Aerobic physical training impact on adipokines in women with polycystic ovary syndrome – Effects of body fat percentage

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ABSTRACT

Objective: We investigated the effects of aerobic training on adipokine concentrations in women with polycystic ovary syndrome (PCOS). **Subjects and methods:** 120 women, including 60 with PCOS and 60 without PCOS, were divided into six groups (n = 20) based on body fat percentages of 22%-27%, 28%-32%, and 33%-37%. All groups were submitted the same evaluations before and after 16 weeks of aerobic training. These included anthropometric and hemodynamic analyses, cardiopulmonary tests, and laboratory tests. Two-way analysis of variance was performed to evaluate the differences between women with and without PCOS, effect of the body fat percentage, and effect of aerobic training. **Results:** Body fat and PCOS were associated with high values of blood glucose, insulin, and testosterone. Body fat also reduced adiponectin levels and increased leptin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). In contrast, the PCOS increased only TNF-α and IL-6 levels. In the PCOS group, aerobic training reduced insulin, triglycerides, leptin, and IL-6 levels. It also promoted an increase in adiponectin and high-density lipoprotein levels. However, aerobic training did not alter TNF-α concentrations. **Conclusion:** The body fat potentiates metabolic impairments that may be harmful to women with PCOS. Aerobic training appears to promote an important beneficial effect on the metabolic regulation of adipokines, except TNF-α. Arch Endocrinol Metab. 2022;66(6):837-47

Keywords
Polycystic ovary syndrome; adipokines; aerobic physical training; inflammatory markers; body fat

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INTRODUCTION

Polycystic ovary syndrome (PCOS) affects a large proportion of women of reproductive age (1,2). This high prevalence is worrying, as these women commonly have increased body fat percentages and insulin resistance. They also experience changes in the concentration of adipokines secreted by the adipose tissue. This leads to high risks of comorbidities, such as type 2 diabetes and cardiovascular diseases (CVDs) (3-5).

Adipokines are associated with several metabolic activities, such as glycemia regulation, insulin sensitivity, endothelial homeostasis, fat metabolism, immunity, and inflammatory responses (6-9). In women with PCOS, it is common to observe increased levels of tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6). This is in addition to reduced adiponectin levels compared to women without PCOS (4,5,10-12).

Aerobic exercise presents significant beneficial results in the regulation of insulin sensitivity, glucose metabolism, and lipid profiles for various conditions (13-16), including PCOS. Aerobic exercise is valuable and has been widely used for the treatment of these and other disorders (17,18). However, little is known about its effects on serum adipokine concentrations (19).

Thus, the aim of this study was to investigate the effect of aerobic physical training on hemodynamics and the serum concentrations of leptin, adiponectin, TNF-α, and IL-6 in women with PCOS. The women were stratified based on the body fat percentage, as this parameter represents an important variable that affects adipokine concentrations.

SUBJECTS AND METHODS

Participants

The current study was a clinical trial that initially included 185 volunteers (18-39 years of age), all the volunteers, with and without PCOS were screened at the Gynecology and Obstetrics Clinic of the Ribeirão Preto Medical School's Hospital (HCFMRP/USP). The volunteers without PCOS were routine outpatient care patients, and all underwent the same procedures and examinations as the volunteers with PCOS, example the regular menstrual cycle and confirmation of the normal androgen levels. Patients with PCOS were diagnosed based on the Rotterdam consensus (20). The volunteers were divided into six experimental groups (n = 20) based on body fat percentages (22%-27%; 28%-32%; 33%-37%) (21). The division of these groups aimed to differentiate the effects of PCOS from those resulting from the percentage of body fat. The inclusion criteria were comprised of a negative history of the following: a) smoking, b) cognitive disturbances, c) pregnancy, d) musculoskeletal disorders, e) CVDs and f) use of any medication, including contraceptives for the last 6 months. The study was approved by the Ethics Committee of the Ribeirão Preto Medical School's Hospital (CAAE: 0459.0.004.000-08). The scientific and legal aspects were disclosed to the volunteers. The participants signed a free and informed consent form agreeing to participate. The authors confirm that all ongoing and related trials for the study were registered in the Brazilian Clinical Trials Registry (RBR-4qsf57).

PCOS diagnosis

Transvaginal pelvic ultrasound was performed using a Voluson 730 Expert Machine (GE Medical Systems, ZIPF, Austria) to analyze the presence or absence of cysts. The ovarian volume and follicle number/size were evaluated. The ovarian volume of the prolate ellipsoid was calculated using the formula depth × width × length × 0.5 (22).

In addition, the exclusion criteria for PCOS diagnosis were based on the results of laboratory tests for total serum testosterone, androstenedione, sex hormone-binding globulin, free androgen, prolactin, 17-hydroxyprogesterone, and thyrotropin levels. Blood samples were collected during the follicular phase in women with regular ovulatory cycles and at any time for those with irregular cycles. All the above laboratory tests for diagnosis were collected at the HCFMRP/USP laboratory between 07:00 and 10:00 a.m. following a 12-hour fast.

Protocols

Data were collected in the morning during two laboratory visits, between 07:00 and 10:00 a.m., with a 48-hour interval. Data were collected during the follicular phase for all women with regular ovulatory cycles and at any time for those with irregular cycles. The first assessment included blood collection at the HCFMRP/USP laboratory.

The second visit was performed at the Laboratory of Exercise Physiology and Cardiovascular Physiotherapy of Ribeirão Preto Medical School. During this visit, the following exams were completed: anthropometric measurements and cardiopulmonary function tests. The duration of each visit was approximately 1 hour.

