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The Role of Serum Adiponectin Levels in Women with Polycystic Ovarian Syndrome

Hanaa A. Amer, Rania A. Abo-Shady, Doaa M. Abd Elaziz, Yara M. Khattab*
Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
*Corresponding Author: Yara Mahmoud Khattab, E-mail : ahmed.elanour@med.asu.edu.eg,
Phone number: 00201111486669

ABSTRACT

Background: Adiponectin is a recently identified adipocyte-derived collagen-like protein. In humans, adiponectin levels were found to be decreased in obese, compared to normal individuals, whereas high adiponectin levels are independently associated with increased insulin sensitivity. The specific role of adiponectin in these metabolic conditions is not clear: it may have a causative role, or it could be regulated by insulin and serve as a marker for insulin resistance. Adiponectin levels hold great promise for use in clinical applications as a potent indicator of underlying metabolic complications.

Aim of the work: The present study was aimed to evaluate the link between adiponectin and polycystic ovarian syndrome (PCOS) and the potential use of adiponectin as a biomarker for PCOS.

Patients and methods: The study included 84 female patients presenting to the Reproductive and Infertility Clinics at Ain Shams University Maternity Hospital, starting from June 2016 till January 2017. They were divided into four groups based on the diagnosis of polycystic ovarian syndrome (PCOS); Cases were selected as: Group I non-obese PCOS group (n = 21), Group II obese PCOS group (n = 21). Controls were selected as: Group III non-obese control group (n = 21) and Group IV obese control group (n = 21). All the Control subjects had normal, regular menstruation, normal ovarian findings on ultrasound, and normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. None displayed hirsutism. PCOS subjects were enrolled when they had satisfied two of the three following inclusion criteria: 1. Oligomenorrhea or amenorrhea. 2. Clinical or biochemical hyperandrogenism. 3. Ultrasonographic polycystic ovarian morphology. Serum adiponectin, metabolic and hormonal parameters were compared in PCOS patients with BMI matched controls. Measurement of plasma adiponectin levels done by Enzyme Immunoassay kit in Ain Shams University Maternity Hospital lab.

Results: Serum adiponectin level was significantly lower among cases than controls (p value < 0.001). No significant difference was found between cases and controls regarding their hormonal profile except for testosterone and insulin levels which were significantly higher among cases (p value <0.001). As regard insulin resistance, there was a significant difference where cases were higher than control (p value <0.001).

Conclusion: It could be concluded that PCOS was found to correlate with low adiponectin levels, independently of BMI. The relationships between adiponectin and insulin resistance and sensitivity, metabolic syndrome, and BMI in women with PCOS suggest that adiponectin potentially could serve as a marker for disease risk and provide opportunity for earlier intervention if knowledge is successfully translated from laboratory to clinical practice.

Keywords: Adiponectin, PCOS, Enzyme-Linked Immuno-Sorbent Assay

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most prevalent worldwide female endocrine disorder [1]. PCOS is the most common cause of anovulatory infertility. PCOS has different etiologic factors and it has a clinical presentation which may include insulin resistance, obesity and ovulatory dysfunction. PCOS is characterized by oligomenorrhea, hyperandrogenism, and/or polycystic ovaries on ultrasound [2,3].

PCOS is also common among infertile arabian female population and it is associated with significant elevations in markers of metabolic syndrome, insulin resistance and cardiovascular risks [4]. Besides hyperandrogenism and chronic anovulation, insulin resistance (IR) is another important characteristic of PCOS. Both obese and lean PCOS patients have reduced insulin sensitivity. IR, which is exacerbated by obesity and hyperandrogenism plays a major role in the development of metabolic disorders, including type 2 diabetes and cardiovascular diseases [5]. Insulin resistance has the critical role in the development of PCOS. There are several reports that emphasize the

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impacts of adipose tissue in pathogenesis of PCOS [6,7].

