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Review

Sex Differences in the Glycemic Response to Structured Exercise Interventions in Adults with Type II Diabetes Mellitus: A Systematic Review

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ABSTRACT

International Journal of Exercise Science 15(3): 948-961, 2022. Despite physiological sex differences in the prevalence, pathogenesis, and responses to pharmacologic therapies of glucose metabolism in type 2 diabetes mellitus (T2DM) and the current evidence regarding the benefits of physical activity in people with T2DM, there is still a lack of information about the response to physical activity in T2DM depending on the sex. Thus, the aim of the present systematic review was to analyze the physiological sex differences response to physical activity programs in adults with T2DM. A systematic review following PRISMA guidelines was performed up to 4th January 2022 in PubMed, SportDiscus and Web of Science databases. The research protocol of this systematic review was registered in PROSPERO (CRD42020189020). The PEDro scale and Cochrane risk of bias tools were used to analyze the quality and risk of bias of the studies included. Glycaemic (blood glucose, HbA1c, AUC glycemia, metabolic clearance rate, QUICKI) insulin (HOMA-IR, insulin levels, C-peptide) and cardiovascular parameters (VO2max, body fat mass, waist circumference, cardiovascular index) were registered. 6 studies met the inclusion criteria. Physical activity showed improvements in the glycaemic and insulin profiles and cardiovascular risk parameters for both men and women, but no relevant and significant differences between sex were found. No significant differences between males and females with regard to the effects elicited by physical activity on glycaemic biomarkers and cardiorespiratory fitness in individuals with T2DM were found. These results seem to lead towards the same physical activity prescription in men and women.

KEY WORDS: Sex, physical activity, health

INTRODUCTION

Diabetes mellitus represents a group of metabolic alterations characterized by chronic hyperglycemia due to defective secretion and/or insulin action, including abnormalities in fat and protein metabolism (3). Currently, type II diabetes mellitus (T2DM) is a significant global health concern (28), with both incidence and prevalence rates increasing to epidemic proportions (2, 7, 8, 26, 32, 37, 43, 50), resulting in excessive human, social, and economic costs (43). Indeed, T2DM has become one of the main causes of both macrovascular (e.g., acute coronary syndromes, stroke, or peripheral artery disease) and microvascular (e.g., peripheral neuropathies, retinopathy and nephropathy) diseases (28, 31), thereby making T2DM an urgent worldwide public health challenge.

The major international medical agencies (2, 8) have stated that regular exercise (together with diet and pharmacology therapy) is a powerful first-line intervention to manage T2DM. There is compelling evidence showing that regular exercise is capable of: a) increasing glucose uptake at the peripheral and systemic level, b) improving insulin sensitivity, and c) improving the known hyperbolic curve of glucose tolerance (50). Furthermore, regular exercise has also demonstrated positive effects on certain chronic cardiovascular [e.g., atherosclerosis (32), hypertension (26)] and metabolic [e.g., obesity (5)] diseases that often appear concurrently in patients with T2DM.

Within the last decade, systematic reviews and meta-analyses have been published aiming to understand which exercise modality/ies (cardiovascular or aerobic training [AT], resistance training [RT], and concurrent training [CT] [the combination of AT and RT in the same training program]) (29, 39) and doses (weekly frequency, volume, intensity, and duration) (22, 42) evoke the greatest benefits on glucose metabolism in people with T2DM. Thus, it has been observed that both AT and RT exercise modalities similarly improve glycemic biomarkers, thereby reducing the risk of cardiovascular events in patients with T2DM. However, CT, or the inclusion of both AT and RT in the same structured training program, may be the most efficient strategy to maximize the benefits on glycemic and cardiovascular outcomes (39). Likewise, it is recommended that a minimum of 150 min of moderate exercise, or 75 minutes of vigorous exercise, per week, across 3 to 5 daily sessions of 30-60 min duration are sufficient to achieve clinically relevant improvements in the glycemic profile (8). Finally, it has been suggested that to ensure long-term patient adherence to the training programs and mitigate potential risks (e.g., musculoskeletal injuries, post-exercise hypoglycemia), the exercise prescription should be carefully adapted for each individual based on comorbidities, contraindications, and realistic personal goals (8, 15, 18).

