

Adiponectin resistin ratio beneficial index of insulin sensitivity in women with PCOS

Dr. K. A. Arul Senghor ^{1*}, Dr. Meera.S ², Dr. V. M. Vinodhni ³, Dr. Anuradha. M ⁴

¹ Professor of Biochemistry, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur – 603203, Kanchipuram, Chennai, Tamil Nadu, India.

² Professor of Biochemistry, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur – 603203, Kanchipuram, Chennai, Tamil Nadu, India.

³ Professor & Head of Biochemistry, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur – 603203, Kanchipuram, Chennai, Tamil Nadu, India.

⁴ Professor & Head of Obstetrics & Gynecology, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur – 603203, Kanchipuram, Chennai, Tamil Nadu, India.

Email: arulsenk@srmist.edu.in¹

DOI: 10.47750/pnr.2022.13.S01.239

Abstract

Objective: Regular physical activity wheels 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. Purpose of the study is to determine insulin resistant status and the effect of brisk walking on the levels of adipocytokines in women with Polycystic ovarian syndrome. **Design:** Prospective study was conducted in infertile women in reproductive age group of 21 to 40 years diagnosed as polycystic ovarian syndrome according to Rotterdam's criteria with irregular menstrual cycle but anxious to conceive. **Methods:** Study included 143 PCOS married women (as per Rotterdam's criteria) and 110 married women as control with atleast one child through natural conception. Anthropometric measurements were documented Adiponectin and Resistin were analyzed. HOMA-IR and HOMA-adiponectin was calculated to assess insulin resistance. Follow-up task of 150 mins/week of physical activity of brisk walking of moderate intensity was advised for 12 weeks and status reassessed. **Results:** Hypoadiponectinemia and hyperresistinemia with elevated markers of insulin resistance (HOMA-IR and HOMA-adiponectin) was observed in 143 PCOS infertile women. The baseline data were compared with estimates after 12 weeks, it was found that adiponectin levels were increased with 4.75% of weight loss and decreased Resistin, HOMA-IR and HOMA-adiponectin was observed. Participants who met 150 mins/week of brisk walking revealed an increase in adiponectin levels with strongly positive correlation ($r = 0.76$) was observed with regression analysis of METs/week physical activity with adiponectin levels. Diagnostic sensitivity and specificity of Adiponectin at a cut-off value of 7.3 $\mu\text{g/ml}$ with 150 mins/week of physical activity was found to be 93.8% and 82.1% respectively. **Conclusion:** Brisk walking of 150 mins/week had resulted in 4.75 % of weight reduction as well as increased Adiponectin levels. Beneficial Adiponectin facilitates ovulatory menstrual cycle and thereby the chance of ovulation is increased in PCOS women.

Keywords: Physical activity 150 mins/week, Adiponectin, Resistin, HOMA-adiponectin, Metabolic.

INTRODUCTION

The most prevalent cause of ovulatory dysfunction and one that affects 5 to 10% of women of reproductive age is polycystic ovary syndrome¹. PCOS is characterized by insulin resistance associated with metabolic features independent of body mass index. Insulin resistance is the key compulsive cause resulting in menstrual irregularity, ovulatory dysfunction, hyperandrogenism and polycystic ovaries². Lifestyle interventions are found to improve both metabolic and reproductive process.

The endocrine system in adipose tissue is thought to be active, secreting a wide range of bioactive chemicals called adipocytokines. In fact adipocytokines are found to have its impact on the normal reproductive process. Evidences suggest that physical activity regulates the endocrine role of visceral adipose tissue and influences to improve insulin sensitivity even in the absence of weight loss³.

Adiponectin, 16 kDa protein mainly produced by the adipose tissue has anti-inflammatory and cardio protective function with beneficial role over ovulatory mechanism and maintenance of normal reproductive process. Researchers have observed that in exercise trained individuals, increased adiponectin concentrations ⁴⁻⁶ and also mRNA expression for adiponectin receptors are enhanced ⁷. Also performing aerobic exercise three times per week had resulted in 3.5% reduction in weight and also favoured adiponectin mRNA gene expression ⁸.