Adipose tissue is not an inert reserve of triglycerides, but rather an active endocrine organ that plays an important role on insulin and other hormones which regulates the energy metabolism. Some studies have shown that there is a strong link between the blood levels of some adipokines, particularly adiponectin, ghrelin and resistin, and the clinical and hormonal indices of PCOS and its associated risks and metabolic disturbances [8].

Adiponectin is identified adipocyte-derived collagen-like protein. Adiponectin is secreted mainly by white adipose tissue, it plays a variety of roles in a variety of tissues and organs, such as insulin-sensitizing, anti-inflammatory, anti-atherosclerosis, regulate lipid metabolism and has a role in cardiovascular protection [9].

In humans, adiponectin levels were found to be decreased in obese, compared to normal individuals, whereas high adiponectin levels are independently associated with increased insulin sensitivity [10]. Low levels (hypoadiponectinemia) are associated with conditions such as obesity, insulin resistance, metabolic syndrome, Type2 DM, and CVD. Conversely, high levels of adiponectin (hyperadiponectinemia) have antiatherogenic, anti-inflammatory and anti-diabetic effects [11].

Although low adiponectin levels have been associated with PCOS which is mainly attributed to obesity among these patients, studies have also suggested that low adiponectin in PCOS may be related to IR in these women. However, the role of adiponectin in younger and lean patients has been examined only in few studies. In these women, it is not certain that to what extent, the IR determines the levels of adiponectin. If adiponectin levels in younger and lean women provide similar association with PCOS as in obese patients, the level of adiponectin may be a useful proxy measure of an ongoing ovarian disease in women with atypical presentation of PCOS [12].

Obesity is associated with increased adipose and plasma leptin levels and lower adiponectin expression [13]. Adipose tissue is a key endocrine organ [14]. Any correlation between adipokines and insulin resistance in women with PCOS should be considered in lean and overweight/obese women separately. Therefore, we evaluate the adiponectin in overweight/obese and lean women with and without PCOS.

The specific role of adiponectin in these metabolic conditions is not clear: it may have a causative role, or it could be regulated by insulin and serve as a marker for insulin resistance. Whichever function is correct; adiponectin is associated with insulin resistance and the metabolic syndrome [15].

Adiponectin levels hold great promise for use in clinical applications as a potent indicator of underlying metabolic complications [16]. This study reviews the link between adiponectin and PCOS and the potential use of adiponectin as a biomarker for PCOS.

AIM OF THE WORK

The present study was aimed at comparing adiponectin levels in women with PCOS to those of healthy women, and to investigate the independent relationship between plasma adiponectin concentrations and hormonal or metabolic variables including insulin resistance.

PATIENTS AND METHODS

The study was conducted in the Reproductive and Infertility Clinics and Ain Shams University Maternity Hospital lab, between June 2016 and January 2017. A total of 84 women aged 19-39 years. They were divided into the following groups based on the diagnosis of polycystic ovarian syndrome (PCOS): Cases were selected as: Group I (non-obese PCOS group): PCOS with body mass index (BMI) <25 kg/m2 (n = 21), Group II (obese PCOS group): PCOS with BMI >25 kg/m2 (n = 21), Controls were selected as: Group III (non-obese control group): Controls with BMI <25 kg/m2 (n = 21) and Group IV (obese control group): Controls with BMI >25 kg/m2 (n = 21). All of the Control subjects had normal, regular menstruation, normal ovarian findings on ultrasound, and normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. None displayed hirsutism. PCOS subjects were enrolled when they had satisfied two of the three following inclusion criteria: (according to the National Institute of Health criteria (NIH consensus criteria) and Rotterdam criteria by the European Society of Human Reproduction and Embryology/ American Society of Reproductive Medicine): 1. Oligomenorrhea or amenorrhea. 2. Clinicl or biochemical hyperandrogenism. 3. Ultrasonographic polycystic ovarian morphology. Patients with congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, hyperprolactinemia and virilizing ovarian or adrenal tumors were excluded from the study.

