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Review

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Physical exercise for obesity and T2DM mitigation in polycystic ovary syndrome: the role of adipose tissue

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Abstract

Polycystic ovary syndrome (PCOS) is a complex disorder with a great heterogeneity of signs and symptoms. However, hyperandrogenism is considered a hallmark of PCOS, presented by most affected women. Women with PCOS are at high risk of developing type 2 diabetes mellitus (T2DM), which is associated with insulin resistance (IR) and hyperinsulinemia. In turn, hyperinsulinemia interferes with the androgen production by ovarian cells, and worsens the hyperandrogenism, initiating a feedback cycle. Women with PCOS are also at a greater risk of developing obesity. Indeed, a dysfunctional adipose tissue in obesity contributes to T2DM in PCOS by affecting insulin action and secretion through multiple mechanisms, such as lipotoxicity, inflammation, and adipokine signaling. Therefore, obesity-disrupted adipose tissue can be seen as an important target for T2DM development in women with PCOS. Because adipose tissue can be positively affected by non-pharmacological and easily accessible strategies such as physical exercise, this review provides a comprehensive summary of the benefits of physical exercise to improve adipose tissue health and decrease the risk of obesity and T2DM in women with PCOS.

Keywords: Polycystic ovary syndrome, type 2 diabetes mellitus, obesity, adipose tissue, physical exercise

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a reproductive disorder that affects up to 10%-13% of women in reproductive age[1,2]. Due to the heterogeneity of signs and symptoms, the diagnosis of PCOS can be challenging. Accordingly, although other criteria have been described, the recently published *2023 Evidence-based Guideline for the Assessment and Management of PCOS*[1] endorses the Rotterdam criteria as the gold standard for clinical diagnosis. This requires the presence of at least two of the following three findings: (1) Oligo- and/or anovulation; (2) Clinical and/or biochemical hyperandrogenism; and (3) Polycystic ovaries on ultrasound after exclusion of other etiologies[3]. In addition, since the anti-Müllerian hormone (AMH) secretion by ovarian follicles is elevated in women with PCOS[4], this guideline also includes AMH determination as an alternative diagnostic method for ultrasonography[1].

Hyperandrogenism is the most common PCOS clinical finding, present in more than 80% of all PCOS-affected women[5]. This includes elevated levels of testosterone (T), bioavailable free T, and free androgen index, as well as elevated androstenedione and dehydroepiandrosterone sulfate (DHEA-S)[5]. The etiology of hyperandrogenism in PCOS is not completely understood, but two distinct pathways might contribute to the high androgen secretion: (1) dysfunction of the hypothalamic-pituitary-gonadal axis and (2) the effect of high insulin levels on androgen synthesis by ovarian cells. PCOS is implicated in an increased GnRH pulse frequency and amplitude by hypothalamic neurons, which in turn increases the frequency and amplitude of luteinizing hormone (LH) pulses and reduces follicular-stimulating hormone (FSH) secretion. As a result, the LH hyperstimulation of ovarian theca cells increases the secretion of T and androstenedione, which inhibits folliculogenesis, promotes the accumulation of small follicles and leads to high AMH production[5].

Several comorbidities are associated with PCOS, including hirsutism, alopecia, and acne[6], which, possibly due to the damage to personal image, contribute to the development of psychological pathologies, including anxiety and depression[1,7]. Furthermore, women with PCOS also have an increased risk for metabolic conditions such as insulin resistance (IR) and type 2 diabetes mellitus (T2DM). High androgen levels in PCOS are implicated in IR and hyperinsulinemia[8,9], and, at the same time, insulin may affect ovarian morphology and function by enhancing androgen synthesis, therefore establishing a vicious cycle between PCOS and T2DM[6]. Hyperandrogenism may also disturb adipose tissue metabolism through adipocyte hypertrophy, increasing the prevalence of obesity in women with PCOS[10,11]. A dysfunctional adipose tissue increases the release of free fatty acids (FFA), proinflammatory cytokines, and dysregulated adipokines, which might lead to IR, β cell dysfunction, and T2DM[12]. Although even lean women with PCOS are more predisposed to develop T2DM, this risk can be 4-fold higher in women with obesity[13,14]; therefore, adipose tissue is an important key for the pathogenesis of T2DM in PCOS.

Many benefits can be obtained through physical exercise, including a reduction in fat mass, an improvement in adipokines and lipid profiles, and an improvement in insulin sensitivity[15,16]. Therefore, the promotion of healthier adipose tissue by practicing physical exercise may be considered a non-pharmacological and easily accessible strategy to mitigate obesity and T2DM in women with PCOS. Thus, the purpose of this review is to provide a comprehensive summary of the benefits of physical exercise to improve adipose tissue health and decrease the risk of obesity and T2DM in women with PCOS.

