

Benefits of Physical Exercise on Risk Factors that Connect Type 2 Diabetes Mellitus and Cardiovascular Disease: Are there Differences between Women and Men?

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Abstract

Type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) are among the top ten causes of death in the world. It is observed that the association between T2DM and cardiovascular risk is not the same for both sexes, with cardiovascular risk associated with T2DM being greater in women. Among the different strategies for the prevention and treatment of T2DM and risk factors for CVD, the physical exercise has been largely recommended because of positive effects for the glycemic control, body mass, blood pressure, and lipid profile. Therefore, this manuscript aimed to review the literature about the risk factors that connect T2DM to CVD, the benefits of different types of physical exercise on these factors, and the differences between women and men in this context. The research was carried out in PubMed and Web of Science databases to find works that highlighted the differences between women and men on risk factors that connect T2DM to CVD and the effects of physical exercise. The most recent works, seminal and/or with the closest relationship with T2DM were selected to review. Some different responses were identified between the sexes, although it was not possible to identify whether such differences are due to the characteristics of the sexes or the absence of specific physical exercise protocols for women. In any case, this review reaffirms the benefits of physical exercise for the control of risk factors that connect T2DM and CVD, both in women and in men, and the need for further studies that consider the differences between sexes and so they can propose increasingly adequate protocols.

Keywords: Type 2 diabetes mellitus; cardiovascular system; physical exercise; women's health.

INTRODUCTION

Diabetes mellitus and cardiovascular disease (CVD) are among the diseases that kill the most in the world. Data from the World Health Organization estimate that, in 2016, 1.6 million people died directly from diabetes mellitus and 17.7 million died from CVD. These numbers tend to grow, as the global prevalence of T2DM is expected to increase from 415 million in 2015 to 642 million in 2040, with more than 90% of cases corresponding to type 2 diabetes mellitus (T2DM) [1]. Interesting to note that, T2DM prevalence is 47% in women and 53% in men, with no difference between sexes [2].

T2DM is characterized by impaired glucose uptake by tissues, resulting in hyperglycemia associated with resistance and/or insufficient production of insulin [3]. Both hyperglycemia and insulin resistance are associated with an increased risk of CVD. Thus, it is not expected that patients with T2DM have higher prevalence of CVD compared to a non-diabetic [4]. Furthermore, CVD is the leading cause of death in individuals with T2DM [3].

It is observed that an association between T2DM and CVD is not equal for the sexes. According to a meta-analysis by Peters et al. [5], the cardiovascular risk associated with T2DM is greater in women than in men.

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In addition, women showed a risk of death from CVD 1.5 times higher than men [6,7] and when diagnosed with T2DM, the risk of myocardial infarction followed by death was 3 to 6 times higher [6].

Among the different strategies for the prevention and treatment of T2DM and the risk factors for CVD, physical exercise has been recommended due to its positive effects in controlling glycemia, body mass, arterial blood pressure and lipid profile [8]. However, the responses to physical exercise stimuli may differ between sexes, and due to the small number of studies carried out with women, the prescription of physical exercise has been based on the findings of studies carried out with men.

Given the above, this study aimed to conduct a literature review on the risk factors that connect to T2DM and CVD, the benefits of different types of physical exercise on these factors, and the differences between men and women in this context.

METHODS

A review on literature was carried out to identify differences between women and men regarding the benefits of physical training on the risk factors that connect T2DM and CVD. The relevant articles to the purpose of this review were searched in the PubMed and Web of Science databases, from January 1990 to June 2021. The search terms used aimed, firstly, to identify the difference between the sexes in obesity, hypertension, dyslipidemia, and sedentary lifestyle, as these are risk factors commonly associated with CVD in individuals with T2DM. For this, the following Boolean search was performed: (sex-differences OR (man AND woman)) AND (obesity OR hypertension OR dyslipidemia OR sedentarism); (sex-differences OR (man AND woman)) AND hypertension; (sex-differences OR (man AND woman)) AND dyslipidemia; (sexdifferences OR (man AND woman)) AND sedentarism.

In a second moment, the search in the databases sought to identify the effects of physical exercise in women and men on the risk factors for CVD mentioned above. The Boolean search performed was: (sex-differences OR (man AND woman)) AND (obesity OR hypertension OR dyslipidemia) AND (physical training OR physical activity OR endurance OR aerobic training OR aerobic exercise OR resistance training OR resistance exercise

OR strength training OR strength exercise OR HIIT OR interval training OR interval exercise). The most recent works, seminal and/or more directly related to T2DM were intentionally selected and reviewed.