Resistin is a 12.5kDa, cysteine rich adipocytokine produced by the macrophages. High resistin levels were found in women with PCOS characterized by insulin resistance, hyperinsulinemia and hyperandrogenism ^{9,10}.

Insulin resistance and hyperinsulinemia was observed to be characteristics findings in 30% non-obese PCOS and 70% obese PCOS women. Increased insulin levels results in increased theca cell steroid production with raised LH levels which have its effect on preovulatory follicles contributing to premature luteinization and follicular arrest¹¹.

Routine sequel of lifestyle modifications has proved to possess health benefits in all age groups. According to the International Androgen Excess and PCOS Society (AE-PCOS) physical activity of 150 mins per week of moderate intensity has been suggested to maintain healthy body quality, regularizes the menstrual cycle and favors increased ovulation rate, thereby increases the chance of pregnancy ¹². Thus regular exercise alleviates insulin resistance and insulin dependent peripheral action is enhanced.

The present study seeks to assess the impact of moderate physical activity on adipocytokines and insulin resistance in PCOS infertile women. The molecular relationship between insulin resistance plays a major pathogenic function in PCOS.

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 ethical committee (IEC: No: 963/IEC/2016) and individual participant's written informed consent for the follow-up study.

Infertile women in reproductive age group of 21 to 40 years diagnosed as polycystic ovarian syndrome according to Rotterdam's criteria¹ with irregular menstrual cycle but anxious to conceive are recruited for the follow-up study.

The infertile women with tubal defects or uterine anomaly, infection, not willing to participate and pregnant women were excluded.

Initial evaluation as per the infertility clinic protocol was done by the Gynecologist. Proforma based details such as medical history, menstrual history and dietary history was documented. During regular visit to infertility OPD, anthropometric measurements such as weight (kg), height (meter), waist circumference (cm), hip circumference (cm) measured and calculation of BMI and WHR were also documented. The initial evaluation includes the current exercise or activity program and physical activity was assessed with baseline Global Physical Activity 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 BIO-RAD equipment using ELISA technique with standardised Human Adiponectin and Resistin Bio Vendor ELISA kits. HOMA-IR and HOMA-adiponectin was calculated.

The following dimensions of the physical activity 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 mins duration of physical activity was recommended. A goal of 150 mins 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 Android mobile Health app to get the step count and duration of physical activity. The frequency and duration of physical activity were recorded in the physical activity monitor chart. The exercise volume was measured in terms of Metabolic Equivalents of task for moderate intensity brisk walking and calculated using a formula MET minutes = MET value of brisk walking at moderate pace (3.5) x duration of physical activity. The effectiveness of moderate exercise whether followed routinely was verified by checking the weight of the participants during their visit to Infertility clinic. Physical activity of 12 weeks brisk walking was successfully completed by 56 participants.

At the end of 12 weeks during the regular visit, blood sample was drawn to re-evaluate Adiponectin, leptin, resistin and insulin levels after physical activity of moderate exercise. Adipocytokines, High fasting insulin levels (> 15 IU/mL), HOMA-IR computed using $(\text{Fasting insulin} \times \text{FPG})/405$, and HOMA-adiponectin calculated using $\text{HOMA-IR}/\text{adiponectin}$ are all indicators of insulin resistance. ¹⁴. Further the participants' undergone follow-up with follicular study for ovulation at 14 - 16th day of menstrual cycle.

Statistical analysis was performed with SPSS version 16.0. The descriptive data are reported as mean \pm SD. Anthropometric and biochemical variables were compared between baseline and data's after 12 weeks of physical activity with paired Student *t* test. The relationship between physical activity and variables were analyzed with regression analysis. Further the ROC analysis was used to assess the diagnostic effectiveness of HOMA-adiponectin as marker of insulin resistance.

RESULT

In this prospective study, 143 infertile women were diagnosed as 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 was decreased 6.29 ± 1.92 $\mu\text{g/ml}$ and resistin levels was increased 28.04 ± 12.07 ng/ml in PCOS as compared to the controls which was statistical significant. Markers of insulin resistance such as HOMA-IR and HOMA-adiponectin were increased and significant difference was observed as compared with controls.