All volunteers were asked to avoid drinking alcoholic beverages and exercise for 48 hours before the assessments. They were also asked to maintain their usual diet for 48 hours before the assessments. All participants were advised to sleep for at least 7-8 hours the night before the visits.

Laboratory tests

All volunteers were asked to fast for 12 hours before the assessments. Blood samples (3.5 mL, BD Vaccutainer® EDTA – Becton, Dickin, and Company, Franklin Lakes, NJ, USA) were used to analyze fasting glycemia (hexoquinase-UV) and insulin (chemiluminescence immunoassay), triglyceride (desidrogenase), and total cholesterol and fraction (esterase-oxidase) levels. For adiponectin and leptin analysis, a radioimmunoassay method was used, while the analyses of IL-6 and TNF-α were performed using chemiluminescent immunoassay. Insulin resistance was assessed using the homeostasis model assessment-insulin resistance (HOMA-IR) index (23).

Anthropometric parameters

Body weight and height were obtained using an analog scale with an altimeter (Welmy, Santa Bárbara d'Oeste, São Paulo, Brazil). The body mass index (BMI) was calculated using the formula W/H^2, where W is the weight in kilograms and H is the height of the subject in meters. Body composition was evaluated using the bioelectrical impedance method (Quantum BIA 101; Q-RJL Systems, Clinton Township, Michigan, USA).

Hemodynamic parameters

Heart rate (HR) data were obtained using an electrocardiographic digital recorder (ML866 PowerLab, ADInstruments, Bella Vista, Australia). The blood pressure (BP) was monitored using the auscultatory method using a stethoscope and sphygmomanometer.

Cardiopulmonary test

An incremental treadmill exercise test (Super ATL Millenium®, Inbramed/Inbrasport, Porto Alegre, RS, Brazil) was performed. A submaximal test was established with the sum of the baseline HR and 85% of the reserve HR (maximum HR – basal HR), following the previously described modified Bruce protocol. Electrical activity was monitored using an electrocardiogram with one lead (CM5). Oxygen and dioxide carbon uptake (VO_2 and VCO_2, respectively) were obtained using a metabolic analyser (Ultima™ CardiO2, Medical Graphics Corp., St. Paul, Minneapolis, USA).

Aerobic physical training

Aerobic training sessions were conducted at the Laboratory of Exercise Physiology and Cardiovascular Physiotherapy of the Ribeirão Preto Medical School. The sessions were performed in groups. They were supervised, monitored, and performed three times per week for 16 weeks on a motorized treadmill. The training intensity was calculated as the sum of HR at rest and 70 %-80% of reserve HR, obtained by means of the following equation: HR recorded at the peak of cardiopulmonary testing – HR at rest. The duration of the training sessions was 1 hour. They were divided into three phases as follows: 5-minutes of warm-up using an intensity lower than the target HR training range (50%-65% of reserve HR), 50-minutes of training using the training HR (70%-80% of reserve HR), and 5-minutes of cool-down using an intensity lower than the training HR (40%-50% of reserve HR). There was an adaptation period during the first 2 weeks of the study during which participants went through 20-30-minute sessions for familiarization and adaptation to the training protocol. The intensity used was equivalent to the sum of HR at rest and 50%-60% of the reserve HR, followed by increases in intensity and duration in the subsequent weeks until the volunteers reached the training HR as described. The participants HRs were monitored throughout the sessions using a pulse frequency meter (Polar RS810).

Regarding adherence, monitoring, and motivation strategies, an individualized training form was completed every day. The supervisor noted the training date and measured the HR, BP, and subjective perception of effort of the volunteers before, during, and after the training session using the Borg scale. Only volunteers who had 90% adherence were included in the final analysis. During all training sessions, the supervisor spoke with the volunteers regarding the importance of regular physical exercise and provided information concerning PCOS. In addition, questions that arose during the training were answered.

Statistics analysis

All statistical tests were performed with Sigma-Plot®, version 11.0 software (Systat Software Inc., San Jose, CA, USA). The Shapiro-Wilk normality test was used, and the data were expressed as the mean ± standard deviation. Two-way analysis of variance, followed by the Student-Newman-Keuls multiple comparison test, was performed to evaluate the differences between women with and without PCOS (PCOS factor), effect of the body fat percentage (body fat factor), and effect of aerobic physical training (training factor). Differences were considered significant at $P < 0.05$.

RESULTS

In the total of 185 volunteers included in the study only 120 volunteers concluded the training protocol (adherence of > 90%), including 60 with PCOS and 60 without PCOS (Figure 1). Table 1 shows the characteristics and hemodynamic parameters, and Table 2 shows the metabolic parameters and adipokine values of all women with and without PCOS (control groups) distributed according to the body fat percentage. These data were obtained prior to aerobic physical training. Participants belonging to all groups were of similar ages and heights. However, there were differences in weights and BMIs due to body fat percentage distribution. The groups with high body fat percentage showed minor values of VO_{2peak} and major values of high low-density lipoprotein (LDL), triglyceride, and glucose levels. The PCOS groups, independently of body fat percentage, showed higher values in androstenedione levels than control groups, while both body fat and PCOS were associated with higher insulin and testosterone levels and HOMA-IR values. The increase in body fat percentage was associated with low adiponectin levels and high leptin, TNF-α, and IL-6 levels. In turn, PCOS was associated with high TNF-α and IL-6 levels.