The study was approved by the Committee of Ethics of Scientific Research, Faculty of Medicine, Ain Shams University, and an informed consent was signed by participating women.

Collection of blood samples: Serum adiponectin, metabolic and hormonal parameters

were determined and compared in PCOS patients with BMI matched controls. Measurement of plasma adiponectin was done by Enzyme Immunoassay kit according the method of **BIOMATIK** [17]. Other investigations included: determination of BMI, FSH, LH, E2, testosterone, fasting insulin, fasting glucose and insulin resistance by using the Homeostasis Model Assessment (HOMA).

Data analysis

Analysis of data was done using SPSS (Statistical Package for Social Science) program version 18. Independent samples t test was used to compare different variables between cases and controls. Pearson correlation test was used to compare correlation between different variables and serum adponectin level among cases and controls. Multiple linear regression analysis was used to measure independent effect of different variables on serum adiponectin level. P value < 0.05 was considered statistically significant.

Ethical Approval: The study was done after approval of ethical board of Ain Shams University and an informed written consent was taken from each participant in the study.

RESULTS

The study included 84 females attending the Outpatient Gynaecology and Obstetrics Clinics at Ain Shams University hospitals. Their age ranged between 19 and 39 years. This table (1) shows that serum adiponectin level is significantly lower among cases than controls (p value < 0.001). No significant difference is found between cases and controls regarding their hormonal profile except for testosterone and insulin levels which are significantly higher among cases (p value <0.001). As regard insulin resistance, there is a significant difference where cases are highrt than control (p value <0.001).

Table (1): Comparison between cases and controls regarding different parameters

	Cases (N=42)			**Controls (N=42)**			**t***	**P value**
	Range	**Mean**	**SD**	**Range**	**Mean**	**SD**		
Age (years)	19-35	26.00	4.28	19-39	28.36	5.25		
BMI (kg/m^2)	19-45	28.43	7.07	19-41	28.02	6.79	0.27	0.79
Adiponectin (ng/dl)	0.06-2.50	0.93	0.85	0.11-10.00	3.54	3.34	4.92	**<0.001**
FSH (mIU/mL)	2.32-9.50	5.38	1.94	2.32-8.43	5.81	1.81	1.05	0.30
LH (mIU/mL)	2.72-9.43	6.26	1.74	2.34-9.41	6.09	1.89	0.42	0.68
E2 (pg/mL)	14.58-57.43	29.62	8.10	9.32-47.43	28.25	7.03	0.83	0.41
Testosterone (ng/dL)	0.25-1.40	0.68	0.31	0.03-0.56	0.22	0.18	8.33	**<0.001**
fasting insulin (mIU/L)	80.00-322.00	159.60	61.01	18.00-160.00	99.12	35.63	5.55	**<0.001**
fasting glucose (mg/dl)	61.00-132.00	91.43	16.79	54.00-132.00	90.67	21.64	0.18	0.86
Insulin resistance	2.04-8.67	3.54	1.39	0.42-4.73	2.24	1.06	4.81	**<0.001**

Figure (1): Serum Adiponectin and Testosterone levels in cases and controls.

