RESEARCH ARTICLE

Effect of Physical Activity on Markers of Insulin Resistance in Infertile Women with Polycystic Ovary Syndrome

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Abstract

Objective: Regular physical activity (PA) regulates important interactive pathways linking energy balance, neuroendocrine function, and hypothalamic pituitary ovarian axis. Consistent physical activities are known to improve insulin sensitivity which exerts its effects *via* adipokines. The purpose of the study is to determine insulin resistant (IR) status and the effect of brisk walking on the levels of adipocytokines in women with polycystic ovarian syndrome (PCOS).

Design: It is a prospective study.

Materials and methods: The study included 143 married women with PCOS (as per Rotterdam's criteria) and 110 married women as controls with at least one child through natural conception. Anthropometric measurements were documented. Adiponectin and resistin were analyzed. Homeostatic Model Assessment of IR (HOMA-IR) and HOMA-adiponectin were calculated to assess IR. A follow-up task of 150 minutes/week of PA of brisk walking of moderate intensity was advised for 12 weeks and the status was reassessed.

Results: Infertile women with PCOS, hypoadiponectinemia, and hyperesistinemia with elevated markers of IR (HOMA-IR and HOMA-adiponectin) were observed. The baseline data were compared with estimates after 12 weeks, it was found that adiponectin levels were increased with 4.75% weight loss, and decreased levels of resistin, HOMA-IR, and HOMA-adiponectin were observed. Participants who met 150 minutes/week of brisk walking revealed an increase in adiponectin levels and a strong positive correlation ($r = 0.76$) was observed with regression analysis of metabolic equivalents of tasks (METs) PA with adiponectin levels. Diagnostic sensitivity and specificity of adiponectin at a cutoff value of 7.3 µg/mL with 150 minutes/week of PA were found to be 93.8 and 82.1%, respectively. It was observed a 16.6% reduction of HOMA-IR and 29% of HOMA-adiponectin in the women who completed 12 weeks of PA had statistically significant *p*-values. An ovarian follicular study revealed positive ovulation in 80% of the participants with >150 minutes/week of brisk walking.

Conclusion: Brisk walking of 150 minutes/week resulted in increased adiponectin levels. Beneficial adiponectin facilitates the ovulatory menstrual cycle and thereby the chance of ovulation is increased in PCOS women.

Keywords: Adiponectin, Homeostatic Model Assessment-adiponectin, Metabolic equivalents of task, Physical activity 150 minutes/week, Resistin.

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Introduction

Polycystic ovary syndrome (PCOS) affects 5–10% of reproductive-aged women and is the most common cause of ovulatory dysfunction.[1] PCOS is characterized by insulin resistance (IR) associated with metabolic features independent of body mass index (BMI). IR is the key compulsive cause resulting in menstrual irregularity, ovulatory dysfunction, hyperandrogenism, and polycystic ovaries.[2] Lifestyle interventions are found to improve both metabolic and reproductive processes. Adipose tissue is considered an active endocrine system that secretes a variety of bioactive molecules known as adipocytokines. In fact, adipocytokines are found to have an impact on the normal reproductive process. Evidence suggests that physical activity (PA) regulates the endocrine role of visceral adipose tissue and influences to improvement of insulin sensitivity even in the absence of weight loss.[3]

Adiponectin, a 16 kDa protein mainly produced by the adipose tissue has an anti-inflammatory and cardioprotective function with a beneficial role in ovulatory mechanism and maintenance of normal reproductive process. Researchers have observed that in exercise-trained individuals, increased adiponectin concentrations[4–6] and messenger RNA (mRNA) expression for adiponectin receptors are enhanced.[7] One of the studies reported that erobic exercise three times per week favored adiponectin mRNA gene expression and resulted in a 3.5% reduction in weight.[8]

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Resistin is a 12.5kDa, cysteine-rich adipocytokine produced by the macrophages. High resistin levels were found in women with PCOS characterized by IR, hyperinsulinemia, and hyperandogenism.[9,10]

Insulin resistance (IR) and hyperinsulinemia were observed to be characteristic findings in 30% of nonobese PCOS and 70% of obese PCOS women. Increased insulin levels result in increased theca cell steroid production with raised LH levels which have an effect on preovulatory follicles contributing to premature luteinization and follicular arrest.[11]