THE RELATION BETWEEN PCOS AND T2DM

IR is found in 80% of women with PCOS independent of the BMI and leads to a compensatory increased insulin secretion[8,9]. Hyperinsulinemia, in turn, affects ovarian morphology and function. Insulin can mimic LH stimulation of ovarian theca cells and potentialize theca cells' sensitivity to LH[17,18]. Consequently, the synergism of LH and insulin stimulates the androgen syntheses by ovarian theca cells, further aggravating

hyperandrogenism. In addition, while hyperinsulinemia enhances androgen production, it decreases sex hormone binding globulin (SHGB) synthesis, resulting in increased total and free T, and consequently disrupts follicle development[5]. Therefore, while hyperandrogenism predisposes IR in PCOS, hyperinsulinemia worsens the high levels of androgens.

Thus, decreasing insulin levels in women with PCOS contributes to reducing androgen and increasing SHBG levels, improving the metabolism and demonstrating the stimulatory relationship between the high insulin levels and androgen release in PCOS[19]. Hyperinsulinemia also disrupts ovarian follicular development, resulting in premature luteinization, through a FSH-induced upregulation of LH receptors in granulosa cells[5]. This may collaborate with the clustering of small follicles in the periphery of the ovary, giving it a polycystic morphology[20].

The relationship between PCOS and IR has already been proven in several studies[8,17,18,21]. In women with PCOS, IR is frequently associated with β cell dysfunction[22,23]. The insulin gene promoter presents an androgen-responsive element that binds to the androgen receptor (AR), and its stimulation by hyperandrogenism in PCOS increases the transcription of the insulin gene and, hence, insulin secretion[24]. Moreover, the high androgen levels in PCOS disrupt the mitochondrial function of pancreatic islets[25], and women with PCOS show increased production of reactive oxygen species (ROS) and oxidative stress, which is inversely correlated with the β cell function[26]. Interestingly, the intrauterine hyperandrogenism that contributes to the increased risk of developing PCOS in daughters from mothers with PCOS increases the number of β cells, the islet expression of AR and other genes related to β cell function, resulting in increased insulin secretion under euglycemic conditions. This programs a disrupted β cell environment that contributes to the altered insulin secretion in PCOS[27].

Women with PCOS have a 2-to-3-fold higher prevalence of obesity, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD), which contributes to an increased risk of developing T2DM[28,29], that mirrors PCOS features such as IR, impaired β cell function, and high body weight[30]. T2DM is the most prevalent type of diabetes, accounting for more than 95% of all cases[31]. During its pathogenesis, defects in the insulin signaling cascade impair glucose uptake in insulin-sensitive tissues such as skeletal muscle and adipose tissue. At this point, β cells augment insulin secretion as a compensatory response to this IR, temporarily maintaining normal glucose levels. However, continuous and high demands for insulin prejudice β cell secretory capacity, eventually leading to β cell failure and apoptosis. Therefore, insufficient secretion and defective action of insulin leads to glucose accumulation in the bloodstream in T2DM, and dysregulation of metabolic processes such as hepatic gluconeogenesis that aggravates hyperglycemia[12].

Preventing and treating T2DM is fundamental to avoiding micro and macrovascular complications. High glucose levels can affect microvasculature through the formation of advanced glycation products (AGE), oxidative stress, and inflammation, resulting in diabetic microangiopathy (retinopathy, nephropathy, neuropathy), and eventually leading to macrovascular complications such as systemic hypertension[32]. Unfortunately, according to the last International Diabetes Federation Atlas[33], T2DM prevalence is predicted to increase from 10.5% (536.6 million) of the global adult population in 2021 to 12.2% (783.2 million) in 2024. Such progression is related to lifestyle changes in modern societies, with increasing sedentary behaviors and declining nutritional quality that includes high consumption of processed meat and sugar-sweetened beverages, resulting in greater obesity prevalence[34,35].

Even though lean women with PCOS have a high risk of T2DM compared to controls[36], this is remarkably increased by a high BMI, as women with PCOS who are obese have a 4-fold increased risk of developing

T2DM compared to normal-weight women with PCOS[13,14]. In this regard, the *2023 International PCOS Guideline* warns that women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance, and T2DM. Therefore, it is strongly recommended that all women with PCOS should be carefully screened for T2DM regardless of age and BMI, with regular intervals of oral glucose tolerance test[1,37].

Additionally, both women with a previous history of gestational diabetes[38,39] and those with type 1 diabetes mellitus (T1DM) and T2DM have greater risk of developing PCOS and the evaluation of PCOS in these women should be considered[1]. In a study with premenopausal women with T2DM, authors found that 82% had polycystic ovaries and 52% presented PCOS symptoms such as cutaneous hyperandrogenism and/or menstrual disturbances[40]. Likewise, the prevalence of PCOS in women with T2DM was around 21% in a meta-analysis study[41]. Although there is an increase in the IR in the peripheral tissues of women with PCOS (i.e., skeletal muscle and adipose tissue), the ovary remains sensitive to the gonadotropin-like action of insulin and its consequent stimulation of androgen synthesis[28,42], which will act on target organs as a classical feature of PCOS.