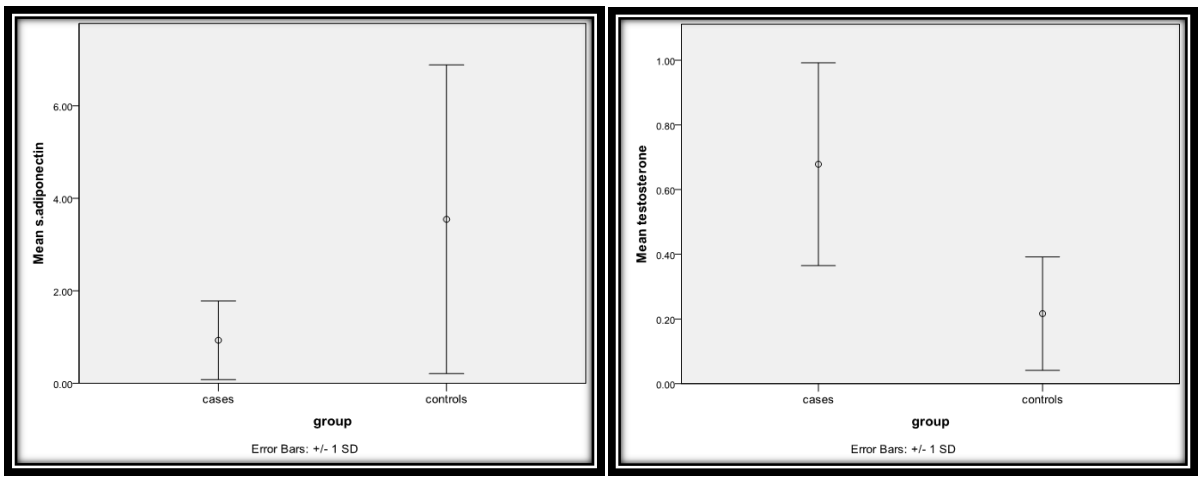
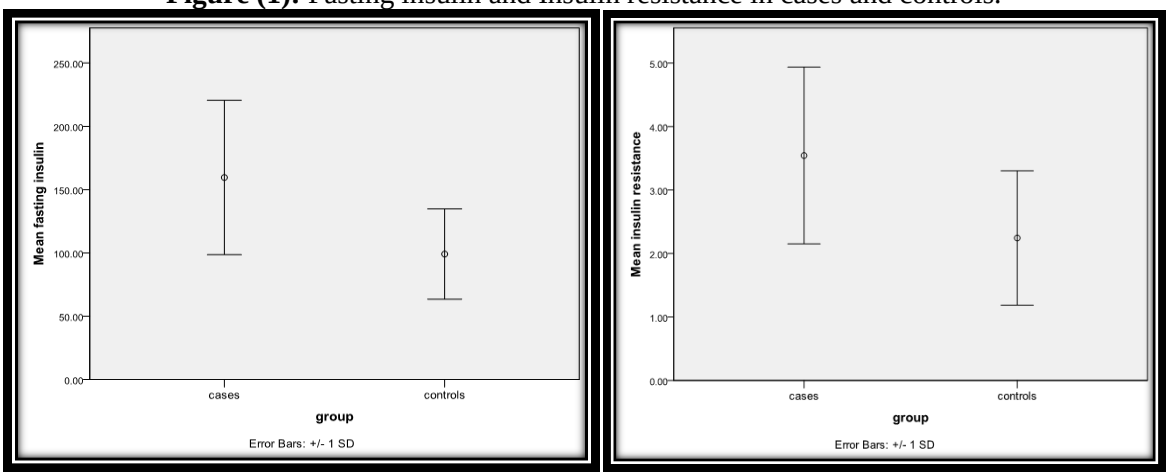


Figure (1): Fasting insulin and Insulin resistance in cases and controls.



Comparison between obese and non-obese PCOS cases regarding different parameters:

Table (2) shows that the adipoectin is a significantly lower in the obese cases than non obese PCOS cases (p value <0.001).Also regarding the hormonal profile, there is a significant difference between obese and non obese concerning LH and Testosterone while no significant difference regarding FSH and E2. This table shows that the insulin resistance is significantly lower in the obese cases then the non obese ones. (p value <0.001).

Table (2): Comparison between obese and non-obese PCOS cases regarding different parameters.

