subjects at risk of type 2 diabetes. According to the authors MRT increased glucose uptake capacity in muscle, while ERT increased insulin sensitivity, which supports their effectiveness for primary prevention.

The study conducted by Liu et al [36] reveal that significant mean differences favours both exercise groups against control group for OGTT2h, fasting insulin and insulin resistance. However, the results are considered clinically more relevant for OGTT2h, because the effect size is large with a limited 95% confidence interval. The other outcomes reveal smaller effect sizes and wider 95% confidence intervals. The mean differences between the exercise groups are not significant. Thus, it is not clear which one is more effective, although both have improved insulin sensitivity.

Withdrawal rate

In our review we recorded dropouts in almost all studies. Houmard et al [31] had the greater withdrawal rate. According to the authors it may be related to the long intervention follow-up.

The importance of adherence and maintenance in exercise programs has been recognized in various study designs [42, 43]. However, although it is considered as a limitation, not always is properly described and analysed, including the strategies to minimize this risk of bias. Some of the reasons pointed as determinant factors to increase adherence to exercise are their adaptation, appropriateness or preference for individual and/or community. Thus, consistent with some authors and the diversity of exercise programs analysed [28, 44], more important than define the best FITT is to understand what are the features that each program should devise to ensure the better benefits to health and, at the same time, are more suitable for different populations, specific condition and individual preferences.

In the study conducted by Mendham et al [43] (not included in this review) in inactive overweight indigenous australian men, the exercise experimental program consisted on a combination of aerobic and resistance exercise, also interspersed with a boxing workout circuit (intensity 70-85% of maximum heart rate, 2-3 times a week, 45-60 minutes for session). Moreover, a sport modality (football or basketball) was performed once a week. At the end of follow-up, besides the benefits on metabolic profile the authors emphasize the importance of including sports and group activities, according to individual/community preferences, as a way to increase adherence.

According to Sanz et al [9] lifestyle programs involving a variety of physical activities are as effective as those based on a single exercise mode. For this reason, using different exercise modalities may be a key to make their practice more feasible, thereby increasing adherence and sustainability for long term regular physical exercise.

LIMITATIONS

The main limitations of this review include few studies for eligibility, reduced sample sizes, demographic heterogeneity (mainly gender distribution), exercise programs with different characteristics within the same modality of exercise, differences in follow-up, use of different methodologies and measurement units for the same outcome and relatively low quality of the articles selected for analysis.

CONCLUSIONS

The evidence found in this systematic review does not allow to answer specifically to our initial guiding question, mainly due to methodological differences between them. However, it was evident from the studies with the longest follow-up that aerobic and resistance exercises performed at a moderate to high intensity at least 3 times a week, with a duration of 40-60 minutes for session, are long-term beneficial for insulin resistance decline or insulin sensitivity increase. In the short term, by reducing the duration of the aerobic exercise for session, but increasing the daily frequency (3 times daily at least) may also be beneficial in glycemic control. Therefore, by controlling the metabolic variables one can prevent the development of type 2 diabetes through risk reduction.

Future research should aim the investigation of those exercises that better ensemble specific subpopulations and that promote adherence to physical activity programs. Those that are more adequate to physical characteristics and personal expectations are more likely for successful results.

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