GENETICS OF PCOS AND T2DM

PCOS is strongly influenced by genetics, with nearly 70% of daughters from PCOS mothers manifesting PCOS symptoms[43]. The genetic inheritance of PCOS is supported by evidence showing that fathers and brothers of women with PCOS may have a higher prevalence of metabolic disorders, T2DM, and hypertension[1]. A recent bioinformatic analysis compared two datasets that contained genetic information on T2DM and PCOS (GSE10946 and GSE18732 datasets, respectively). The analysis resulted in four common genes differently expressed in both diseases (*BIRC3*, *DEPTOR*, *TNNL3*, *ADRA2A*). These genes are respectively related to smooth muscle contraction, channel inhibitor activity, apoptosis, and tumor necrosis factor α (TNFα) signaling pathways[44].

Shaaban *et al.* found some associations between PCOS and polymorphisms in genes related to secretion and signaling of insulin, including insulin receptor (*INSR*) gene, adiponectin gene (*ADIPOQ*), *PPARG*, calpain protein (*CAPN10*), a cysteine protease that participates in proinsulin processing, and melatonin receptors (*MTNR1A* and *MTNR1B*)[45]. These melatonin receptors are expressed in pancreatic islets whose polymorphisms are related to IR and lower β cell function. On the other hand, the importance of the INSR substrate 1 and 2 (*IRS1/2*) gene to PCOS pathophysiology does not have the same replicability, and the relevance of the insulin gene is controversial[45].

Despite the strong genetic inheritance in PCOS pathophysiology, its etiology is multifaceted and might involve epigenetic and environmental clues. In this regard, the PCOS-like reproductive and metabolic traits induced by the prenatal androgenization of mice can be detected in the third offspring (F3) generation, which presents increased fat mass, larger adipocytes, and altered adipogenesis - markers of metabolic dysfunction that indicate IR[43]. This metabolic disturbance was related to a transgenerational change in the oocyte gene expression[43]. In women, it is proposed that the unfavorable *in* utero environment of patients with PCOS, marked by high androgens and AMH levels, has a fetal programming effect, predisposing the offspring to develop PCOS[43,46,47]. This is possibly due to epigenetic changes in DNA methylation that can also be transgenerationally transmitted[48-51]. Thereafter, bad lifestyle habits such as poor-quality diet, sedentary lifestyle, stress, and endocrine disruptors trigger the onset of PCOS symptoms in the daughters of mothers with PCOS[50,52].

T2DM is referred to as a polygenic disorder[53], with a strong familial inheritance of 58%-65% relative risk for T2DM in monozygotic twins and 16%-30% in dizygotic twins[54]. Several gene polymorphisms were found to be associated with T2DM pathogenesis, including the rs7903146 polymorphism in the *TCF7L2* gene[55], a major regulator of insulin secretion that influences the insulin transcriptional network[56]. This polymorphism was associated with a 41% increased risk for T2DM, becoming the single gene variant with higher association with T2DM[57]. In fact, the strongest associations were identified in genes that are related to secretion and action of insulin, or even incretin response; however, a large number of identified single-nucleotide polymorphisms (SNPs) are not associated with any of these actions, but with cellular signaling, cell cycle, mitosis, apoptosis and some other functions, reinforcing the complex polygenicity of genetic predisposition of T2DM[54].

ADIPOSE TISSUE: A COMMON PLAYER IN PCOS AND T2DM TEAMS

Adipose tissue is no longer seen only as a place to store fat to be mobilized in periods of energetic needs. In fact, adipose tissue is a very heterogeneous group of tissues with an intense plasticity potential, and it can act as a key metabolic regulator in whole-body physiology[58]. Far beyond the basic classification of adipose tissue in white adipose tissue (WAT - the professional of energy storage) and brown adipose tissue (BAT - the thermogenesis promoter)[59], adipose tissue depots have an important endocrine function by releasing multiple peptide hormones (adipokines) that regulate several functions such as systemic metabolic state, appetite, and inflammatory response[60].

WAT expansion is determined by the balance between adipocyte hyperplasia (adipogenesis), fat synthesis through adipocyte hypertrophy (lipogenesis), and fat breakdown (lipolysis)[59]. Excessive caloric intake combined with sedentary behavior results in a positive energy balance where these excess calories will be stored in WAT, causing its expansion and leading to obesity[61,62]. However, while high levels of adipogenesis, mainly in subcutaneous WAT (sWAT), are more associated with a healthier metabolic status, high levels of lipogenesis, mainly in visceral WAT (vWAT) depots, induce a WAT remodeling with enlarged adipocytes and increased intracellular lipid droplets, associated with a proinflammatory status and systemic IR[62,63].

In addition, genetic aspects also play a crucial role in the obesity process. Although there are rare cases of monogenic obesity, inherited with a Mendelian pattern, obesity is seen as a polygenic disease in the same way as T2DM, where hundreds of polymorphisms in key genes might contribute to obesity development[64]. Some genes whose polymorphisms showed important associations with obesity include: the β-3 adrenergic receptor gene (*ADRB3*) that stimulates lipid mobilization in WAT[65], melanocortin-4 receptor (MC4R) that regulates food intake and energy homeostasis[66], obesity-associated gene (*FTO*) associated with fat accumulation[67], and much more.