Table 3 shows the characteristics and hemodynamic parameters, and Table 4 presents the metabolic parameters and adipokines values of the PCOS groups before and after 16 weeks of aerobic physical training. After the 16 weeks of aerobic physical training there were reduction in body fat percentage, HR and systolic BP (SBP). It also increased VO_{2peak}. However, the inverse relationship between the body fat percentage and VO_{2peak} remained. In metabolic parameters, after the physical training the high-density lipoprotein (HDL) showed higher values and the triglyceride, insulin and HOMA-IR showed lower values than before training. In turn, the groups with high body fat percentage presented increased total cholesterol, LDL, triglyceride, glucose, insulin, testosterone, and androstenedione levels and HOMA-IR values. For adipokines, after the physical training there were increased adiponectin and reduced leptin and IL-6 levels. Even though, the groups with high body fat percentage still presented low levels of adiponectin and increased leptin, TNF-α, and IL-6 levels.

Table 5 shows the characteristics and hemodynamic parameters, and Table 6 presents the metabolic parameters and adipokine values of the control groups before and after 16 weeks of aerobic physical training. After the physical training, the groups showed lower body fat percentage, HR, and BP values compared with before training. It also increased VO_{2peak}. Nevertheless, the inverse relationship between the body fat percentage and VO_{2peak} remained. With regard to metabolic parameters, after the physical training there was increase in HDL levels and reduction in triglyceride levels. In turn, the groups with high body fat percentage showed increased values of total cholesterol, LDL, triglyceride, and HOMA-IR. Table 6 also shows that after physical training there were increase in adiponectin and decrease in leptin and IL-6 levels. However, the groups with high body fat percentage showed reduced adiponectin and increased leptin, TNF-α, and IL-6 levels.

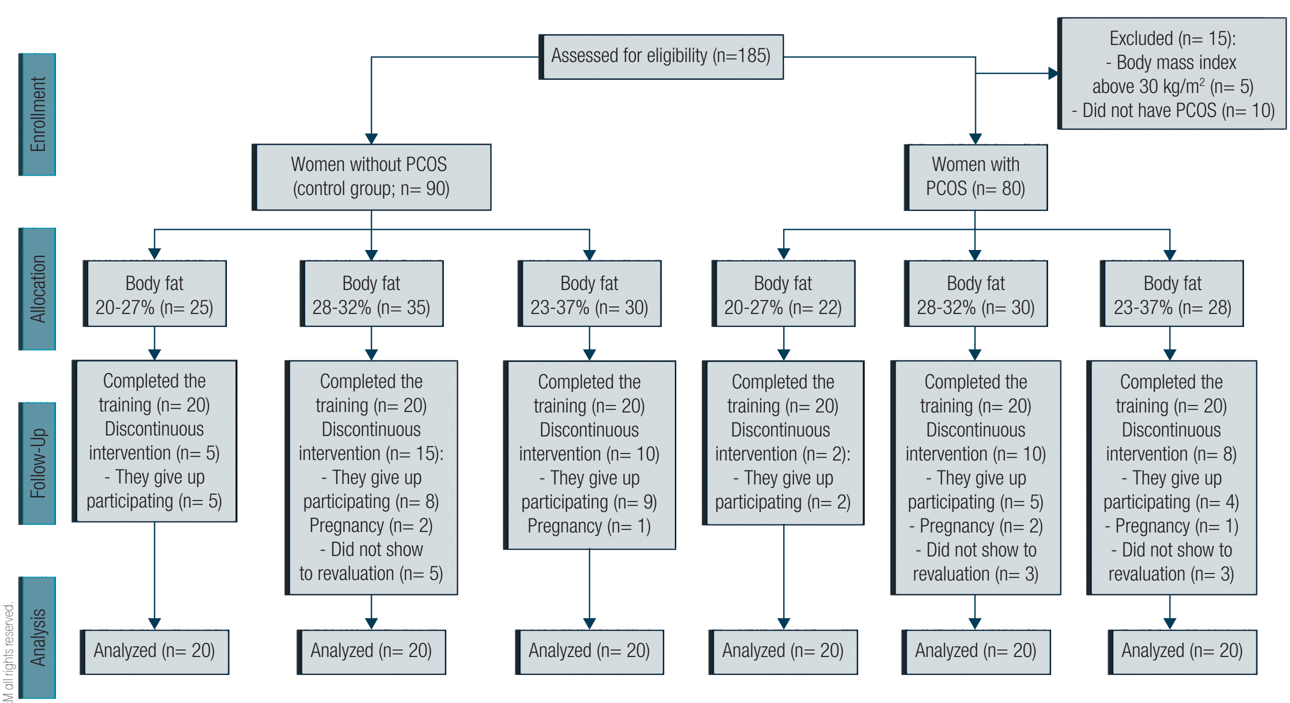

Figure 1. Flow diagram of the study.

Table 1. Characteristics and hemodynamic parameters obtained before aerobic physical training in all groups