Parameters	Non-obese PCOS cases (N=21)			Obese PCOS cases (N=21)			t*	P value
	Range	Mean	SD	Range	Mean	SD		
Adiponectin(ng/dl)	1.19-2.50	1.71	0.46	0.06-0.30	0.15	0.06	15.42	**<0.001**
FSH (mIU/mL)	2.32-8.34	4.93	1.90	2.78-9.50	5.83	1.93	1.52	0.14
LH (mIU/mL)	3.78-9.43	7.10	1.34	2.72-8.34	5.42	1.71	3.55	**0.001**
E2 (pg/mL)	18.35-57.43	28.27	8.47	14.58-44.71	30.97	7.68	1.08	0.29
Testosterone (ng/dL)	0.25-0.65	0.44	0.10	0.56-1.40	0.92	0.26	7.89	**<0.001**
fasting insulin (mIU/L)	80.00-160.00	125.10	23.54	95.00-322.00	194.10	67.65	4.415	**<0.001**
fasting glucose (mg/dl)	67.00-117.00	93.29	14.50	61.00-132.00	89.57	18.98	0.713	0.48
Insulin resistance	2.04-3.97	2.86	0.62	2.11-8.67	4.22	1.61	3.610	**0.001**

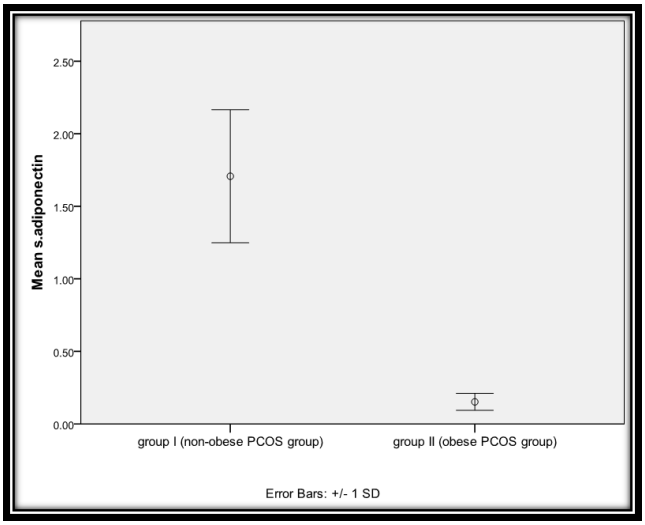


Figure (3): Serum adiponectin in obese and non-obese PCOS cases.

Correlation between serum Adiponectin level and different parameters in all PCOS cases (group I & II): Table (3) shows significantly negative correlation between adiponectin and BMI, LH, testosterone, fasting serum insulin and insulin resistance (p value<0.001).

Table (3): Correlation between serum Adiponectin level and different parameters in all PCOS cases (group I & II).

	Serum Adiponectin	
	r*	**P value**
Age (years)	0.08	0.63
BMI (kg/m^2)	-0.80	**<0.001**
Adiponectin (ng/dl)	-0.15	0.33
FSH (mIU/mL)	0.52	**<0.001**
LH (mIU/mL)	-0.13	0.43
E2 (pg/mL)	-0.74	**<0.001**
Testosterone (ng/dL)	-0.52	**<0.001**
fasting insulin (mIU/L)	0.09	0.58
fasting glucose (mg/dl)	-0.45	**0.003**

Correlation between serum Adiponectin level and different paramters in non-obese PCOS cases with (BMI <25 kg/m^2) (group I):

Table (4) shows no significant correlations between adiponectin and age, FSH, LH, E2, testosterone and insulin resistance among group I cases.

Table (4): Correlation between serum Adiponectin level and different paramters in non-obese PCOS cases.

	Serum Adiponectin	
	r*	**P value**
Age (years)	0.30	0.19
FSH (mIU/mL)	0.27	0.23
LH (mIU/mL)	0.37	0.10
E2 (pg/mL)	0.10	0.65
Testosterone (ng/dL)	-0.22	0.35
fasting insulin (mIU/L)	0.16	0.48
fasting glucose (mg/dl)	-0.11	0.65
insulin resistance	0.10	0.66

Correlation between serum Adiponectin level and different parameters in obese PCOS cases with (BMI >25 kg/m^2) (group II):

Table (5) shows no significant correlation between adiponectin and age, FSH, LH, E2, testosterone and insulin resistance among group II cases.