The pathological WAT remodeling process is characterized by rapid and disorganized growth of existing adipocytes, which eventually undergo hypoxia considering the rate-limited angiogenesis process, leading to adipocyte inflammation and death[68]. This induces macrophage recruitment and infiltration in WAT, accentuating the inflammation through the release of proinflammatory cytokines. Additionally, an intense fibrosis process is seen in obesity[68]. This dysfunctional WAT releases many molecules involved in the IR of tissues such as skeletal muscle, liver, and WAT itself[12]. Individuals with obesity have increased serum levels of FFA that can lead to intracellular accumulation of diacylglycerol (DAG) and ceramide, promoting damage by oxidative stress and inhibitory phosphorylation of IRS1/2, impairing insulin signaling[12].

In the liver, the increased lipid availability and the presence of inflammatory mediators are the genesis of NAFLD, since lipids are stored as hepatic triglycerides, leading to hepatic steatosis, or undergo mitochondrial oxidation, which may increase the production of ROS and oxidative stress. Additionally, DAG formation, as an intermediate molecule in triglyceride synthesis, contributes to hepatic IR through the activation of PKC and inhibition of IRS1/2[69]. Although NAFLD's contribution to T2DM and metabolic syndrome is not yet completely clear, it involves the hepatic IR, leading to altered lipoproteins and increased VLDL production, increased lipogenesis and gluconeogenesis which augments hepatic glucose output[69]. In the same way, in pancreatic β cells, chronic exposure to FFA like palmitate induces intracellular lipid accumulation, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress, leading to reduced insulin secretion and apoptosis[70,71].

WAT from lean individuals releases high levels of adiponectin (an insulin-sensitizing adipokine); however, the WAT from individuals with obesity decreases adiponectin production and increases the production of leptin and inflammatory cytokines such as TNFα and IL-1β[72,73]. Leptin acts mainly in the central nervous system, modulating appetite, but in β cells, it can inhibit insulin secretion[74]. TNFα is a well-known factor that interferes with insulin cascade by affecting IRS1/2[75] and promotes β cell apoptosis[76]. Additionally, β cell exposure to IL-1β also induces apoptosis, mediated by the JNK pathway[11]. Together, all those obesity-induced mechanisms contribute to the insufficient production and deficient action of insulin observed in T2DM pathophysiology[77].

The occurrence of PCOS can also be linked to functional abnormalities in WAT since androgen excess can induce adipocyte hypertrophy[9,78]. Women with PCOS (BMI between 20-35 kg/m^2) exhibited lower *ADIPOQ* expression in sWAT, higher central fat mass and sWAT adipocyte area compared to women without PCOS. Additionally, only in women with PCOS was adipocyte area positively correlated with T serum levels[79]. Moreover, women with PCOS exhibited lower expression of GLUT4 and IRS1, as well as higher levels of oxidative stress in vWAT, which correlated with waist circumference (WC) and homeostatic model assessment for insulin resistance (HOMA-IR) index[80]. A PCOS rat model, treated with dihydrotestosterone (DHT) for 90 days, showed increased food intake, body weight, and vWAT hypertrophy in contrast to control group, as well as decreased mitochondrial content in visceral and sWAT[10]. In another study, DHT-treated mice showed increased body weight, retroperitoneal vWAT and BAT weights however, those parameters were prevented by the transplantation of WAT from AR knockout mice[81].

As we see, PCOS shares common aspects with T2DM pathophysiology and, given the PCOS' effects on WAT expansion, dysfunctional WAT in cases of obesity and/or PCOS might be an important element in understanding how these three conditions are related [Figure 1]. Therefore, promoting healthy body composition and improving glucose metabolism are primary actions for managing obesity and the risk of T2DM in women with PCOS.

PHYSICAL EXERCISE IN PCOS: LOOKING AT OBESITY AND T2DM

The adoption of a balanced diet and regular physical exercise has been extensively recommended to improve anthropometric, metabolic, and hormonal parameters, as well as lowering T2DM risk[82] and improving ovarian functions[83,84]. The benefits of dietary modifications for weight loss and glycemic control in women with PCOS have been discussed in previous studies[1,82,85]. Here, we focus on the favorable effects of physical exercise on body composition, glucose metabolism, and T2DM.