	22%-27%		28%-32%		33%-37%		PCOS Factor	Body Fat Factor	Interaction
	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	P	P	P
Characteristics									
Age, years	32 ± 7	34 ± 5	33 ± 7	35 ± 7	31 ± 4	33 ± 7	0.084	0.686	0.994
Height, cm	165 ± 7	162 ± 7	166 ± 7	165 ± 5	163 ± 5	161 ± 6	0.109	0.064	0.875
Weight, kg	63 ± 6	59 ± 4	72 ± 7	69 ± 6	79 ± 11	76 ± 9	0.054	<0.001	0.985
BMI, kg/m²	23.1 ± 2.6	22.6 ± 2.9	26.3 ± 3	25.5 ± 3	29.8 ± 4.3	29.9 ± 4.5	0.410	<0.001	0.955
Body fat percentage	23.6 ± 1.7	24.4 ± 2.1	29.8 ± 3.2	30.3 ± 1.5	35.7 ± 3.2	35.2 ± 1.5	0.482	<0.001	0.449
Hemodynamic Parameters									
HR, bpm	74 ± 13	76 ± 10	73 ± 8	78 ± 5	76 ± 12	77 ± 9	0.137	0.855	0.747
SBP, mmHg	111 ± 11	115 ± 13	113 ± 11	112 ± 9	117 ± 10	118 ± 8	0.627	0.077	0.454
DBP, mmHg	71 ± 7	73 ± 13	76 ± 9	71 ± 9	75 ± 9	78 ± 9	0.962	0.119	0.139
MBP, mmHg	87 ± 9	90 ± 13	91 ± 10	87 ± 9	92 ± 9	94 ± 8	0.852	0.094	0.273
VO_{2peak}, mL/kg/min	31 ± 3	30 ± 3	28 ± 5	29 ± 3	26 ± 5	25 ± 6	0.751	<0.001	0.357

Data are presented as mean ± standard deviation. PCOS: polycystic ovary syndrome; BMI, body mass index; HR: heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; VO_{2peak}: oxygen consumption at peak of exercise; mL: milliliter; kg: kilogram; min: minute.

Table 2. Metabolic and adipokines parameters obtained before aerobic physical training in all groups

	22%-27%		28%-32%		33%-37%		PCOS Factor	Body Fat Factor	Interaction
	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	P	P	P
Metabolic Values									
Total Cholesterol, mg/dL	196 ± 17	200 ± 24	212 ± 45	205 ± 32	209 ± 16	219 ± 32	0.708	0.054	0.466
HDL, mg/dL	45 ± 8	44 ± 8	42 ± 11	42 ± 5	43 ± 7	41 ± 6	0.529	0.230	0.846
LDL, mg/dL	107 ± 11	103 ± 16	107 ± 16	108 ± 17	114 ± 13	118 ± 25	0.965	0.009	0.484
Triglycerides, mg/dL	115 ± 21	109 ± 19	121 ± 34	140 ± 33	149 ± 39	165 ± 44	0.124	<0.001	0.181
Glucose, mg/dL	86 ± 8	85 ± 12	88 ± 11	93 ± 12	90 ± 10	95 ± 9	0.138	0.013	0.353
Insulin, µU/mL	9.14 ± 1.5	10.2 ± 3	9.6 ± 3	12.9 ± 3	9.7 ± 2	14.3 ± 2.5	<0.001	<0.001	0.007
HOMA-IR	1.94 ± 0.3	2.16 ± 0.7	2.09 ± 0.6	2.98 ± 0.7	2.14 ± 0.4	3.35 ± 0.7	<0.001	<0.001	0.003
Testosterone, nmol/L	1.55 ± 0.7	2.51 ± 1.1	1.59 ± 0.4	3.81 ± 1.7	1.62 ± 0.9	4.08 ± 1.6	<0.001	0.005	0.011
Androstenedione, nmol/L	4.22 ± 2.1	7.78 ± 2.9	4.26 ± 1.5	8.92 ± 3.1	4.45 ± 2.3	9.29 ± 3.3	<0.001	0.320	0.501
Adipokines Values									
Leptin, ng/mL	16.5 ± 6.9	18.1 ± 7.9	22.6 ± 7.2	24.7 ± 9.1	33.5 ± 8.3	33.1 ± 9	0.460	<0.001	0.760
Adiponectin, ng/mL	12.3 ± 5.4	11.8 ± 5.3	8.7 ± 5.9	8.7 ± 5.7	7.1 ± 4.8	7.3 ± 4.4	0.885	<0.001	0.955
TNF-α, pg/mL	3.8 ± 2.9	4.2 ± 3.1	4.4 ± 2.4	5.4 ± 1.9	5.7 ± 1.9	6.9 ± 2.6	0.048	<0.001	0.783
IL-6, pg/mL	1.8 ± 1.8	2.0 ± 1.8	2.1 ± 1.5	3.2 ± 2.5	4.2 ± 2.7	6.7 ± 3.4	0.004	<0.001	0.109

Data are presented as mean ± standard deviation. PCOS: polycystic ovary syndrome; mg/dL: milligram per deciliter; HDL: high-density lipoprotein; LDL: low-density lipoprotein; µU/mL,: micro units per milliliter; HOMA-IR: homeostatic model assessment for insulin resistance; nmol/L: nanomole per liter; ng/mL: nanograms per milliliter; TNF-α: tumor necrosis factor alpha; pg/mL: picogram per milliliter; IL-6: interleukin-6.

Table 3. Characteristics and hemodynamics parameters obtained before and after aerobic physical training in PCOS groups

	22%-27%		28%-32%		33%-37%		Body Fat Factor	Training Factor	Interaction
	Before	After	Before	After	Before	After	P	P	P
Characteristics									
Age, years	34 ± 5	-	35 ± 7	-	33 ± 7	-	-	-	-
Height, cm	162 ± 7	-	165 ± 5	-	161 ± 6	-	-	-	-
Weight, kg	59 ± 4	58 ± 4	69 ± 6	67 ± 6	76 ± 9	74 ± 8	<0.001	0.150	0.946
BMI, kg/m²	22.6 ± 2.9	22.1 ± 2.9	25.5 ± 3	24.7 ± 2,9	29.9 ± 4.5	28.8 ± 4.4	<0.001	0.314	0.977
Body fat percentage	24.4 ± 2.1	23.8 ± 2.3	30.3 ± 1.5	28.4 ± 1.5	35.2 ± 1.5	34.4 ± 1.9	<0.001	0.001	0.271
Hemodynamic Parameters									
HR, bpm	76 ± 10	68 ± 9	78 ± 5	69 ± 8	77 ± 9	68 ± 8	0.811	<0.001	0.994
SBP, mmHg	115 ± 13	109 ± 12	112 ± 9	107 ± 9	118 ± 8	112 ± 8	0.056	0.032	0.771
DBP, mmHg	73 ± 13	70 ± 12	71 ± 9	70 ± 9	78 ± 9	74 ± 9	0.063	0.187	0.597
MBP, mmHg	90 ± 13	85 ± 12	87 ± 9	85 ± 8	94 ± 8	89 ± 8	0.051	0.086	0.681
VO_{2peak}, mL/kg/min	30 ± 3	34 ± 3	29 ± 3	33 ± 3	25 ± 6	29 ± 5	<0.001	<0.001	0.970