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

Anthropometric Indicators	Control (n=110)	PCOS (n=143)	P value
Age yrs	25.7 \pm 5.58	23.91 \pm 3.97	0.047*
Wt (kg)	50.26 \pm 4.24	68.06 \pm 6.28	0.000***
Ht (m²)	1.54 \pm 0.04	1.54 \pm 0.037	0.945
BMI	21.08 \pm 1.83	27.3 \pm 3.72	0.000***
WC (cm)	8.41 \pm 5.35	92.34 \pm 4.49	0.000***
HC (cm)	95.43 \pm 6.63	104.65 \pm 6.97	0.000***
WHR	0.82 \pm 0.025	0.85 \pm 0.36	0.000***
ADN ($\mu\text{g/ml}$)	15.14 \pm 2.03	6.57 \pm 1.86	0.000***
RES (ng/ml)	13.4 \pm 3.6	28.04 \pm 12.07	0.000***
FPG (mg/dl)	90.14 \pm 6.62	102.1 \pm 14.37	0.031*
Insulin (mIU/ml)	5.32 \pm 1.27	16.57 \pm 6.48	0.000***
HOMA-IR	1.18 \pm 0.285	4.16 \pm 1.66	0.000***
HOMA-a	0.081 \pm 0.028	0.73 \pm 0.48	0.000***

Wt – weight, Ht – height, BMI – body mass index, WC – waist circumference, HC – hip circumference, WHR – waist hip ratio, ADN – Adiponectin, RES – Resistin, FPG – fasting plasma glucose, HOMA-a – HOMA-adiponectin

In terms of mean and standard deviation, values are expressed.

*p value less than 0.05 is regarded as significant.

Not significant, or NS. ***Extremely Significant **Very Significant

About 79 participants enrolled for further follow-up, out which only 56 women completed the physical activity of brisk walking of moderate intensity. As per table (2) anthropometric variables and adipocytokine levels were compared before and after physical activity of brisk walking. As compared to the initial mean weight, after 12 weeks of physical activity there observed a mean difference of 3 kg of weight loss which accounts to 4.75% of reduction of weight.

TABLE 2: Comparison of anthropometric and Adipocytokine levels before and after 3 months moderate physical activity follow-up of PCOS infertile females

[Comparison by paired Student's t test - Paired Differences at 95% Confidence Interval]

PCOS Infertile females (n=56)	Baseline	After 3 mths 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**
Wt – weight, WC – waist circumference, PAI – Physical activity index score, ADN – Adiponectin, RES – Resistin, HOMA a – HOMA-adiponectin			

In terms of mean and standard deviation, values are expressed.

*p value less than 0.05 is regarded as significant.

Not significant, or NS. ***Extremely Significant **Very Significant

Paired student t test revealed significant increase in adiponectin and 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 physical activity (PA).

Furthermore, as per table (3) to assess the actual reduction of insulin resistant state the data's were compared between the participants with 150 mins of physical activity and without 150 minutes per week of physical activity. Group A (20 participants) met 150 mins/wk of PA had 491.74 ± 42.67 of 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 $p < 0.05$.

TABLE 3: Comparison of anthropometric and Adipocytokine levels in PCOS infertile females with physical activity of duration less than and greater than 150 mins per week

PCOS Infertile females	Physical activity less	Physical activity greater	p value
than 150 mins per week	than 150 mins per week		
(n=36)	(n=20)		
PA mins / week	95.42 ± 13.82	163.68 ± 13.27	0.0001***
MET mins per week	333.96 ± 48.39	491.75 ± 42.67	0.0001***
Average duration of physical activity	23.85 ± 4.36	40.94 ± 3.47	0.0001***
Wt (kg)	62.7 ± 7.64	59.48 ± 9.44	0.0001***
ADN ($\mu\text{g/ml}$)	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***
PA – Physical activity, MET – Metabolic equivalents of task, Wt – weight, ADN – Adiponectin, RES – Resistin, HOMA a – HOMA-adiponectin			

In terms of mean and standard deviation, values are expressed.

*p value less than 0.05 is regarded as significant.