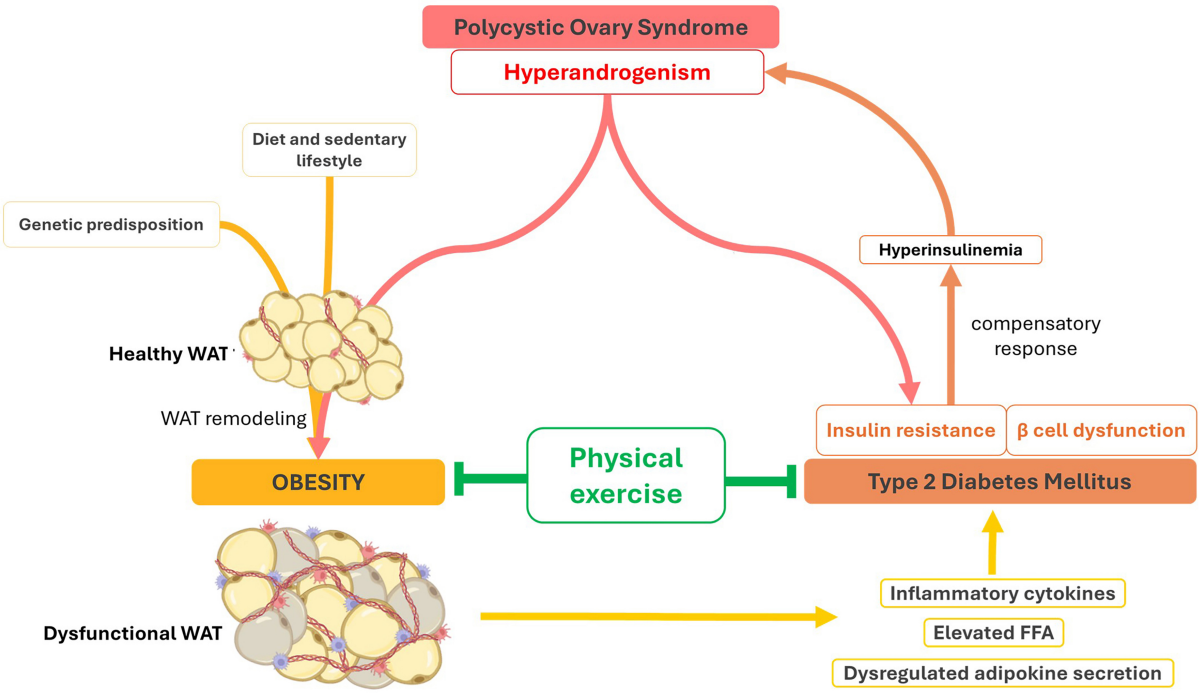

Figure 1. Connections between PCOS, obesity and T2DM. PCOS can influence the development of obesity and T2DM. Hyperandrogenism found in women with PCOS may induce the WAT remodeling process and, in the presence of genetic predisposition, poor dietary choices, and a sedentary lifestyle, it can lead to obesity. An obesity-disrupted WAT can contribute to T2DM development through mechanisms such as inflammation, lipotoxicity, and adipokine signaling. Insulin resistance found in T2DM, and enhanced by hyperandrogenism in PCOS, induces a compensatory response of pancreatic β cells to secrete more insulin. Hyperinsulinemia affects ovarian morphology and function, reinforcing hyperandrogenism in PCOS. In that scenario, the practice of physical exercise can help in the mitigation of obesity and T2DM in women with PCOS. PCOS: Polycystic ovary syndrome; T2DM: type 2 diabetes mellitus; WAT: white adipose tissue; FFA: free fatty acids.

The number of studies that investigated the effects of physical exercise in women with PCOS has increased over the years. In recent research conducted in the electronic databases of PubMed from inception to September 2024 using keywords PCOS and physical exercise or physical activity, 982 manuscripts were found. When the keywords obesity or diabetes were included, 526 and 352 manuscripts were found, respectively [Figure 2]. These data highlight the relevance of physical exercise in the management of PCOS and how much progress we have made in knowledge on the subject.

Since 2000, more than 630 systematic reviews and meta-analyses about PCOS have been published, most of them with a focus on lifestyle and pharmacological interventions to improve metabolic, hormonal profile and ovarian function. Regarding physical exercise, both aerobic and resistance exercises can positively impact BMI, WC, body fat, and glucose metabolism in women with PCOS[82,86-88].

Results from the systematic review and meta-analysis conducted by Kite *et al.* found reductions in BMI with aerobic exercise in women with BMI ≥ 30 kg/m^2[87]. They also observed reductions in WC and body fat, suggesting that exercise promotes favorable changes to body composition in women with PCOS and obesity compared to those receiving no intervention. Fasting blood glucose did not change, but fasting insulin and HOMA-IR were reduced following exercise, with no evidence of change in the control groups.

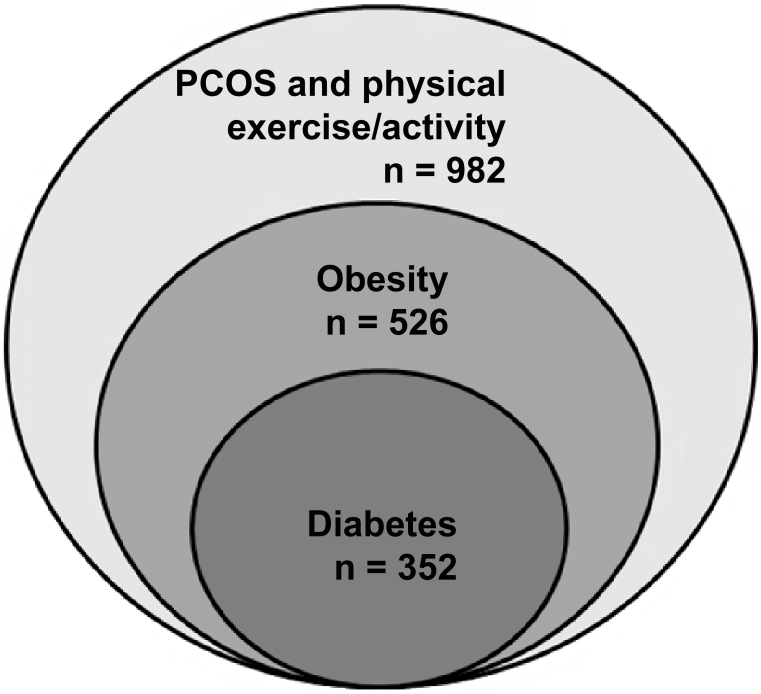

Figure 2. Number of manuscripts published with the descriptors PCOS, physical exercise/physical activity, obesity, and diabetes in the electronic databases of PubMed since 1952. PCOS: Polycystic ovary syndrome.