Data are presented as the mean ± standard deviation. PCOS: polycystic ovary syndrome; BMI: body mass index; HR: heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; VO_{2peak}: oxygen consumption at peak of exercise; mL: milliliter; kg: kilogram; min: minute.

Table 4. Metabolic and adipokines parameters obtained before and after 16 weeks of aerobic physical training in PCOS groups

	22%-27%		28%-32%		33%-37%		Body Fat Factor	Training Factor	Interaction
	Before	After	Before	After	Before	After	P	P	P
Metabolic Values									
Total Cholesterol, mg/dL	200 ± 24	191 ± 23	205 ± 32	198 ± 28	219 ± 32	210 ± 27	0.011	0.098	0.987
HDL, mg/dL	44 ± 8	47 ± 7	42 ± 5	46 ± 5	41 ± 6	45 ± 6	0.172	0.002	0.895
LDL, mg/dL	103 ± 16	101 ± 12	108 ± 17	102 ± 14	118 ± 25	109 ± 19	0.009	0.093	0.624
Triglycerides, mg/dL	109 ± 19	111 ± 15	140 ± 33	118 ± 26	165 ± 44	132 ± 27	<0.001	0.001	0.027
Glucose, mg/dL	85 ± 12	87 ± 8	93 ± 12	86 ± 6	95 ± 9	92 ± 7	0.004	0.121	0.116
Insulin, µU/mL	10.2 ± 3	9.8 ± 2.1	12.9 ± 3	10 ± 1.8	14.3 ± 2.5	11 ± 2	<0.001	<0.001	0.018
HOMA-IR	2.16 ± 0.7	2.11 ± 0.5	2.98 ± 0.7	2.16 ± 0.4	3.35 ± 0.7	2.5 ± 0.6	<0.001	<0.001	0.010
Testosterone, nmol/L	2.51 ± 1.1	2.56 ± 0.8	3.81 ± 1.7	4.15 ± 1.3	4.08 ± 1.6	4.77 ± 1.5	<0.001	0.164	0.598
Androstenedione, nmol/L	7.78 ± 2.9	6.92 ± 2.3	8.92 ± 3.1	8.18 ± 2.7	9.29 ± 3.3	9.48 ± 2	0.006	0.356	0.653
Adipokines Values									
Leptin, ng/mL	18.1 ± 7.9	14.5 ± 6	24.7 ± 9.1	17.9 ± 6.5	33.1 ± 9	24.5 ± 6.5	<0.001	<0.001	0.354
Adiponectin, ng/mL	11.8 ± 5.3	13.3 ± 5.3	8.7 ± 5.7	11.9 ± 5	7.3 ± 4.4	10.4 ± 3.8	0.005	0.005	0.683
TNF-α, pg/mL	4.2 ± 3.1	4.0 ± 2.2	5.4 ± 1.9	5.8 ± 1.5	6.9 ± 2.6	6.4 ± 2.1	<0.001	0.862	0.668
IL-6, pg/mL	2.0 ± 1.8	2.3 ± 1.4	3.2 ± 2.5	2.8 ± 1.9	6.7 ± 3.4	4.3 ± 1.6	<0.001	0.046	0.019

Data are presented as mean ± standard deviation. PCOS: polycystic ovary syndrome; mg/dL: milligram per deciliter; HDL: high-density lipoprotein; LDL: low-density lipoprotein; µU/mL: micro units per milliliter; HOMA-IR: homeostatic model assessment for insulin resistance; nmol/L: nanomole per liter; ng/mL: nanograms per milliliter; TNF-α: tumor necrosis factor alpha; pg/mL: picogram per milliliter; IL-6: interleukin-6.

Table 5. Characteristics and hemodynamic parameters obtained before and after aerobic physical training in control groups

	22%-27%		28%-32%		33%-37%		Body Fat Factor	Training Factor	Interaction
	Before	**After**	**Before**	**After**	**Before**	**After**	**P**	**P**	**P**
Characteristics									
Age, years	32 ± 7	-	33 ± 7	-	31 ± 4	-	-	-	-
Height, cm	165 ± 7	-	166 ± 7	-	163 ± 5	-	-	-	-
Weight, kg	63 ± 6	61 ± 5	72 ± 7	68 ± 6	79 ± 11	77 ± 10	<0.001	0.064	0.727
BMI, kg/m²	23.1 ± 2.6	22.3 ± 2.2	26.3 ± 3	24.7 ± 2.4	29.8 ± 4.3	29.2 ± 3.6	<0.001	0.088	0.767
Body fat percentage	23.6 ± 1.7	22.9 ± 1.8	29.8 ± 3.2	26.4 ± 2.6	35.7 ± 3.2	34.5 ± 2.3	<0.001	<0.001	0.050
Hemodynamic Parameters									
HR, bpm	74 ± 13	67 ± 9	73 ± 8	64 ± 6	76 ± 12	69 ± 1	0.268	<0.001	0.893
SBP, mmHg	111 ± 11	106 ± 22	113 ± 11	107 ± 8	117 ± 10	112 ± 7	0.020	0.004	0.925
DBP, mmHg	71 ± 7	70 ± 9	76 ± 9	70 ± 8	75 ± 9	74 ± 7	0.115	0.030	0.285
MBP, mmHg	87 ± 9	84 ± 10	91 ± 10	85 ± 8	92 ± 9	89 ± 7	0.052	0.010	0.557
VO_{2peak}, mL/kg/min	31 ± 3	34 ± 3	28 ± 5	31.5 ± 4	26 ± 5	30.5 ± 5	<0.001	<0.001	0.699