Not significant, or NS. ***Extremely Significant **Very Significant

(Fig 1), Pearson correlation analysis of METs / week with adiponectin showed highly significant positive correlation ($r = + 0.874$, $R^2 = 0.76$, $p 0.000$), 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. Receiver's operating curve analysis revealed the diagnostic performance of Adiponectin to assess insulin sensitivity had area under the curve as 0.964 (fig 2); and at a cut-off value of adiponectin 7.3 $\mu\text{g/ml}$ the sensitivity is 93.8% and specificity 82.1% below which indicates insulin resistant state.

Fig: 1 Regression analysis of Physical activity (METs per week) with Adiponectin in infertile PCOS women

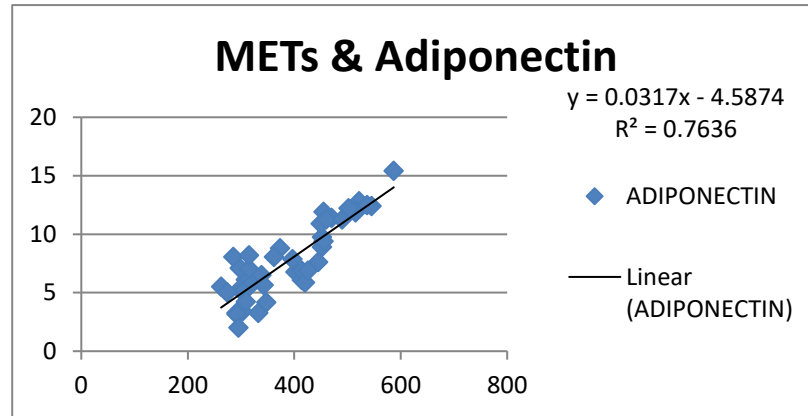
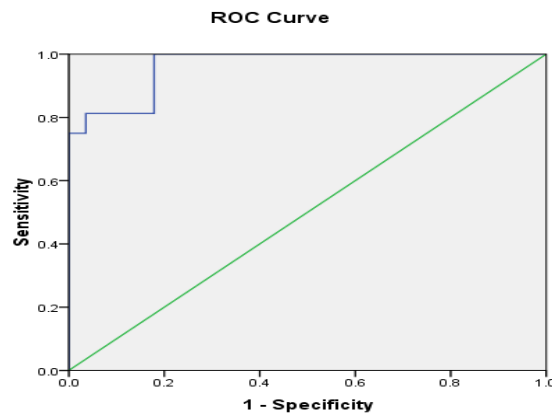


Fig 2: Receiver's operating curve analysis : ADIPONECTIN in infertile women after 3 months of Physical activity of brisk walking



At a cut-off value of adiponectin 7.3 $\mu\text{g/ml}$, area under the curve is 0.964, the sensitivity is 93.8% and specificity is 82.1%.

Similarly, Resistin had area under the curve as 0.768, at a cut-off value 18.1 ng/ml the diagnostic sensitivity and specificity to measure insulin resistance is 78.6% and 56.2% respectively.

DISCUSSION

PCOS is the commonest cause of ovulatory dysfunction, with hormonal imbalance and insulin resistance 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 mins/week of physical activity of brisk walking of moderate intensity and had 5% weight loss. The mechanistic increase of adiponectin with weight reduction programme 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 negative association with insulin resistance ¹⁵.

Antagonistic presentation of Resistin levels revealed the severity of insulin resistant status of the individuals. Serum Resistin levels were found to be increased in women who participated in less than 150 mins of PA /wk or less than METs /wk of energy

expenditure. In support to our work one of the studies had demonstrated reduced Adiponectin Resistin ratio in obese PCOS women¹⁶. Steppan et al had described the potential link of Resistin between PCOS, obesity and insulin resistance. In our study, following 5% reduction of weight loss after 12 week of brisk walking decreased Resistin levels was observed. Resistin seems to have a potential link with insulin dependent peripheral action via inducing suppressor of cytokine signaling 3 which in turn impairs insulin signal transduction pathway. This compelling evidence found the close link between resistin and insulin resistance affecting reproductive function^{17,18}. Treatment with antioxidants has found to rectify menstrual irregularities and decreases insulin resistance¹⁹. 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 PCOS²⁰.