Routine sequel of lifestyle modifications has proved to possess health benefits in all age-groups. According to the International Androgen Excess and PCOS (AE-PCOS) Society PA of 150 minutes/week of moderate-intensity has been suggested to maintain healthy body quality, regularize the menstrual cycle, and favor increased ovulation rate, thereby increasing the chance of pregnancy.[12] Thus regular exercise alleviates IR and insulin-dependent peripheral action is enhanced. One of the studies concluded that exercise would facilitate fibroblast growth factor-21 (FGF-21) adiponectin axis. The data revealed that following a 12-week intervention would inhibit adipose tissue inflammation and increase FGF-21 significantly reducing tumor necrosis factor α-induced impairment of adiponectin release.[5] Thus exercise regulates the cross-talk between the FGF-21 adiponectin axis that demonstrated alleviation of the IR environment. The mechanistic link of IR plays a key pathological role in PCOS and the present study aims to evaluate the effect of moderate PA on adipocytokines and IR in PCOS infertile women.

Materials and Methods

In this prospective study 143 PCOS infertile women attending the infertility clinic enrolled for participation. Commencement of the study occurred after obtaining the Institutional Ethics Committee (IEC) (IEC: No: 963/IEC/2016) and individual participant's written informed consent for the follow-up study. As per Rotterdam's criteria for PCOS;[12] (a) ovulatory dysfunction or an irregular menstrual cycle, (b) hyperandrogenism, and (c) polycystic ovaries (ultrasound findings of >12 ovarian follicles) were included. The infertile women in the reproductive age-group of 21–40 years diagnosed with PCOS[1] with irregular menstrual cycle but anxious to conceive were recruited for the follow-up study. The infertile women with tubal defects uterine anomalies and infection were not willing to participate and pregnant women were excluded.

Initial evaluation as per the infertility clinic protocol was done by the gynecologist. Pro forma-based details such as medical history, menstrual history, and dietary history were documented. During regular visits to the infertility outpatient department, anthropometric measurements such as weight (kg), height (meter), waist circumference (cm), and hip circumference (cm) were measured and calculation of BMI and waist–hip ratio (WHR) were also documented. The initial evaluation includes the current exercise or activity program and PA was assessed with a baseline global PA questionnaire.[13]

After overnight fasting, blood samples were analyzed to check the routine protocol of hormonal parameters, insulin, adiponectin, leptin, and resistin were analyzed with biochemical-radiochemical equipment using the enzyme-linked immunosorbent assay (ELISA) technique with standardized human adiponectin and resistin biovendor ELISA kits. Homeostatic Model Assessment of IR (HOMA-IR) and HOMA-adiponectin was calculated.

The following dimensions of the PA were advised for the participants: The mode of brisk walking was advised for 5 days a week with a specified time frame of 30–45 minutes duration of PA was recommended. A goal of 150 minutes of brisk walking per week at an intensity of perceived exertion of 13 was advised as per Borg's scale. Participants were advised to use the Android mobile Health app to get the step count and duration of PA. The frequency and duration of PA were recorded in the PA monitor chart. The exercise volume was measured in terms of metabolic equivalents of the task for moderate-intensity brisk walking and calculated using a formula MET minutes = MET value of brisk walking at moderate pace (3.5) × duration of PA. The effectiveness of moderate exercise whether followed routinely was verified by checking the weight of the participants during their visit to the infertility clinic. PA of 12 weeks of brisk walking was successfully completed by 56 participants.

At the end of 12 weeks during the regular visit, a blood sample was drawn to reanalyze adiponectin, leptin, resistin, and insulin levels after PA of moderate exercise. Adipocytokines, the markers of IR such as elevated fasting insulin levels (>15 μIU/mL), HOMA-IR was calculated with (fasting insulin × fasting plasma glucose)/405 and HOMA-adiponectin calculated as HOMA-IR/adiponectin.[14]

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 16.0. The descriptive data are reported as mean ± standard deviation (SD). Anthropometric and biochemical variables were compared between baseline and data after 12 weeks of PA with paired student *t*-tests. The relationship between PA and variables was analyzed with regression analysis. Further, the receiver operating characteristic (ROC) analysis was used to assess the diagnostic effectiveness of HOMA-adiponectin as a marker of IR.