Data are presented as the mean ± standard deviation. BMI: body mass index; HR: heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; VO_{2peak}: oxygen consumption at peak of exercise; mL: milliliter; kg: kilogram; min: minute.

Table 6. Metabolic and adipokines parameters obtained before and after aerobic physical training in control groups

	22%-27%		28%-32%		33%-37%		Body Fat Factor	Training Factor	Interaction
	Before	**After**	**Before**	**After**	**Before**	**After**	**P**	**P**	**P**
Metabolic Values									
Total Cholesterol, mg/dL	196 ± 17	190 ± 12	212 ± 45	201 ± 30	209 ± 16	206 ± 28	0.041	0.175	0.822
HDL, mg/dL	45 ± 8	49 ± 7	42 ± 11	47 ± 9	43 ± 7	46 ± 7	0.314	0.014	0.862
LDL, mg/dL	107 ± 11	110 ± 10	107 ± 16	111 ± 22	114 ± 13	111 ± 11	0.038	0.609	0.502
Triglycerides, mg/dL	115 ± 21	110 ± 11	121 ± 34	113 ± 21	149 ± 39	123 ± 25	<0.001	0.009	0.175
Glucose, mg/dL	86 ± 8	85 ± 5	88 ± 11	86 ± 5	90 ± 10	89 ± 7	0.102	0.373	0.959
Insulin, µU/mL	9.14 ± 1.5	8.54 ± 1.6	9.6 ± 3	8.9 ± 2.1	9.7 ± 2	9.4 ± 2	0.275	0.159	0.904
HOMA-IR	1.94 ± 0.3	1.79 ± 0.3	2.09 ± 0.6	1.9 ± 0.4	2.14 ± 0.4	2.1 ± 0.4	0.049	0.081	0.831
Testosterone, nmol/L	1.55 ± 0.7	1.66 ± 0.6	1.59 ± 0.4	1.73 ± 0.4	1.62 ± 0.9	1.72 ± 0.7	0.887	0.322	0.994
Androstenedione, nmol/L	4.22 ± 2.1	4.15 ± 1.7	4.26 ± 1.5	4.37 ± 1.2	4.45 ± 2.3	4.04 ± 1.2	0.941	0.688	0.790
Adipokines Values									
Leptin, ng/mL	16.5 ± 6.9	13.5 ± 3.4	22.6 ± 7.2	13.9 ± 3.9	33.5 ± 8.3	18.9 ± 6.7	<0.001	<0.001	<0.001
Adiponectin, ng/mL	12.3 ± 5.4	14.3 ± 4.5	8.7 ± 5.9	11.1 ± 5.9	7.1 ± 4.8	10.4 ± 3.8	<0.001	0.007	0.840
TNF-α, pg/mL	3.8 ± 2.9	3.8 ± 1.9	4.4 ± 2.4	4.1 ± 1.7	5.7 ± 1.9	4.9 ± 1.5	0.006	0.424	0.712
IL-6, pg/mL	1.8 ± 1.8	1.8 ± 1.3	2.1 ± 1.5	1.8 ± 0.9	4.2 ± 2.7	2.6 ± 1.4	<0.001	0.046	0.091

Data are presented as mean ± standard deviation. mg/dL: milligram per deciliter; HDL: high-density lipoprotein; LDL: low-density lipoprotein; µU/mL: micro units per milliliter; HOMA-IR: homeostatic model assessment for insulin resistance; nmol/L: nanomole per liter; ng/mL: nanograms per milliliter; TNF-α: tumor necrosis factor alpha; pg/mL: picogram per milliliter; IL-6: interleukin-6.

Table 7 shows the characteristics and hemodynamic parameters, and Table 8 shows the metabolic parameters and adipokine values of all women with and without PCOS (control groups) distributed according to the body fat percentage. These data were obtained after aerobic physical training. The groups with high body fat percentage showed the highest values of the weight and BMI. It was also showed the lowest VO_{2peak} values and major values of SBP and MBP. Regarding to metabolic parameters, the groups with high body fat percentage showed highest levels of total cholesterol, triglycerides, and glucose. Additionally, they showed minor adiponectin values. Both body fat and PCOS showed high insulin, testosterone, androstenedione, leptin, TNF-α, and IL-6 levels and HOMA-IR values (Table 8).

DISCUSSION

Our results indicate that an increase in the body fat percentage is associated with important metabolic and adipokine changes in women with and without PCOS. However, women with PCOS had higher metabolic parameters and adipokine values than women without PCOS. The results also suggest that aerobic physical training is essential, primarily in women with PCOS. It promotes important metabolic adjustments, such as a reduction in triglyceride, blood glucose, insulin, leptin, and IL-6 levels and HOMA-IR values, in addition to increasing adiponectin concentrations. These alterations were particularly salient in the group with the highest percentage of body fat.