It has been documented that sex-related differences appear to be particularly relevant for noncommunicable diseases, including T2DM (17). Several organizations now call for the inclusion of the sex dimension in biomedical research to improve the scientific quality and societal relevance of the produced knowledge, technology, and/or innovation (13, 33). However, the current guidelines for the management of T2DM do not consider sex, yet there is moderate evidence pointing to biological and psychosocial differences between males and females in regard to the pathogenesis, progression, and complications of T2DM. Additionally, sex differences may be present in response to certain glucose lowering drugs (17), and in the potential for inducing gains in muscle mass (48). This last point is particularly relevant, given that skeletal muscle processes up to 80% of the postprandial glucose (9) and stores 80% of carbohydrates (12). Therefore, it can be hypothesized that sex-related differences in muscle mass gains elicited by regular exercise led males to have greater benefits on insulin sensitivity and glucose control than females with T2DM. Consequently, there is a clear need to shed light on potential sex-related differences in the effects elicited by structured exercise programs on glycemic and cardiovascular outcomes in patients suffering from T2DM. This knowledge may assist healthcare practitioners in the decision-making process for patient-centered exercise prescription to manage T2DM.

Therefore, the main purpose of this systematic review was to analyze potential sex-related differences in the effects elicited by structured exercise programs on glycemic biomarkers and cardiovascular risk factors.

METHODS

The current systematic review (PROSPERO ID: CRD42020189020) was carried out in accordance with the recommendations and criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (20). The PRISMA checklist is presented in appendix 1.

Study selection

Eligibility criteria were established and agreed upon by all authors based on the concept of population, intervention/indicator, comparator/control, and outcome (PICO) (38) (for more information please see appendix 2). Thus, to be included, each study had to be a) a clinical trial which analyzed the effects of a structured exercise program on clinical results related to diabetes (hyperinsulinemic euglycaemic clamp, glycated haemoglobin [HbA1c] levels, fasting plasma glucose [FPG], fasting blood glucose [FBG], fasting plasma insulin [FPI], homeostatic model assessment HOMA]) and cardiovascular risk factors (e.g., body mass index [BMI], VO2max), b) the participants in the study had to be adults (aged > 18 years) with T2DM diagnosed, c) results must be provided separately by sex, d) the study had to be published or carried out before 4th January 2022 and e) the study could be written in English, Spanish, Italian, or French. Animal studies, review articles, and acute exercise studies were excluded.

Search strategy

A systematic computerized search was conducted up to 4th January 2022 in the databases PubMed, Web of Science and SPORTDiscus. In addition, a complementary search of the reference lists of included articles and a Google Scholar search were performed. This was done using backward citation tracking (to manually search the reference list of a journal article), and forward citation tracking (scanning a list of articles that had cited a given paper since it was published) (36). Citations were tracked using Google Scholar to make sure that studies were not missed inadvertently. When additional studies that met the inclusion criteria were identified, they were included in the final pool of studies. Relevant keywords were used to construct Boolean search strategies: (diabetes[tiab] OR type 2 diabetes[tiab]) AND (exercise[tiab] OR physical activity[tiab] OR training[tiab]) AND (gender differences[tiab] OR sex differences[tiab] OR men/women[tiab]) (for more information see appendix 3).

Study selection
Two reviewers independently (A.P-L. and E.S-C) selected studies for inclusion in a two-step process. First, studies were screened based on title and abstract. In a second stage, full text studies were reviewed to identify those studies that met the eligibility criteria. A study was excluded immediately once it failed to meet a single inclusion criterion. Disagreements were resolved through consensus or by consulting a third reviewer (A.L-V). To avoid possible double counting of patients included in more than one report by the same authors or working groups, patient recruitment periods were evaluated and if necessary, authors were contacted for clarification. The corresponding author was contacted as needed to obtain data not included in the published report.