Results

In this study, 143 infertile women were diagnosed with PCOS as per Rotterdam's criteria. As shown in Table 1 anthropometric variables and adipocytokine levels were compared between healthy controls and PCOS. Mean adiponectin levels were decreased (6.57 ± 1.86 μg/mL) and resistin levels were increased (28.04 ± 12.07 ng/mL) in PCOS as compared to the controls which was statistically significant. Markers of IR such as HOMA-IR and HOMA-adiponectin were increased and significant difference was observed as compared with controls.

About 85 participants enrolled for further follow-up, out of which only 44 women completed the PA of brisk walking of moderate intensity. As per Table 2 anthropometric variables and adipocytokine levels were compared before and after PA of brisk walking. As compared to the initial mean weight, after 12 weeks of PA, there observed a mean difference of 3 kg of weight loss which accounts for a 4.75% reduction in weight.

The paired student *t*-test revealed a significant increase in adiponectin and a decrease in resistin levels as compared to the baseline data. It was observed a 16.6% reduction of HOMA-IR and 29% of HOMA-adiponectin in the women who completed 12 weeks of PA.

Furthermore, as per Table 3 to assess the actual reduction of IR state the data were compared between the participants with 150 minutes of PA and without 150 minutes/week of PA. Group II (20 participants) met 150 minutes/week of PA and had 491.74 ± 42.67 metabolic equivalents of task minutes per week (METs/week). Whereas HOMA-IR (2.12 ± 0.44) and HOMA-adiponectin (0.19 ± 0.06) was found to be decreased with statistical significance $p < 0.05$.

Figure 1, Pearson correlation analysis of METs/week with adiponectin showed a highly significant positive correlation ($r = + 0.874$, $R^2 = 0.76$, and $p = 0.000$), negative correlation with resistin ($r = -0.55$), HOMA-IR ($r = -0.632$) and HOMA-adiponectin

($r = -0.60$) with statistically significant p-value 0.000. ROC analysis revealed the diagnostic performance of adiponectin to assess insulin sensitivity had an area under the curve as 0.964 and at a cutoff value of adiponectin 7.3 µg/mL the sensitivity is 93.8% and specificity 82.1% below which indicates IR state.

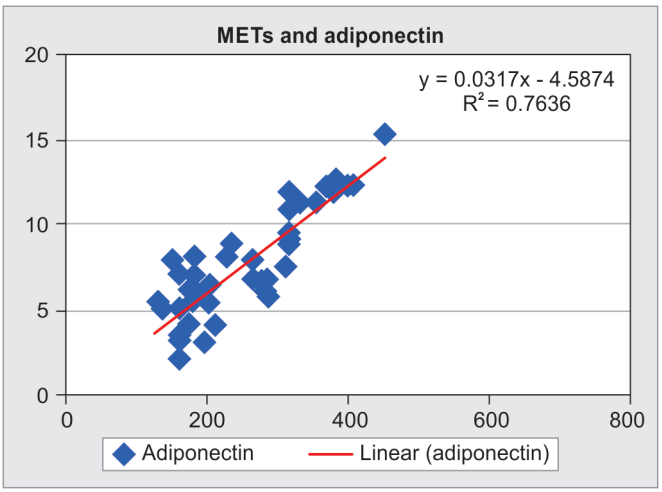

Fig. 1: Regression analysis of PA (METs per week) with adiponectin in infertile PCOS women

At a cutoff value of adiponectin, 7.3 µg/mL, the area under the curve is 0.964, the sensitivity is 93.8% and the specificity is 82.1%. Similarly, resistin had an area under the curve of 0.768, at a cutoff value of 18.1 ng/mL the diagnostic sensitivity and specificity to measure IR are 78.6 and 56.2%, respectively. The ovarian follicular study revealed that 80% of the participants with 150 minutes/week had ovulation positive. Further, the Chi-squared test analysis proved the association of PA of brisk walking with ovulation (Table 4).

Discussion

Polycystic ovary syndrome (PCOS) is the most common hormonal condition that affects women in the reproductive age-group. Characterized by ovulatory dysfunction and IR independent of body mass. The outcome of the present study showed hypoadiponectinemia with elevated HOMA-adiponectin in PCOS infertile women. The study reveals the evident role of beneficial adiponectin in regulating the normal reproductive process.