A total of 39% PCOS women participated in life style modification of brisk walking. The study revealed increase in the beneficial adiponectin, decrease in HOMA-IR and HOMA-adiponectin in women who met the AEPCOS guidelines of 150 mins /week. The present study revealed the diagnostic importance of Adiponectin with a cut-off value less than 7.3 µg/ml and Resistin cut-off value greater than 18.1 ng/ml as insulin resistant state. We found that individuals participating with more than 150 mins/week of PA of moderate intensity or 450 METs/week are likely to possess enhanced insulin sensitivity²¹. Thus physical activities are needed to promote insulin sensitivity, hormonal balance, regularize menstrual cycle and thus chance of ovulation is favoured^{22,23}.

The present study provides the platform of self-motivation to brisk walking. Furthermore study has to be carried out in PCOS women with discontinuation of brisk walk and reassess the adipocytokine levels in the participants.

CONCLUSION

Women with PCOS who adhered to the AEPCOS physical activity recommendations were like to have higher favourable Adiponectin levels and lower Resistin levels. Thus lifestyle modification measures such as diet control and physical activity of moderate intensity should be included as a part of the routine treatment regimen that augments the chance of ovulation and improve the quality of life of infertile PCOS women.

PRACTICAL IMPLICATIONS:

- In women, physical activity of moderate intensity results in improvisation of insulin sensitivity.
- Brisk walking of 30 minutes duration can trim the waistline, reduced weight and improve general well-being of an individual.
- In fact women who follow standard routine walking protocol promotes ovulatory cycle especially in women with pcos which is contributed by increased adiponectin levels that has anti-inflammatory action.

CONFLICT OF INTEREST:

NIL

FUNDING SUPPORT:

The research work utilized the facility in the institution and did not receive any external funding.

REFERENCES

1. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19:41–47. <https://doi.org/10.1093/humrep/deh098>.