Data extraction
With the aim of guaranteeing the maximum objectivity possible, a codebook was produced that specified the standards followed in coding each of the characteristics of the studies. The moderator variables of the studies selected were coded and grouped into three categories according to Lipsey (21) recommendations: substantive, methodological and extrinsic variables. Appendix 4 displays a brief description of the moderator variables coded separately by category.

The methodological quality of the studies selected was evaluated using the Physiotherapy Evidence Database Scale (PEDro) (47). A total score out of 10 is derived for each study, adding the criteria that are satisfied. A PEDro score ranging from 6 to 10 is indicative of high quality, whereas scores of 4–5 indicate fair quality and scores 3 or less indicate poor quality (6). The Cochrane risk of bias tool (14) was employed for an in-depth analysis of the level of bias risk in the studies included. The risk of bias of each study was analyzed from 6 domains, which were later classified as low, unclear, or high risk of bias.

To assess the inter-coder reliability of the coding process, two researchers (A.P-L. and E.S-C) coded all the selected studies (including methodological quality assessment and risk of bias). For the quantitative moderator variables, intra-class correlation coefficients (ICCs) were calculated, whereas for the qualitative moderator variables, Cohen's kappa coefficients were applied. On average, the ICC was 0.89 (range 0.86–1.0), indicating good reliability (19) and the kappa coefficient was 0.93 (range 0.90–1.0), which shows perfect agreement (25). The inconsistencies between the two coders were resolved by consensus or by consulting with a third reviewer (A.L-V). When the inconsistencies were due to ambiguity in the coding book, this was corrected. The codebook can be obtained from the corresponding author upon request.

RESULTS

Study Selection

A total of 1687 references were identified through all search strategies, from which 550 were removed in the first screening level as duplicates. Then 1070 studies were eliminated after reading the title and abstract. Afterwards, 67 full-text articles were assessed for eligibility, where 61 were excluded because of the following reasons: 48 did not provide results separated by sex, five were not T2DM population, four analyzed a single-bout of exercise (acute effects), and four were not exercise interventions. Fourteen corresponding authors were contacted to obtain raw data separated by sex, but none of them answered. Finally, six studies that compared chronic effects of structured exercise programs on glycaemic and insulin markers and/or cardiovascular risk factors in T2DM population separately by sex were included in the present systematic review (1, 16, 34, 35, 40, 45). The selection process of the articles is advertised in Figure 1.