Serum adiponectin levels were found to be increased in participants who followed the protocol of 150 minutes/week of PA of brisk walking of moderate intensity and had 4.75% weight loss. The mechanistic increase of adiponectin with a weight reduction

Table 1: Comparison of anthropometric and biochemical variables in PCOS and control

Anthropometric indicators (n = 110)	*Control (n = 110)*	*PCOS (n = 143)*	*p-value*
Age-years	25.7 ± 5.58	23.91 ± 3.97	0.047*
Wt (kg)	50.26 ± 4.24	68.06 ± 6.28	0.000***
Ht (mt^2)	1.54 ± 0.04	1.54 ± 0.037	0.945
BMI	21.08 ± 1.83	27.3 ± 3.72	0.000***
WC (cm)	84.1 ± 5.35	92.34 ± 4.49	0.000***
HC (cm)	95.43 ± 6.63	104.65 ± 6.97	0.000***
WHR	0.82 ± 0.025	0.85 ± 0.36	0.000***
ADN (µg/mL)	15.14 ± 2.03	6.57 ± 1.86	0.000***
RES (ng/mL)	13.4 ± 3.6	28.04 ± 12.07	0.000***
FPG (mg/dL)	90.14 ± 6.62	102.1 ± 14.37	0.031*
Insulin (mIU/mL)	5.32 ± 1.27	16.57 ± 6.48	0.000***
HOMA-IR	1.18 ± 0.285	4.16 ± 1.66	0.000***
HOMA-a	0.081 ± 0.028	0.73 ± 0.48	0.000***

ADN, adiponectin; BMI, body mass index; FPG, fasting plasma glucose; HC, hip circumference; Ht, height; HOMA-a, homeostasis model assessment of insulin resistance-adiponectin; WC, waist circumference; WHR, waist-hip ratio; Wt, weight; RES, resistin; the mean and standard deviation are used to express the values; *statistical significance is defined as a p-value < 0.05; **, highly significant; ***, very highly significant; NS, not significant

Table 2: Comparison of anthropometric and adipocytokine levels before and after 3 months of moderate PA follow-up of PCOS infertile females (comparison by paired student's t-test—paired differences at 95% confidence interval)

PCOS infertile females (n = 44) brisk walking	*Baseline*	*After 3 months of brisk walking*	*p-value*
Wt (kg)	63.036 ± 6.01	60.21 ± 7.3	<0.05*
WC (cm)	88.22 ± 5.9	87.68 ± 5.78	NS
PAI	38.068 ± 8.9	55.32 ± 6.82	0.0001***
Insulin mIU/mL	15.04 ± 6.57	13.19 ± 4.7	0.001**
ADN (µg/mL)	6.29 ± 1.92	7.8 ± 1.22	0.005**
RES (ng/mL)	28.04 ± 12.07	22.94 ± 9.49	0.001**
HOMA-IR	3.84 ± 0.97	3.2 ± 1.24	0.003**
HOMA-a	0.807 ± 0.78	0.572 ± 0.54	0.002**

ADN, adiponectin; HOMA-a, HOMA-adiponectin; PAI, physical activity index score; RES, resistin, WC, waist circumference; Wt, weight; the mean and standard deviation are used to express the values; *statistical significance is defined as a p-value of <0.05; **, highly significant; ***, very highly significant; NS, not significant

Table 3: Comparison of anthropometric and adipocytokine levels in PCOS infertile females with PA of duration less than and greater than 150 minutes/week

PCOS infertile females	*PA <150 minutes/week (n = 24)*	*PA greater than 150 minutes/week (n = 20)*	*p-value*
PA minutes/week	95.42 ± 13.82	163.68 ± 13.27	0.0001***
MET minutes/week	333.96 ± 48.39	491.75 ± 42.67	0.0001***
Average duration of PA	23.85 ± 4.36	40.94 ± 3.47	0.0001***
Wt (kg)	62.7 ± 7.64	59.48 ± 9.44	0.0001***
ADN (µg/mL)	6.13 ± 2.14	9.32 ± 1.46	0.0001***
RES (ng/mL)	25.71 ± 9.95	18.12 ± 6.4	0.0001***
HOMA-IR	3.46 ± 0.86	2.12 ± 0.44	0.0001***
HOMA-a	0.73 ± 0.34	0.19 ± 0.06	0.0001***