THE GEARS BETWEEN T2DM AND CVD

The risk factors that are commonly associated with CVD in individuals with T2DM are: obesity, especially visceral obesity, hypertension, dyslipidemia [4] and sedentary lifestyle [8]. These risk factors have a different prevalence between men and women. For example, women, after menopause, have a higher prevalence of obesity [9], an increase in visceral fat deposition and in the prevalence of dyslipidemia [10,11] and perform less regular physical exercise when compared to men [7].

The first gear between T2DM and CVD that can be highlighted is obesity. The fact that more than 60% of individuals with T2DM are obese (BMI ≥ 30 kg/m²) reveals a close relation between these comorbidities [12]. However, women tend to develop T2DM with a higher BMI than men [5,7]. In fact, at the time of diagnosis of T2DM, women have, on average, a BMI 1.8 kg/m² higher than men [13]. In addition, for each unit of increment in women's BMI, cardiovascular risk increases by 8% [14].

More important than the amount of total body fat in predicting cardiovascular risk is the accumulation of visceral fat. Under physiological conditions, there is a sexual dimorphism in fat distribution, so that women are more likely to deposit fat in subcutaneous deposits, mainly in the gluteal-femoral region, while men are prone to greater visceral fat deposition [15]. However, in the presence of T2DM, this sexual dimorphism tends to be lost, such that 70% of women with T2DM have visceral obesity against 40% of men [10].

Visceral fat accumulation and T2DM share mechanisms associated with the development of CVD, such as inflammation and oxidative stress [16]. Thus, diabetic and obese individuals have high levels of circulating inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and C-reactive protein (CRP) [16,17]. One of the effects of these inflammatory cytokines is to reduce the bioavailability of nitric oxide (\bullet NO).

\bullet NO is a vasodilator molecule capable of promoting vascular remodeling, protecting it from damage and

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maintaining the endothelium in a quiescent and anti-inflammatory state [16]. With the reduction of •NO bioavailability, the endothelium changes from a quiescent state to an activated state [16,17]. This condition maintains and potentiates inflammation, as it stimulates the expression of other inflammatory cytokines, which may chronically be associated with atherogenesis [16].

Regarding oxidative stress, the hyperglycemia characteristic of T2DM and the large amount of non-esterified fatty acids released by the visceral adipose tissue are responsible for triggering the excessive production of reactive oxygen species (ROS) [16- 18]. Similar to inflammation and insulin resistance, ROS reduce the bioavailability of •NO [16].

Another gear that connects T2DM and CVD is high blood pressure. Individuals with T2DM are more likely to develop hypertension [19], while the diagnosis of hypertension in people with T2DM doubles the risk of cardiovascular disease in men and quadruples in women [19,20]. The additive cardiovascular risk resulting from the presence of these two morbidities is associated with their cumulative effect on the production of inflammatory cytokines and oxidative stress and consequent reduction in •NO bioavailability [17,21].

In hypertension, the walls of the arteries are damaged due to the excessive shear stress to which they are submitted. This triggers inflammatory and oxidative stress responses. Additionally, this shear stress on the artery wall accelerates the degradation of elastin fibers, such that collagen fibers may eventually replace the elastin fibers, increasing arterial stiffness [17]. Stiffer arteries increase cardiovascular risk [22] and favor the continuation of the process of injury to arterial walls by shear [17].

Furthermore, high blood pressure is associated with increased activity of the sympathetic nervous system and the renin-angiotensin system. The greater sympathetic activity favors vasoconstriction, as well as greater proliferation of vascular smooth muscle cells [22]. The proliferation of these cells leads to an increase in arterial stiffness [22]. While with greater activation of the renin-angiotensin system, there is greater formation of angiotensin-2, which is associated with endothelial dysfunction and has proinflammatory and pro-fibrotic effects [22].

The third gear that somehow connects T2DM to the risk of developing CVD is dyslipidemia. This condition is characterized by low levels of high-density lipoprotein (HDL) and high levels of low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) [8]. HDL works by promoting the removal of cholesterol from vessel walls to the liver, and has anti-inflammatory, anti-thrombotic and anti-oxidant properties [15]. While LDL and VLDL, when accumulated in the subendothelial space, activate inflammatory pathways responsible for the formation of atherosclerotic plaques [23]. In T2DM, the LDL clearance rate is reduced because of insulin resistance [15], which is also responsible for accentuating oxidative stress [16], increasing the levels of oxidation of lipoproteins [8]. This explains how dyslipidemia increases cardiovascular risk in the T2DM.