In the current study, all PCOS groups presented with laboratory hyperandrogenism. However, only the 28%-32% and 33%-37% groups had increased insulin resistance. The literature suggests that in PCOS, hyperandrogenism and insulin resistance are influenced by positive feedback (4,11,12,24). It seems that the association of an increased body fat percentage promotes an additive effect in this relationship. In turn, aerobic physical training seems to attenuate this process. We observed significant reductions in insulin concentrations and HOMA-IR values in the 28%-32% and 33%-37% groups, in addition to other positive metabolic effects. This reaffirms the relevance of this non-pharmacological tool in the treatment of women with PCOS (2,3,17,18).

Our study investigated important adipokines that are frequently altered due to an increase in the body fat percentage. Leptin is a protein that suppresses food intake, increases energy expenditure, and regulates neuroendocrine functions, such as glucose and fat metabolism (6). However, in overweight and obese individuals, its concentration is increased. This suggests resistance. This condition, together with other inflammatory markers, such as IL-6, was also evaluated in the current study and has been associated with the pathogenesis of atherosclerosis (25,26). Even an isolated increase in this adipokine, regardless of other factors, is considered a risk factor for coronary heart disease (27). Leptin concentrations appeared to increase with increasing the body fat percentage. Accordingly, the increase in leptin concentration associated with PCOS is very controversial, especially in women with a BMI of less than 25 kg/m² (4,11,28). In this case, the consensus is that there is a direct positive relationship between leptin concentrations and an increase in the BMI in these women (4,11,12).

On the contrary, after 16-weeks of aerobic physical training, there were significant reductions in leptin concentrations in all groups with higher body fat percentages. The causes of this finding might be related to the potential improvement in leptin sensitivity (29). There are other reasons that may explain this observation. One of these reasons may correspond to a reduction in weight associated with a reduction in the body fat percentage (29). Other reasons may involve the reduction of insulin concentrations and HOMA-IR values (28), although further investigation is warranted.

Adiponectin is an adipokine associated with glycemic regulation, insulin sensitivity, and reduced androgen production by the ovaries (4,7,11,30). It also has an anti-atherogenic role (25,31). However, its relationship with PCOS is controversial (7,32,33). In our study, unlike leptin, adiponectin concentrations were negatively associated with the body fat percentage. However, it is uncertain whether this relationship is totally independent of PCOS (10). This is primarily because the same result was observed in women without PCOS.

As for the effects of aerobic physical training on adiponectin concentrations, the literature remains incipient (33-35). However, in the current study, aerobic physical training increased adiponectin concentrations, specifically in the groups with a high body fat percentage (28%-32% and 33%-37%). In this study, this increase seemed to be associated with a reduction in the body fat percentage. This result corroborates a previous study that observed a reduction in body weight associated

Table 7. Characteristics and hemodynamic parameters of PCOS and control groups, divided according to the body fat percentage, obtained after aerobic physical training

	22%-27%		28%-32%		33%-37%		PCOS Factor	Body Fat Factor	Interaction
	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	P	P	P
Characteristics									
Age, years	32 ± 7	34 ± 5	33 ± 7	35 ± 7	31 ± 4	33 ± 7	0.084	0.686	0.994
Height, cm	165 ± 7	162 ± 7	166 ± 7	165 ± 5	163 ± 5	161 ± 6	0.109	0.064	0.875
Weight, kg	61 ± 5	58 ± 4	68 ± 6	67 ± 6	77 ± 9	74 ± 8	0.064	<0.001	0.752
BMI, kg/m²	22.3 ± 2.2	22.1 ± 2.9	24.7 ± 2	24.7 ± 3	29.2 ± 3.6	28.8 ± 4.4	0.733	<0.001	0.967
Body fat percentage	22.9 ± 1.8	23.7 ± 2.4	26.4 ± 2.6	28.4 ± 1.5	34.5 ± 2.3	34.3 ± 1.9	0.022	<0.001	0.081
Hemodynamic Parameters									
HR, bpm	67 ± 8	68 ± 9	64 ± 5	69 ± 8	69 ± 10	68 ± 8	0.351	0.587	0.346
SBP, mmHg	106 ± 11	109 ± 12	107 ± 8	109 ± 9	112 ± 7	114 ± 7	0.176	0.022	0.959
DBP, mmHg	70 ± 9	70 ± 12	70 ± 8	71 ± 9	74 ± 7	74 ± 9	0.627	0.097	0.867
MBP, mmHg	84 ± 10	85 ± 12	85 ± 8	86 ± 9	89 ± 6	90 ± 7	0.380	0.043	0.967
VO_{2peak}, mL/kg/min	34 ± 3	34 ± 3	32 ± 4	33 ± 3	30 ± 5	29 ± 5	0.767	<0.001	0.261

Data are presented as mean ± standard deviation. PCOS: polycystic ovary syndrome; BMI: body mass index; HR: heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; $VO_{2peak:}$ oxygen consumption at peak of exercise; mL: milliliter; kg: kilogram; min: minute.