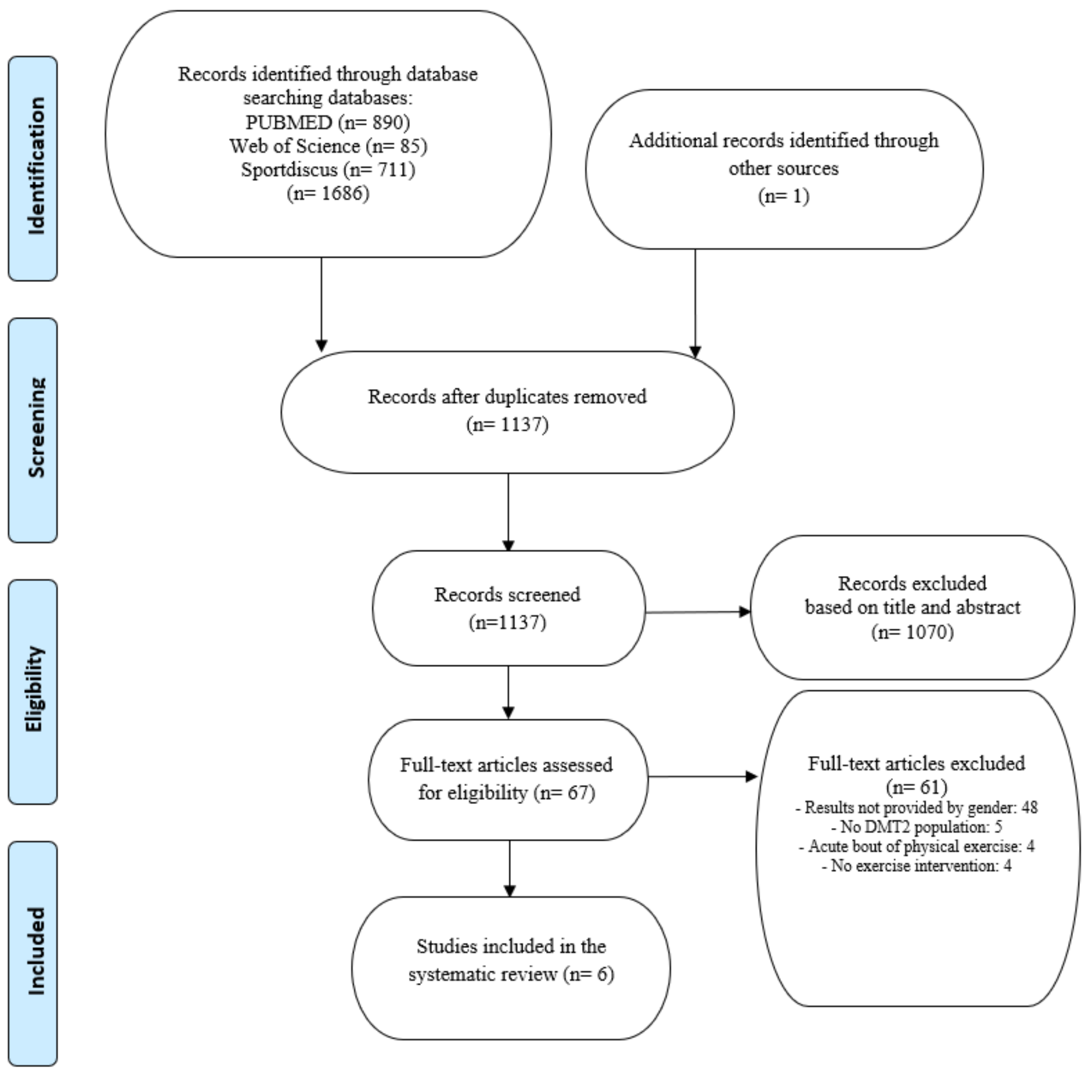

Figure 1. Flow chart of the selection of studies in the systematic review.

Descriptive characteristics of the studies
The included studies were carried out between 1984 and 2019, with two studies from the United States of America (16, 35), one from Canada (45), one from Pakistan (40), one from Norway (34), and one from Spain (1). The total sample size was 198 (118 males and 80 females). The length of the exercise programs ranged from 10 to 52 weeks, with a training frequency of 7 days/week (1), 5-6 days/week (35), and 3 days/week (45). The modality of exercise was AT in four of the trials (1, 16, 35, 40) and concurrent training in two studies (34, 45). The main characteristics of the studies selected are displayed in Table 1. With regard to the age groups of the participants recruited in the six studies finally selected, one of them was performed in young adults (35), three in adults (16, 34, 40) and two in older adults (1, 45).

Quality of the selected studies and risk of bias
The methodological quality of the studies ranged from fair to good (PEDro scale score: mean 5.5 points, minimum 4 points and maximum 7 points). Four studies had participants randomly allocated in groups (1, 16, 40, 45) and only two studies (1, 40) performed blinding of consultants that measured at least one variable or output. Table 2 shows detailed scores on the PEDro scale for each study. Regarding the Cochrane Risk of Bias tool on the risk of bias assessment, it resulted in > 90% for most of the items, which means high risk of bias (appendix 5).

Glycaemic biomarkers
The six studies finally selected in the current systematic review employed a wide variety of glycaemic biomarkers as dependent variables (table 1). The biomarkers more frequently used for these studies to explore potential exercise-induced improvements in insulin sensitivity were: HbA1c (16, 34, 40, 45), FBG (1, 16, 34, 40, 45), FPI (16, 35, 40) and HOMA-IR (16, 34, 40). Three (out of six) studies (34, 35, 45) reported sex-related differences in the magnitude of the improvements observed in some insulin sensitivity measures (FPG, AUCG, HOMA-IR and Insulin C-peptide [IC]) in response to supervised training programs. In particular, whereas two studies (34, 35) found sex-related differences in favor of males in the changes elicited by structured training programs on three glycaemic biomarkers (FPG, HOME-IR and IC), one study (45) reported opposed results, that is, greater insulin sensitivity improvements (AUCG) in females in comparison with their male peers with T2DM.