2. Shroff R, Syrop CH, Davis W, Van Voorhis BJ, Dokras A: Risk of metabolic complications in the new PCOS phenotypes based on the Rotterdam criteria. *Fertil Steril* 2007; 88:1389–1395. DOI: 10.1016/j.fertnstert.2007.01.032.
3. Verheggen, R.J.; Maessen, M.F.; Green, D.J.; Hermus, A.R.; Hopman, M.T.; Thijssen, D.H. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: Distinct effects on body weight and visceral adipose tissue. *Obes. Rev.* 2016, 17, 664–690. doi: 10.1111/obr.12406.
4. Abbenhardt C, McTiernan A, Alfano CM, et al. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. *J Intern Med.* 2013; 274(2):163–75. doi: 10.1111/joim.12062.
5. Acharya SD, Brooks MM, Evans RW, Linkov F, Burke LE. Weight loss is more important than the diet type in improving adiponectin levels among overweight/obese adults. *J Am Coll Nutr.* 2013; 32(4):264–71. doi: 10.1080/07315724.2013.816607.
6. Ambeba EJ, Styn MA, Kuller LH, Brooks MM, Evans RW, Burke LE. Longitudinal effects of weight loss and regain on cytokine concentration in obese adults. *Metabolism.* 2013; 62:1218–1222. doi: 10.1249/MSS.0000000000000670
7. Christiansen T, Paulsen SK, Bruun JM, Ploug T, Pedersen SB, Richelsen B. Diet-induced weight loss and exercise alone and in combination enhance the expression of adiponectin receptors in adipose tissue and skeletal muscle, but only diet-induced weight loss enhanced circulating adiponectin. *J Clin Endocrinol Metab.* 2010; 95(2):911–9. doi: 10.1210/jc.2008-2505.
8. Nurnazahiah A, Lua PL, Shahril MR. Adiponectin, leptin and objectively measured physical activity in adults: a narrative review. *Malays J Med Sci.* 2016;23(6):7–24. <http://dx.doi.org/10.21315/mjms2016.23.6.2>
9. Panidis D., Koliakos G., Kourtis A., Farmakiotis D., Mouslech T., Rousso D.: Serum resistin levels in women with polycystic ovary syndrome. *Fertil Steril* 2004; 81: pp. 361-366. DOI:<https://doi.org/10.1016/j.fertnstert.2005.02.017>.
10. Yilmaz M., Bukan N., Demirci H., Ozturk C., Kan E., Ayvaz G., et. al.: Serum resistin and adiponectin levels in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2009; 25: pp. 246-252. doi: 10.1080/09513590802653833.
11. A.F. Gursoy, A. Tokmak S. Eroglu and H. Yesilyurt. Effect Of Insulin Resistance on the occurrence of pregnancy in women treated empirically for unexplained infertility. *Acta Endocrinol (Buchar).* 2017 Jul-Sep; 13(3): 314–321. doi: 10.4183/aeb.2017.314
12. Shaobing Wang et al. Effects of exercise intervention on the improvement of polycystic ovary syndrome doi:<http://dx.doi.org/10.5772/intechopen.88896>.
13. Maria Hagstromer, Pekka Oja and Michael Sjostrom. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutrition:* 2005; 9(6), 755–762 DOI: 10.1079/PHN2005898.
14. Brunna Sullara Vilela, Ana Carolina Junqueira Vasques, Roberta Soares, Lara Cassani, Adriana Costae Forti, José Carlos Pareja, Marcos Antonio Tambascia, BRAMS Investigators, Bruno Geloneze. The HOMA-Adiponectin (HOMA-AD) closely Mirrors the HOMA-IR Index in the screening of Insulin Resistance in the Brazilian Metabolic Syndrome Study (BRAMS). *PLoS One.* 11(8): e0158751 (2016). doi: 10.1371/journal.pone.0158751.
15. Tarik Becic , Christian Studenik and Georg Hoffmann. Exercise Increases Adiponectin and Reduces Leptin Levels in Prediabetic and Diabetic Individuals: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medical Sciences.* 2018, 6, 97: 1 – 18. doi:10.3390/medsci6040097
16. Pangaribuan B, Yusuf I, Mansyur M, Wijaya A. Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. *Ther Adv Endocrinol Metab.* 2011;2(6):235-245. doi:10.1177/2042018811423770.
17. Sarray S, Madan S, Saleh LR, Mahmoud N, Almawi WY. Validity of adiponectin-to-leptin and adiponectin-to-resistin ratios as predictors of polycystic ovary syndrome. *Fertil Steril.* 2015 Aug;104(2):460-6. doi: 10.1016/j.fertnstert.2015.05.007. Epub 2015 Jun 6. PMID: 26051098.
18. Golbahar J, Das NM, Al-Ayadhi MA, Gumaa K. Leptin-to-adiponectin, adiponectin-to-leptin ratios, and insulin are specific and sensitive markers associated with polycystic ovary syndrome: a case-control study from Bahrain. *Metab Syndr Relat Disord.* 2012 Apr;10(2):98-102. doi: 10.1089/met.2011.0075. Epub 2011 Nov 22. PMID: 22107332.
19. Olufisayo Grace Oyebanji, Modupe Fisayo Asaolu. Assessment of antioxidant status of women with polycystic ovarian syndrome. *Asian Pacific Journal of Reproduction.* 2020; 9(1): 9-15.
20. Spritzer PM, Lecke SB, Satler F & Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. *Reproduction* 2015; 149 R219–R227. (doi:10.1530/REP-14-0435)
21. Lamb JD, Johnstone EB, Rousseau JA, Jones CL, Pasch LA, Cedars MI, Huddleston HG. Physical activity in women with polycystic ovary syndrome: prevalence, predictors, and positive health associations. *Am J Obstet Gynecol.* 2011 Apr;204(4):352.e1-6. doi: 10.1016/j.ajog.2010.12.006. Epub 2011 Feb 2. PMID: 21288501.
22. de Lima Nunes R, Dos Santos IK, Cobucci RN, Pichini GS, Soares GM, de Oliveira Maranhão TM, Dantas PMS. Lifestyle interventions and quality of life for women with polycystic ovary syndrome: A systematic review and meta-analysis protocol. *Medicine (Baltimore).* 2019 Dec;98(50):e18323. doi: 10.1097/MD.00000000000018323. PMID: 31852122; PMCID: PMC6922537.
23. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2011 Jul 6;(7):CD007506. doi: 10.1002/14651858.CD007506.pub3. Update in: *Cochrane Database Syst Rev.* 2019 Mar 28;3:CD007506. PMID: 21735412.