Notably, women have lower values for total cholesterol and LDL fraction and higher values for HDL cholesterol [24]. However, in the condition of T2DM, this female characteristic is nullified. Women, in this condition, start to present lower HDL values than healthy women or even men [25], while the amounts of total cholesterol and LDL fraction are equal to those of men, becoming higher than in healthy women [25].

Finally, sedentarism is the fourth piece that connects T2DM with increased risk of CVD. This condition is directly correlated with visceral obesity, hypertension, dyslipidemia and DM [28], and is more prevalent in women [7]. When T2DM is combined with a sedentary lifestyle, mortality from CVD is dramatic. Specifically for women with T2DM and sedentary, the risk of developing CVD is 40% higher than in women who perform physical exercise [20]. Considering these data, the practice of physical exercise becomes an important ally for the prevention and treatment of T2DM and the risk factors that bridge the gap with CVD.

BENEFITS OF PHYSICAL EXERCISE

There are many benefits of physical exercise practice for health promotion and prevention and treatment of non-communicable chronic diseases, such as T2DM. In this session, we presented studies that show how different types of physical exercise improve the condition of men and women in the face of comorbidities associated with T2DM such as obesity, hypertension, and dyslipidemia, which are responsible for the increase in cardiovascular risk.

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According to the American Diabetes Association, lifestyle changes based on physical exercise and dietary re-education are essential for the management of T2DM2 [26]. These changes can promote a moderate reduction in body mass (5%), reflecting an improvement in insulin action, a reduction in fasting glucose [27] and the risk of micro and macrovascular complications [17,20]. In cases where T2DM progresses with impaired insulin production, drug therapy should still be carried out along with lifestyle changes [3].

An important aspect for the management of T2DM, highlighted in this review, refers to the organic differences between men and women. Although it is known that this 9 can have repercussions on the

results of the therapeutic strategies adopted, conducts based on the findings of studies carried out in men or experimental models of males are frequently observed. Given this scenario, it is possible that only a part of the population responds effectively to the prescribed treatment [7,11].

Regarding the effects of physical exercise, both men and women respond positively in controlling blood glucose, body mass, arterial blood pressure and lipid profile (Figure 1). However, the magnitude of the response, the type of physical exercise and the execution time to obtain the effects may differ between men and women. Considering these aspects is essential to enhance the treatment of T2DM and minimize the risk factors for CVD.

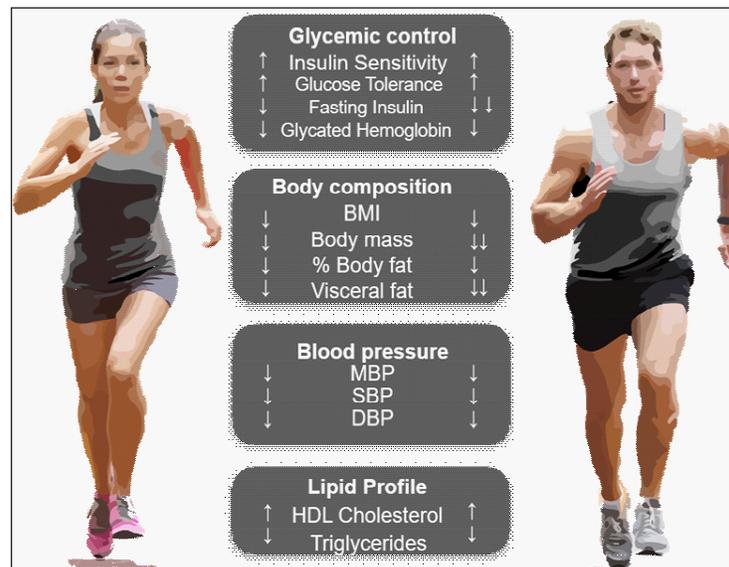


Figure 1. Effects of aerobic exercise on risk factors for CVD in women and men. ↑: increase; ↓: decrease; BMI: body mass index; MBP: mean blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure. The effects on fasting insulin, body mass, visceral fat and blood pressure were more pronounced in men after aerobic exercise.