Other cardiovascular risk factors
The selected studies examined the effects of structured exercise [AT (1) and CT (34, 45)] programs on other cardiovascular risk factors (i.e., cardiorespiratory fitness [VO2max] and body composition and anthropometric parameters [body mass, body mass index [BMI], body fat mass and waist circumference]). Three studies (out of six) observed statistically significant sex-related differences in the magnitude of the post training changes elicited in cardiorespiratory fitness (i.e., VO2max) (two studies in favor of males [+24.7% vs +15.0% (34) and +22.5% vs +12.3% (35)] and other in favor of females [+2.1% vs +9.1% (16)]). No other sex-related differences were found in the effects elicited by structured exercise programs on the remaining of the cardiovascular risk factors explored.

Table 1. Characteristics of the included studies.

Study/Country	Participants	Exercise modality	Dosage	Results: Glycaemic biomarkers	Results: Cardiovascular risk factors
Reitman et al. (1984) (35) USA	Total = 6 ♂ = 3 (28.6 ± 10.8 y) ♀ = 3 (24 ± 4.6 y)	Aerobic training	10 weeks 5-6 days per week 20-40 min per day of intermittent exercise at 60-90% VO2max	**FPG† = -29.4%* (♂) vs. -17.3%* (♀)** FPI^NS = -25.4% (♂) vs. -30.9% (♀) SPI^NS = -21.1% (♂) vs. -21.4% (♀) MCR = +15.6% (♂) vs. +9.9% (♀)	Body mass^NS = -1.1% (♂) vs. -0.7% (♀) **VO_2max† = +22.5%* (♂) vs. +12.3% (♀)**
Tessier et al. (2000) (45) Canada	Total = 19 (69.3 ± 4.2 y) ♂ = 12 ♀ = 7	Concurrent training	16 weeks 3 days/week Walking and endurance exercises Intensity from 35–59% to 60–79% of the HRmax	HbA_{1c}^NS = 0% (♂) vs. 0% (♀) FBG^NS = +4.7% (♂) vs. +1.0% (♀) FR^NS = -2.6% (♂) vs. -5.3% (♀) **AUC_G† = -3.1% (♂) vs. -15.9%* (♀)**	Body mass^NS = -0.1% (♂) vs. -0.4% (♀)
Kanaley et al. (2012) (16) USA	Total = 22 ♂ = 10 (49.9 ± 1.6 y) ♀ = 12 (48.1 ± 1.0 y)	Aerobic training	16 weeks 3 days/week Walking 30-45 min at 65% VO_2peak	HbA_{1c}^NS = -0.5% (♂) vs. +0.3% (♀) FBG^NS = -7.0% (♂) vs. 0% (♀) FPI^NS = -17.6% (♂) vs. +44.2% (♀) HOMA-IR^NS = +1.9% (♂) vs. +6.3% (♀) QUICKI^NS = +5.7% (♂) vs. -2.6% (♀)	Body mass^NS = +0.1% (♂) vs. -1.8% (♀) BMI^NS = +0.3% (♂) vs. -1.7% (♀) BFM^NS = -1.0% (♂) vs. -1.6% (♀) **VO_2max† = +2.1%* (♂) vs. +9.1%* (♀)**