When different intensities of aerobic exercise were compared, Patten *et al.* reported small improvements in BMI and WC only after aerobic vigorous-intensity continuous training 70% to 90% of maximum heart rate (HRmax) or 60% to 85% maximum oxygen uptake (VO2max) compared with [moderate-intensity continuous training (MICT) 55% to 70% HRmax or 40% to 60% VO2max] or high-intensity interval training (HIIT) (≥ 90% HRmax or ≥ 85% VO2max)[89]. Decreases in BMI were more evident when exercise was complemented with dietary intervention, and positive effects in WC or other markers of body composition, including increased lean mass and decreased adiposity, can occur without changes in body weight. Aerobic vigorous-intensity continuous training and resistance exercise also resulted in improvement of IR as indicated by moderate decreases in HOMA-IR.

In another systematic review and meta-analysis, Breyley-Smith *et al.* showed that both aerobic MICT and HIIT reduced WC in women with PCOS[90]. However, only MICT led to a statistically significant benefit. As discussed by the authors, despite the small magnitude of exercise effect alone, the results support the use of aerobic exercise as a strategy to control central obesity in women with PCOS.

Almenning *et al.* showed that HIIT for 10 weeks improved IR in women with PCOS compared with the non-exercise group[84]. This response was not observed with resistance exercise (strength training). Body weight or WC did not change in any group, but fat percentage decreased after both exercise types. Both body and visceral fat percentages were positively correlated with HOMA-IR before and after physical exercises, showing the connection between adiposity and IR. Additionally, with HIIT, Mohammadi *et al.*

found decreased BMI, waist-to-hip ratio, visceral fat, fasting insulin, and IR[91]. Collectively, these results revealed that variation of aerobic exercise such as HIIT is interesting to include in the exercise routine of women with PCOS because it offers good results for BMI, adiposity, and IR with less exercise time commitment.

Recently, Ruiz-González *et al.* showed that strategies that combined diet with weight loss drugs were the most likely to result in BMI reduction, followed by exercise combined with diet and weight loss drugs, and exercise combined with diet and ovulation inducers[92]. In this research, the authors included aerobic MICT, resistance exercise, and a combination of both types.

Moderate-to-high intensity aerobic exercise has been frequently used to prevent metabolic complications, reestablish ovulation, and increase the likelihood of pregnancy[84]. In addition, aerobic exercise increases cardiorespiratory fitness, reduces total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, and increases high-density lipoprotein cholesterol (HDL-C) in women with PCOS[91,93-95].

Although aerobic exercise is often prescribed for women with PCOS, it is important to consider practicing resistance exercise since it can improve body composition, glucose metabolism, and sexual dysfunction[84,86,96,97]. According to Kogure *et al.*, women with PCOS who did resistance exercise did not change their BMI, but reduced WC and fasting glucose levels and increased lean muscle mass compared with the baseline values[86]. Vizza *et al.* also found a reduction in WC, an increase in lean mass and fat-free mass, and an improvement in glycosylated hemoglobin (HbA1c) compared with the control group[96]. However, they did not observe changes in fat mass or percent of body fat in HOMA-IR2 and fasting insulin. On the other hand, Saremi and Yaghoubi and Kite *et al.* reported better fasting insulin in women with PCOS compared to control[87,98].

Kite *et al.* reinforced that resistance exercise may be beneficial for women with PCOS because it also improves triglycerides, total cholesterol, and LDL-C[98,99]. Furthermore, just like aerobic exercises, resistance exercises also reduce total cholesterol and LDL-C in high-fat diet-induced obese mice[100]. These effects are crucial for reducing cardiometabolic risk associated with PCOS. However, as discussed by Kite *et al.*, it is still necessary to expand the number of studies with resistance exercise to better elucidate the effects of this type of exercise, since the studies published have used small samples with heterogenous characteristics and different exercise prescriptions[99]. Table 1 shows the effects of aerobic and resistance exercises for the prevention of obesity and T2DM, as well as for the reduction of cardiometabolic risk in women with PCOS.

EXERCISE-INDUCED ADAPTATIONS TO ADIPOSE TISSUE

The connection between adipose tissue and chronic diseases such as T2DM is clearly demonstrated in the literature. The excess of adipose tissue and the expansion of adipose tissue in non-adipose tissue modify the production of chemical molecules, resulting in systemic inflammation and adverse influence on energy homeostasis, metabolism, insulin sensitivity, and inflammation[12,101].