In a research review, Lin et al. [28] showed that aerobic physical exercise of moderate or high intensity practiced by women and men with or without T2DM was efficient in increasing insulin sensitivity and reducing glycated hemoglobin (HbA1c) and fasting insulin. They also observed that the reduction in fasting insulin was less pronounced in women than in men. However, they did not identify a reduction in fasting glucose ($p=0.06$), nor a difference in the magnitude of response to exercise intensity. On the other hand, Johnson et al. [29] found an improvement in insulin sensitivity in overweight or obese women and men undergoing moderate aerobic exercise, which was not observed after high-intensity physical exercise.

According to the meta-analysis by Snowling & Hopkins [30], the resistance exercise in women and men with T2DM resulted in a reduction in HbA1c levels and an improvement in insulin sensitivity. There were no differences in postprandial and fasting blood glucose, nor between sexes. Resistance physical exercise also improved insulin sensitivity in women without T2DM, although this is not observed in men in the same condition³¹. On the other hand, men without T2DM may have reduced fasting blood glucose, which was not observed in women without T2DM [31].

The high-intensity interval physical exercise (HIIT) was effective in increasing insulin sensitivity and reducing

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fasting blood glucose, especially in overweight or obese individuals trained for at least 12 weeks [32]. Notably, these effects of HIIT on insulin sensitivity outweigh those of aerobic exercise. However, HIIT does not appear to be effective in reducing HbA1c levels in individuals with T2DM. Furthermore, there is no evidence to support sex differences in responses to HIIT.

As previously mentioned, inflammation is one of the factors responsible for the impairment of glycemic metabolism, which is typical of T2DM. In turn, physical exercise can promote an improvement in glycemic metabolism through anti-inflammatory effects. These effects are mediated, in part, by the reduction in visceral fat, which is largely responsible to produce inflammatory cytokines, such as IL-6 and TNF- α [33]. Furthermore, physical exercise increases plasma concentrations of adiponectin and IL-10, cytokines with an anti-inflammatory effect, which also act by improving insulin sensitivity [33]. It is important to emphasize that, during the aerobic exercise session, there is a transient increase of IL-6 in plasma and muscle cells, proportional to the intensity and duration of the exercise [33,34]. This increase is enough to promote greater expression of GLUT-4 in muscle cells, which is strongly associated with insulin sensitivity [34].

If the reduction in body mass is important to improve carbohydrate metabolism, choosing physical exercises that promote greater lipid oxidation favors this condition. Aerobic exercise with moderate intensity is a widely used non-pharmacological strategy for the loss of body mass [35,36]. However, variables such as sex, age, level of physical fitness, exercise intensity, nutritional consumption and health condition influence the maximum rate of fat oxidation [37].

Apparently, women oxidize more lipids and less carbohydrates than men during submaximal aerobic exercise with the same intensity [7,38], which is possibly associated with the effects of estrogens. During exercise, they cause a reduction in the circulating levels of catecholamines, by stimulating the degradation of these neurohormones in the brain and/or by inhibiting secretion by the adrenal gland [38]. Although the mechanisms behind this are not known, the consequence is a lower activation of α -adrenergic receptors, which inhibit lipolysis, but not

of β -adrenergic receptors, which stimulate lipolysis, pointing to the greater sensitivity of the latter in women of the than men [39].

As the intensity of aerobic exercise generally used is between 55% to 70% of the maximum oxygen consumption (VO₂ max) [40], it is extremely important to consider the health condition and age to obtain a better effect of physical exercise. Studies carried out with elderly obese [41] or diabetic adult women [42] indicated that the highest rate of lipid oxidation occurs when exercise is performed with intensity below 55% of VO₂ max (with intervals between 24% and 51% of VO₂ max). In addition, all women in the trained groups had a reduction in body mass, BMI, percentage of body and visceral fat and a reduction in waist-to-hip ratio compared to their control peers.

When obese and/or diabetic women are compared to obese and/or diabetic men, they present less reduction in the percentage of visceral fat and body mass, although both reduce several variables that determine body composition (BMI, waist circumference, body mass, percentage of fat body) [43,44].

Resistance exercises are another strategy to promote general metabolic health in individuals with T2DM2 through improvements in mitochondrial performance and increase in muscle mass [45]. High-intensity resistance exercises (75% to 85% 1RM) were efficient in reducing fat mass and increasing lean mass in elderly diabetics of both sexes, with no difference between them [30,46]. A 6-week protocol of moderate to high intensity resistance exercises (65% to 85% 1RM) was effective in reducing the fat mass percentage and increasing lean mass in middle-aged diabetic men and women [47]. However, because men have a higher percentage of fat-free mass, they tend to obtain greater effect with resistance exercises [44].