Shakil-Ur-Rehman, et al. (2018) (40) Pakistan	Total = 51 ♂ = 36 (59.1 ± 5.8 y) ♀ = 15 (51.3 ± 8.8 y)	Aerobic training	25 weeks 3 days/week Treadmill Starting with 30 min per week with a 0° treadmill inclination. Increases of 30 min and 3° of inclination each 5 weeks	HbA_{1c}^{NS} = -1.0%* (♂) vs. -1.0%* (♀) FBG^{NS} = -6.2%* (♂) vs. -11.1%* (♀) FPI^{NS} = -29.5%* (♂) vs. -36.9%* (♀) $HOMA\text{-}IR^{NS}$ = -36%* (♂) vs. -44%* (♀)	BMI^{NS} = -6.9%* (♂) vs. -7.7%* (♀) VO_2max^{NS} = +8.7%* (♂) vs. +8.8%* (♀)
Alonso-Domínguez et al. (2019) (1) Spain	Total = 89 ♂ = 52 (64.4 y [59-68]) ♀ = 37 (65.9 y [62-68])	Aerobic training	52 weeks 7 days/week Walking at 50% HRmax	FBG^{NS} = -25.2%* (♂) vs. -21.5%* (♀)	$CAVI^{NS}$ = -3.6%* (♂) vs. -1.2% (♀) $baPWV^{NS}$ = -2.6% (♂) vs. +1.9% (♀)
Rehman (2019) (34) Norway	Total = 11 (51.6 ± 5.0 y) ♂ = 5 ♀ = 6	Concurrent training	12 weeks 3 days/week (2 supervised and 1 at home sessions) Aerobic training: 2 high intensity interval sessions (90-95% HRmax) and 1 moderate intensity session (70% HRmax) Resistance training: 2 sessions of 3 sets of 10-20 repetitions of 4 exercises	HbA_{1c}^{NS} = -0.2% (♂) vs. -0.2%(♀) FBG^{NS} = -7.2% (♂) vs. 0%(♀) **HOMA-IR† = +3.0% (♂) vs. -25%*(♀)** **IC† = 0% (♂) vs. -27.3%*(♀)**	WC^{NS} = -2.9% (♂) vs. -0.5%(♀) **VO_2max† = +24.7%* (♂) vs. +15.0%*(♀)**

Table 2. Analysis of the selected studies' methodological quality (*n* = 6).

Study	1	2	3	4	5	6	7	8	9	10	11	Score
Reitman et al. (1984)	-	-	-	-	-	-	-	+	+	+	+	4
Tessier et al. (2000) (45)	+	+	-	+	-	-	-	+	+	+	+	6
Kanaley et al. (2012)	+	-	-	+	-	-	-	+	+	+	+	5
Shakil-Ur-Rehman et al.	+	+	-	+	-	-	+	+	+	+	+	7
Alonso-Domínguez et	+	+	-	+	-	-	+	+	+	+	+	7
Rehman (2019) (34)	+	+	-	-	-	-	-	-	+	+	+	4

Table note: The numbers of the columns corresponded to the following items of the PEDro scale.

1. *Eligibility criteria were specified (not included in score).*
2. *Subjects were randomly allocated to groups.*
3. *Allocation was concealed.*
4. *The groups were similar at baseline regarding the most important prognostic indicator.*
5. *There was blinding of all subjects.*
6. *There was blinding of all therapists who administered the therapy.*
7. *There was blinding of all consultants who measured at least one key outcome.*
8. *Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.*
9. *All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by intention to treat.*
10. *The results of between-group statistical comparisons are reported for at least one key outcome.*
11. *The study provides both point measures and measures of variability for at least one key outcome.*

DISCUSSION

Previous systematic reviews and meta-analyses (29, 39, 42, 46) have documented that both exercise modality and exercise dose modulate the chronic effects elicited by structured training programs on insulin sensitivity and risk of cardiovascular events in patients with T2DM. However, the impact of physiological factors such as biological sex on metabolic and cardiovascular responses to regular exercise has not been similarly addressed despite the well-documented differences between males and females in terms of risk (10, 44), pathogenesis (4, 11, 27), prevalence (23, 49), micro and macrovascular complications (24, 30) and responses to T2DM pharmacologic therapies (41). Therefore, the purpose of this study was to analyze whether there may be sex-specific effects of regular structured exercise on insulin sensitivity measures and cardiovascular risk factors in adults with T2DM.

The results of the study selection process carried out in this systematic review warned that in spite of the fact that numerous studies have demonstrated that regular exercise has positive effects on glycemic and cardiovascular outcomes in patients with T2DM (29, 39, 42), only six clinical trials have provided data to address the question of whether biological sex modifies these outcomes. The limited number of studies and small sample sizes prevented us from performing meta-analyses either quantifying the pooled effect sizes by sex, or from exploring potential interactions between the fixed factors sex and exercise modality. It should be also highlighted that the methodological quality of three (16, 34, 35) of the studies included were categorized as fair (< 5 points in the PEDro scale) with each showing very high (> 90%) publication bias, therefore implying that the findings described should be consider with a degree of caution.