Table 8. Metabolic parameters and adipokines values of PCOS and control groups, divided according to the body fat percentage, obtained after aerobic physical training

	22%-27%		28%-32%		33%-37%		PCOS Factor	Body Fat Factor	Interaction
	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	Control (n = 20)	PCOS (n = 20)	P	P	P
Metabolic Values									
Total Cholesterol, mg/dL	191 ± 12	191 ± 23	201 ± 30	198 ± 28	206 ± 28	210 ± 27	0.940	0.014	0.831
HDL, mg/dL	49 ± 7	47 ± 7	47 ± 9	46 ± 5	46 ± 7	45 ± 6	0.431	0.268	0.943
LDL, mg/dL	110 ± 10	101 ± 12	104 ± 10	102 ± 14	111 ± 11	109 ± 19	0.084	0.073	0.381
Triglycerides, mg/dL	110 ± 11	111 ± 15	113 ± 21	118 ± 26	123 ± 25	132 ± 27	0.220	0.002	0.672
Glucose, mg/dL	85 ± 5	87 ± 8	86 ± 5	86 ± 6	89 ± 7	92 ± 7	0.204	0.006	0.639
Insulin, µU/mL	8.5 ± 1.6	9.8 ± 2.1	9.0 ± 2.1	10 ± 1.8	9.4 ± 1.8	11 ± 2	<0.001	0.037	0.825
HOMA-IR	1.79 ± 0.3	2.11 ± 0.5	1.91 ± 0.4	2.16 ± 0.4	2.07 ± 0.4	2.5 ± 0.6	<0.001	0.003	0.632
Testosterone, nmol/L	1.66 ± 0.6	2.56 ± 0.8	1.73 ± 0.4	4.15 ± 1.3	1.72 ± 0.7	4.77 ± 1.5	<0.001	<0.001	<0.001
Androstenedione, nmol/L	4.15 ± 1.7	6.92 ± 2.3	4.37 ± 1.2	8.18 ± 2.7	4.04 ± 1.2	9.48 ± 2	<0.001	0.020	0.010
Adipokines Values									
Leptin, ng/mL	13.5 ± 3.4	14.5 ± 6	13.9 ± 3.9	17.9 ± 6.5	18.9 ± 6.7	24.5 ± 6.5	<0.001	<0.001	0.178
Adiponectin, ng/mL	12.3 ± 5.4	13.3 ± 5.3	11.1 ± 5.9	11.9 ± 5	10.4 ± 3.8	10.4 ± 3.8	0.918	0.007	0.695
TNF-α, pg/mL	3.8 ± 2.9	4.0 ± 2.2	4.1 ± 1.7	5.8 ± 1.5	4.9 ± 1.5	6.4 ± 2.1	0.001	<0.001	0.119
IL-6, pg/mL	1.8 ± 1.8	2.3 ± 1.4	1.8 ± 0.9	2.8 ± 1.9	2.6 ± 1.4	4.3 ± 1.6	<0.001	<0.001	0.256

Data are presented as mean ± standard deviation. PCOS: polycystic ovary syndrome; mg/dL: milligram per deciliter; HDL: high-density lipoprotein; LDL: low-density lipoprotein; µU/mL: micro units per milliliter; HOMA-IR: homeostatic model assessment for insulin resistance; nmol/L: nanomole per liter; ng/mL: nanograms per milliliter; TNF-α: tumor necrosis factor alpha; pg/mL: picogram per milliliter; IL-6: interleukin-6.

with an increase in adiponectin in obese individuals, with and without PCOS (36). Another cause could be the reduction in leptin and insulin concentrations (13,33,37). In this case, there appears to be an inverse relationship between leptin and adiponectin levels (38). In addition, physical exercise has been shown to play a favorable role in insulin sensitivity (14,15,18). This increase in insulin sensitivity seems to stimulate the increased production of adiponectin (39).

Regarding concentrations of TNF-α and IL-6, both cytokines are known to negatively influence insulin sensitivity (40,41). They are significant markers of low-grade chronic inflammation in several conditions, such as type 2 diabetes mellitus, obesity, and CVD (41,42). Our results showed that TNF-α and IL-6 levels were higher in women with PCOS than in those without PCOS. These findings corroborate the literature (43,44). Our results suggest that the increased body fat percentage in these women increases the levels of these inflammatory cytokines. However, aerobic physical training did not change TNF-α values, even though it positively interfered with insulin, adiponectin, and leptin levels and HOMA-IR values. These are important regulatory factors of TNF-α concentrations (43,45). In contrast, IL-6 levels were significantly reduced after 16 weeks of aerobic physical training, mainly in the groups with the highest body fat percentage. The cause of this reduction is uncertain. However, it suggests that the reduction of other factors, such as insulin, might have influenced the IL-6 concentration in these women (46). Nonetheless, further studies are required to identify the mechanisms involved in this response, as aerobic physical training did not affect insulin levels in groups without PCOS.

The study has some limitations, such as the absence of groups with higher percentages of body fat, which could further highlight the negative effects of excess body fat on the regulation of adipokines; the study of women who used contraceptives, evaluating their effects on the investigated parameters; and lack of evaluation of PCOS phenotypes and responses to physical training.

In conclusion, our results showed that a gradual increase in the body fat percentage potentiates metabolic impairment in women with PCOS. The results also confirmed a direct relationship between an increased body fat percentage and changes in adipokine levels. These findings highlight the role of aerobic physical training as an important therapeutic tool in the regulation of adipokines and other metabolic parameters in PCOS. This is especially true in women with a high body fat percentage. On the contrary, aerobic physical training did not seem to affect TNF-α levels. This was observed in all women with and without PCOS.

Data availability: the datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors contributions: HCDS conceived and designed the study, acquired, analyzed, interpreted the data, and revised it critically for important intellectual content. SVP acquired, analyzed, and interpreted the data, drafted the article, and revised the manuscript. TPF acquired, analyzed, and interpreted the data and drafted the manuscript. RAF conceived and designed the study and critically revised it for important intellectual content. ACG conceived and designed the study and critically revised it for important intellectual content. All authors approved the final version of the manuscript.

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