On the other hand, physical exercise improves the handling of lipid excess and promotes healthy adipose tissue[15] functioning as a metabolic guardian against the development of T2DM. De Glisezinski *et al.* showed that moderate aerobic exercise increases the rate of lipolysis in human adipose tissue, decreasing the triacylglycerols stored[16]. The augmented lipolytic activity was also observed in women with PCOS and obesity, which could favor weight loss through aerobic exercise[102]. In addition, aerobic exercise improves lipid oxidation in the skeletal muscle of individuals and animals due to an increase in the activity of oxidative enzymes, expression of triglyceride and fatty acid transport proteins, and higher mitochondrial

Table 1. Effects of physical exercise against the development of obesity and T2DM

Aerobic exercise	Resistance exercise
↓ BMI	↔/↓ BMI
↓ WC	↓ WC
↓ Body/visceral fat	↔/↓ Body fat
↔/↓ Fasting glucose	↑ Lean muscle mass
↓ Fasting insulin	↓ Fasting glucose
↓ Insulin resistance	↔/↓ Fasting insulin
↓ Total cholesterol	↓ HbA1c
↓ LDL-C and triglycerides	↔/↓ Insulin resistance
↑ HDL-C	↓ Total cholesterol
↑ Cardiorespiratory fitness	↓ LDL-C and triglycerides

↑: Increase; ↓: decrease; ↔: unchanged. Aerobic and resistance exercises induce changes in body composition and glucose metabolism that are involved in the prevention of obesity and T2DM, as well as in the reduction of cardiometabolic risk in women with PCOS. BMI: Body mass index; WC: waist circumference; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; T2DM: type 2 diabetes mellitus.

density and capillarization[103-105].

Resistance exercise can also increase lipid oxidation in skeletal muscle, favoring the reduction of body adiposity in humans[106,107]. Polak *et al.* showed that the resistance exercise increased the responsiveness to the beta-adrenergic receptor stimulation of lipolysis and anti-lipolytic action of catecholamines via alpha-adrenergic 2A receptor in subjects with obesity[108]. They also found better whole-body and adipose tissue insulin responsiveness.

In previous reports, our group showed in animals that the WAT remodeling induced by aerobic exercise is associated with the prevention of obesity and IR[109,110]. Using a diet-induced obesity and IR animal model, we found lower vWAT in trained mice, which was associated with increased lipolytic activity, reduced lipogenic capacity, and increased activity of enzymes responsible for lipid oxidation[109]. In addition, we observed a reduction in insulin signaling proteins and an increase in the expression of lipolysis signaling proteins in the sWAT[110]. These results revealed that aerobic exercise favored fat oxidation instead of fat storage, which is pivotal to preventing IR and T2DM.

Functional BAT is important for metabolic and cardiovascular health and has therefore been investigated as a potential therapeutic target for obesity, T2DM, and cardiovascular diseases[111]. Chondronikola *et al.* showed that BAT activation in healthy individuals increased insulin sensitivity[112]. In obese or aged animals, BAT activation or transplantation normalized glucose tolerance and IR[113,114].

Despite being the most metabolically active adipose deposit, the effect of physical exercise on BAT is still controversial. Vidal and Stanford reported that the thermogenic activity of BAT can increase, reduce, or remain unchanged after aerobic physical exercise[115]. These responses depend on the physical exercise protocol, the experimental model investigated, and the ambient temperature at which the physical exercise was performed. In addition, Wang *et al.* observed that trained mice fed a high-fat diet had better insulin action, IL-6 and TNFα levels, increased thermogenic activity and multilocular adipocytes in the BAT[116]. In humans, moderate aerobic exercise but not HIIT improved glucose metabolism in the BAT[117]. However, Martinez-Tellez *et al.* showed no effect of combined aerobic and resistance exercises on BAT volume or glucose uptake in humans[118]. As discussed by Lehnig & Stanford[119], physical exercise itself is a type of heat

production and is less likely to enhance thermogenesis by BAT.

Recruitment of beige adipocytes can contribute to the enhancement of energy metabolism because they function similarly to brown adipocytes in energy generation in the form of heat[120]. In a previous study, Otero-Díaz *et al.* showed that 12 weeks of aerobic exercise increased the expression of brown and beige genes in abdominal sWAT of non-diabetic individuals with different BMIs (normal, overweight and with obesity)[121]. Recently, Chou *et al.* found that only aerobic exercise upregulated thermogenic gene expressions in epididymal vWAT of mice with obesity, which was associated with increased circulating irisin[100]. Increased irisin concentration was also observed after resistance exercise in individuals with overweight and obesity[122]. In addition to stimulating WAT browning, irisin also enhances glucose uptake in the BAT[123] and fatty acid oxidation[124], which can positively contribute to preventing IR and T2DM in women with PCOS.

In addition to irisin secretion, exercise-induced adaptation in skeletal muscle also resulted in increasedβ-aminoisobutyric acid (BAIBA) and fibroblast growth factor 21 (FGF21), which are associated with the induction of browning in the WAT. These effects are responsible for improvements in glucose disposal, fatty acid oxidation, and lipolysis, which are important for the prevention and treatment of T2DM[125,126].