Of the six studies selected in the current systematic review, only three reported sex-specific effects of supervised training programs [AT (35) and CT (34, 45)] on four different measures of insulin sensitivity (FPG, AUCG, HOMA-IR and IC) in patients with T2DM. In particular, two studies (34, 35) observed greater exercise-induced improvements in FPG, HOMA-IR and IC for males than females with T2DM, and one (35) reported the opposite, with females showing a statistically significant reduction in AUCG scores after a CT program. However, when these three studies are carefully scrutinized, some limitations can be identified that should be considered. First, in each of these three studies that found sex-related differences, there were four different insulin sensitivity measures used as dependent variables, however, only one or two of them showed sex-specific effects (table I). For example, Tessier et al. (45) analyzed the effects of a 16-week CT program on four measures of insulin sensitivity (i.e., HbA1c, FBG, FR y AUCG) in 12 males and 7 females, showing that the only statistically significant sex-related difference was found in the AUCG post-training scores of females. Likewise, Rehman (34) carried out a 12-week CT program in 5 males and 6 females with T2DM and found statistically significant pre-post training effects on HOMA-IR and IC scores (but not on HbA1c, FBG) in males only. Thus, these studies did not show consistent sex-specific effects of the supervised training programs applied to individuals with T2DM on all or most of the insulin sensitivity measures assessed in each. Secondly, it should be noted that the aforementioned three studies had the smallest sample sizes (n < 20). These limited samples may foster high degrees of heterogeneity in the pre-and post-training differences reported, which may have biased the inference analyses carried out for intra and inter-group comparisons. Given this, the findings described in the six studies that were selected collectively suggest that there are no sex-specific effects of structured AT and CT programs on insulin sensitivity. Whether the same findings might also occur with RT programs is not known, as no studies have been found describing the effects elicited by such exercise modality on insulin sensitivity measures separately for males and females previously diagnosed with T2DM. On the other hand, it is important to remember that as one gets older, insulin sensitivity decreases, therefore having a large age range between studies could have affected the result as well.

Whether there may be sex-related differences in the documented positive effects of AT and CT programs on cardiorespiratory fitness in patients with T2DM could not be elucidated due to the limited available evidence and the heterogeneity of the results reported by the clinical trials. In this sense, while three studies (16, 34, 35) observed statistically significant sex-related differences in the magnitude of the improvements produced by 12 (35) and 16 (16) week structured exercise programs on VO2max, one study (39) did not find such differences. In addition, of the three studies that did find significant sex-related differences of regular exercise on VO2max, the favorable changes by sex were not consistent across the three (16, 34, 35). Finally, and with regard to the effects elicited by supervised training programs on anthropometric measures in patients with T2DM, only one of the six studies (40) found statistically significant post intervention improvements in body mass index for males and females and no sex-related differences were reported.

One of the main limitations of this systematic review is the small number of studies that fulfilled the inclusion criteria established (n = 6), the small sample sizes (n ~< 30) and age differences, which makes their individual and collective results to be considered with a degree of caution. Furthermore, of the six included studies, only two (35, 40) explored the chronic effects of CT programs on glycemic and cardiovascular outcomes and none analyzed the effects of RT programs on such measures. Besides, the studies did not report relevant information such as physical activity status prior to the intervention and the length of time subjects have had T2DM. Consequently, whether there may be significant interactions between the factors sex and modality of exercise remains unclear. Therefore, studies analyzing separately by sex the effects of structured training programs (RT and CT mainly) on glycemic and cardiovascular measures in large cohort of individuals with T2DM are warranted.

Conclusions: The main findings of the present systematic review inform that, although yet inconclusive, there is particular evidence suggesting no significant differences between males and females with regard to the effects elicited by AT and CT programs on insulin sensitivity cardiorespiratory fitness, body composition and anthropometric measures in individuals with T2DM.

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