A previous study that investigated the combined practice of aerobic and resistance exercises by obese and T2DM women for 16 weeks, revealed the effectiveness of this type of training in reducing subcutaneous and visceral adiposity [48]. In another study comparing aerobic, resistance and combined exercise protocols in obese and hypertensive individuals of both sexes for 8 weeks (1h per session, 3x/week), the authors showed that aerobic exercise promoted a greater reduction in body mass, BMI and fat mass. On the other hand, combined exercise induced a lower percentage of fat

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mass and a higher percentage of lean mass compared to sedentary individuals [49]. In this study, there was no comparison between the sexes.

Although there is a lot of divergence in high intensity exercise protocols for diabetics, both men and women benefit from this type of exercise, mainly with a reduction in visceral fat [50-52].

The beneficial effect of physical exercise on blood pressure is widely known in the literature. Aerobic exercises performed at low and moderate intensities promote a reduction in systolic, diastolic, and mean blood pressure in obese, diabetic, and hypertensive individuals of both sexes. This effect can be observed both acutely, right after an exercise session, and chronically, after a training period. However, when comparing the magnitude of response, women have a smaller reduction in blood pressure [53,54].

The resistance and strength physical exercises are essential for the maintenance of health of individuals with hypertension. In a study carried out with diabetic and hypertensive individuals submitted to 12 weeks of resistance physical exercise, a decrease in systolic and diastolic blood pressure was observed only immediately after the physical exercise session (acute effect). However, there was no reduction in resting blood pressure after the training period (chronic effect) in both sexes [57]. In another study, resistance exercise with moderate intensity induced a decrease in systolic and diastolic blood pressure at rest and in norepinephrine levels in obese individuals with T2DM2. There were no differences in the magnitude of blood pressure response between sexes [58].

Other types of physical exercises were conducted to investigate blood pressure responses. In one of the studies, obese and diabetic women who underwent 16 weeks of HIIT (90% -100% of heart rate reserve, with active recovery less than 70% of heart rate reserve), had a reduction only in systolic blood pressure [59]. Another research showed that the association between high-intensity physical exercise and resistance exercise for 12 weeks reduced systolic and diastolic blood pressure of individuals with T2DM and hypertension of both sexes [56].

Regarding the effects of aerobic exercise on the lipid profile, data from metaanalysis with men and women revealed the potential of this type of exercise to reduce triglyceride levels and increase HDL cholesterol levels [28]. On the other hand, the LDL cholesterol only

showed a tendency to reduction ($p=0.08$) and total cholesterol remained unchanged. According to the authors, more significant LDL cholesterol responses to aerobic exercise may occur in individuals with T2DM, hypertension and dyslipidemia, mainly due to the higher values found in this population [28].

The effects of resistance exercise are much less pronounced on the lipid profile. According to a meta-analysis, individuals with T2DM undergoing this type of exercise do not present significant differences in the levels of triglycerides, total cholesterol, and HDL and LDL fractions. Furthermore, no differences were shown between the sexes [30]. These results are also consistent in healthy men and women [60]. Similarly, HIIT did not promote changes in the levels of triglycerides, total cholesterol, and HDL and LDL fractions [32]. Thus, it is not surprising that sexes differences have not been reported [32].

CONCLUSION

In summary, aerobic, resistance and HIIT physical exercises are beneficial for the control of risk factors that connect T2DM and CVD, such as obesity, hypertension, dyslipidemia, and physical inactivity itself. It was evident that both women and men are benefited from the practice of physical exercise, although some different responses between the sexes are observed. It was not possible to identify whether such differences are due to female and male characteristics or the absence of specific physical exercise protocols for women and men. Therefore, there is a clear need for studies to better understand the responses of the female body to physical exercise, which will help to choose safer and more efficient protocols for the prevention and treatment of T2DM and CVD risk factors.

Financial support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP #2018/22361-9)

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Citation: Daniela Boschetti, Luis Felipe Martucci, Fabiana S. Evangelista, Anna Karenina Azevedo-Martins. *Benefits of Physical Exercise on Risk Factors that Connect Type 2 Diabetes Mellitus and Cardiovascular Disease: Are there Differences between Women and Men?. Archives of Physical Health and Sports Medicine*. 2021; 4(1): 20-28.

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