Physical exercise improves the adipocytes' function by modulating the secretion of peptides and non-peptides, which have endocrine, paracrine, and systemic actions. Adiponectin is one of the adipokines that have been investigated the most, and its actions contribute to alleviating IR by stimulating lipid oxidation and anti-inflammatory responses[127]. Some studies found that circulating adiponectin increased after exercise[128,129], while others showed no changes after exercise[130,131]. Circulating adiponectin also increased after aerobic exercise in rodents[132,133] and in patients who have pre-diabetes or T2DM[134]. In addition, the adiponectin concentration increased in trained women with PCOS with HIIT exercise for 12 weeks[81].

Reduction in adipose tissue mass in rodents and humans leads to a decrease in leptin concentrations[135]. Lower leptin concentration increases tissue sensitivity to insulin and reduces intracellular lipid contents by AMPK activation and signaling mediators of the central nervous system[136]. Aerobic exercise decreased serum leptin levels in both lean and individuals with obesity[137,138] and in women with PCOS[139]. Furthermore, reductions in leptin concentration were observed after three different protocols of resistance exercise in humans (hypertrophy, strength, and muscular endurance) compared to baseline[140], and in young females with obesity trained with both HIIT and plyometric training[141]. Conversely, Almenning *et al.* showed that neither resistance training (strength) nor HIIT changed the levels of leptin and adiponectin in women with PCOS[84]. In animals fed a cafeteria diet, aerobic exercise prevented hyperleptinemia, which is associated with the development of leptin resistance[121].

Despite the positive effects of resistance exercise, the data set in humans suggests that endurance exercise appears to be more effective in decreasing body fat mass and adipocyte size, increasing fatty acid mobilization and oxidation during and post-exercise, and modulating adipokine secretion[142].

Increased levels of inflammatory cytokines such as TNFα and IL-6 are associated with adipose hypertrophy and IR and can modulate ovarian follicular function[142]. Aerobic exercise can counteract the inflammatory status of women with PCOS[143]. In a previous study, Dantas *et al.* demonstrated that aerobic exercise decreased IL-6 and TNFα in overweight/obese women with PCOS[144]. The effects of different types of exercise on inflammatory markers in women with PCOS were elucidated in a recent systematic review and meta-analysis conducted by Hafizi Moori *et al.*, revealing that both aerobic and resistance exercises can be

effective in decreasing inflammatory markers and increasing anti-inflammatory markers, which is crucial to protect women with PCOS against T2DM and cardiovascular risk[145].

PHYSICAL EXERCISE RECOMMENDATIONS

According to Patten *et al.*, a minimum of 120 min per week of aerobic vigorous-intensity continuous exercise over 10-12 weeks is necessary for health improvements[89]. Due to the positive effects of resistance training, it could be considered for women with PCOS. Furthermore, they recommended that women should sustain this level of exercise for continued health maintenance.

The results of a systematic review and meta-analysis conducted by Ruiz-González *et al.* reinforce the importance of reaching a minimum of 150 min of weekly exercise[92]. Health benefits were obtained from 4 weeks to 12 months of interventions based on resistance exercise and its combination with continuous and HIIT aerobic exercise.

The *2023 Evidence-based Guideline for the Assessment and Management of PCOS*[1] recommended a minimum of 150 to 300 min of moderate-intensity exercise or 75 to 150 min of vigorous-intensity aerobic exercise per week for the prevention of weight gain and maintenance of health, and a minimum of 250 min/week of moderate-intensity exercise or 150 min/week of vigorous intensities for promotion of modest weight loss and prevention of weight regain. In any case, muscle-strengthening activities (e.g., resistance/flexibility) are recommended on two non-consecutive days per week.

It is important to keep in mind that physical exercise and a healthy diet combination can amplify the positive effects on body composition and glucose metabolism. Regarding the first, exercise prescription should be done by physical education professionals who will the intervention characteristics to each woman. They can also supervise the exercise session to optimize results safely and promote better adherence.

CONCLUSION

Obesity is a central condition, although not in all cases, for the development of T2DM in women with PCOS. This relationship seems linear, but the interconnections between the diseases are quite complex, and frequently include the dysfunction of adipose tissue. Aerobic and resistance physical exercises, in combination with a balanced diet, are very powerful tools that promote adipose tissue health, consequently preventing and treating obesity and T2DM in women with PCOS.

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Authors' contributions

Wrote the sections abstract, genetics of PCOS and T2DM, and adipose tissue: a common player in T2DM and PCOS teams, contributed to the sections introduction and the relation of PCOS and T2DM, and designed graphical abstract and Figure 1: Santos MP

Designed the structure of the article, contributed to the writing of sections introduction, adipose tissue: a common player in T2DM and PCOS teams, and the relation of PCOS and T2DM, designed graphical abstract and Figure 1, and reviewed the article: Azevedo-Martins AK

Wrote the section the relation of PCOS and T2DM and contributed to the writing of introduction, and genetics of PCOS and T2DM: Aquino NSS, Rodrigues AO
Wrote the sections physical exercise in PCOS: looking at obesity and T2DM section, exercise-induced adaptations to adipose tissue as a key to avoid T2DM and physical exercise recommendation, designed Figure 2 and Table 1, and reviewed the article: Evangelista FS

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All authors declared that there are no conflicts of interest.

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