ADN, adiponectin; HOMA a, HOMA-adiponectin; MET, metabolic equivalents of task; PA, physical activity; RES, resistin; Wt, weight; the mean and standard deviation are used to express the values; *statistical significance is defined as a *p*-value of <0.05; **, highly significant; ***, very highly significant; NS, not significant

Table 4: Association of PA and ovulation positive in PCOS women with brisk walking

PA	*Ovulation positive*	*Ovulation negative*	*Total*	*Chi-squared value*	*p-value*
Brisk walking >150 minutes/week	16 (80%)	4 (20%)	20	17.64	0.000
Brisk walking <150 minutes/week	4 (16.7%)	20 (83.3%)	24		

Pearson Chi-squared (χ2) test; $p < 0.05$, statistically significant at 95% confidence interval

program was demonstrated by researchers that following aerobic exercise three times a week had resulted in increased mRNA adiponectin expression, enhanced mRNA expression of adiponectin receptors 1 and 2, and high-molecular-weight adiponectin concentration are considered to be increased which have a negative association with IR.[15]

Antagonistic presentation of resistin levels revealed the severity of the IR status of the individuals. Serum resistin levels were found to be increased in women who participated in <150 minutes of PA/week or less than METs/week of energy expenditure. In support of this work, one of the studies demonstrated a reduced adiponectin resistin ratio in obese PCOS women.[16] Pangaribuan B et al. described the potential link of resistin between PCOS, obesity, and IR. In our study, following a 5% reduction of weight loss after 12 weeks of brisk walking decreased resistin levels were observed. Resistin seems to have a potential link with insulin-dependent peripheral action *via* inducing suppressor of cytokine signaling three, which in turn impairs the insulin signal transduction pathway. This compelling evidence found that there is a close link between resistin and IR affecting reproductive function.[17,18] Treatment with antioxidants has been found to rectify menstrual irregularities and decrease IR.[19] The emerging data reported the antagonistic effect of adiponectin and resistin as the mechanistic link that exists in dysregulated adipose tissue with chronic low-grade inflammatory environment resulting in the development of reproductive dysfunction in women with PCOS.[20]

This study revealed an increase in the beneficial adiponectin and a decrease in HOMA-IR and HOMA-adiponectin in women who met the AE-PCOS guidelines of 150 minutes/week of brisk walking. We found that individuals participating with >150 minutes/week of PA of moderate-intensity or 450 METs/week are likely to possess enhanced insulin sensitivity.[21] Researchers have highlighted the mechanism of restoration of ovulation with regular PA of moderate intensity is by improved insulin sensitivity and regularized hypothalamic–pituitary–ovarian axis mediated gonadotropin hormone-releasing hormone cycle that leads to ovulatory menstrual cycle. Thus, physical activities are needed to promote insulin sensitivity, hormonal balance, and regularize the menstrual cycle, and thus the chance of ovulation is favoured.[22,23]

Further follow-up with ovarian follicular study in the women presented with rupture of dominant ovarian follicle in 80% of the women who performed regular brisk walking with >150 minutes/week compared to the infertile women (17%) with <150 minutes/week of brisk walk. The finding is in concordance with Kiranmayee et al.,[24] Birch Petersen et al.[25] reported that PA had triggered the ovarian reserve profile favorable for normal reproductive outcomes in women <30 years of age.

The study highlighted the benefit of brisk walking of 150 minutes/week which played a significant role in the elevation of the beneficial adiponectin in women with PCOS. Thus, women with regular PA of moderate intensity resumed the ovulatory menstrual cycle. Thus, a favorable adipocytokine profile with elevated adiponectin levels decreased resistin, HOMA-IR, and HOMA-a were observed after accomplishment of 150 minutes/week or 450 METs of brisk walk and had restored ovulatory menstrual cycle.

Conclusion

Brisk walking for 150 minutes/week had resulted in weight reduction with increased beneficial adiponectin levels and decreased markers of IR. Thus, PA of moderate intensity as per the AE-PCOS guidelines provides a favorable adipocytokine profile that facilitates the chance of ovulation in women with PCOS.

Practical Implications

In women, PA of moderate intensity results in improvisation of insulin sensitivity. Brisk walking of 30 minutes duration can trim the waistline, reduce weight, and improve the general well-being of an individual. In fact, women who follow standard routine walking protocol promote the ovulatory cycle, especially in women with

PCOS which is contributed by increased adiponectin levels that have anti-inflammatory action.

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