Table (5): Correlation between serum Adiponectin level and different parameters in obese PCOS cases**.**

	Serum Adiponectin	
	r*	**P value**
Age (years)	-0.08	0.74
FSH (mIU/mL)	-0.24	0.31
LH (mIU/mL)	-0.21	0.36
E2 (pg/mL)	0.04	0.85
Testosterone (ng/dL)	0.16	0.50
fasting insulin (mIU/L)	-0.21	0.37
fasting glucose (mg/dl)	0.22	0.34
insulin resistance	-0.08	0.73

Multiple linear regression analysis for factors affecting level of serum Adiponectin:

Multiple linear regression analysis shows that age, presence of PCOS, BMI, fasting insulin level, fasting glucose level and insulin resistance have independent effect on serum adiponectin level (p value < 0.05).

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**Sig.**	**95.0% Confidence Interval for B**	
	B	**SE**	**Beta**			**Lower Bound**	**Upper Bound**
Age	.097	.047	.754	2.070	**0.042**	.004	.189
PCOS	-1.759	.590	-.352	-2.982	**0.004**	-2.933	-.585
BMI	-.159	.042	-1.306	-3.773	**<0.001**	-.243	-.075
Fasting insulin	.038	.012	1.531	3.117	**0.003**	.014	.063
fasting glucose	.067	.017	1.753	4.003	**<0.001**	.033	.100
insulin resistance	-2.113	.535	-1.917	-3.954	**<0.001**	-3.178	-1.049

DISCUSSION

In this study, comparison was done between PCOS cases and controls as regard serum adiponectin and the results showed that serum adiponectin level is significantly lower among PCOS cases than controls, also no significant difference was found regarding their hormonal profile except for testosterone level which was significantly higher among cases. As regard metabolic profile, the results showed a statistically significant higher level of both fasting insulin and insulin resistance (IR) in PCOS cases group in comparison to controls. The same results were concluded by **Chin et al.** who conducted a retrospective study on 422 patients, 224 women with PCOS and 198 women without PCOS, and evaluated the adiponectin levels in overweight/obese and lean women with polycystic ovary syndrome (PCOS) and concluded that Adiponectin was negatively correlated with insulin resistance (IR) and body mass index (BMI); The adiponectin was significantly lower in PCOS women than in those without PCOS [18].

In contrast to this study, **Orio et al.** examined obese and normal weight PCOS women, compared with obese and normal weight controls, both in PCOS women and controls, serum adiponectin levels were significantly lower in obese women compared with that in normal weight women, with no difference detected between PCOS and controls [19].

Comparison was done between obese and non-obese PCOS cases as regard serum adiponectin and the level were statistically significantly lower in obese PCOS cases in comparison to non-obese PCOS cases. The same comparison is done regarding testosterone level and insulin resistance (IR) and the level was statistically significant higher in obese PCOS cases in comparison to non-obese PCOS cases. These results are similar to **Ardawi et al.** who found that

adiponectin levels were significantly decreased in obese females and both in obese and lean females with PCOS, compared with that in lean women without PCOS. Thus it appears that the decrease in adiponectin that can be attributed to the PCOS is less than the decrease attributed to obesity itself [20].

In this study a correlation was done between serum adiponectin and hormonal & metabolic profile in all PCOS cases (obese and non-obese) and showed a negative correlation with BMI, LH level, testosterone level and insulin resistance (IR), but failed to show a correlation with either obese or non-obese PCOS cases alone. Which means that adiponectin was independently associated with PCOS. These results were similar to **Chin et al.** who concluded also that adiponectin was negatively correlated with insulin resistance, body mass index (BMI), and total testosterone.

Niafar et al. examined the role of adiponectin as a biomarker of insulin resistance in PCOS. Ninety women with PCOS (45 with and 45 without metabolic syndrome) were enrolled in this study. They concluded that Serum adiponectin levels were suppressed in patients with both metabolic syndrome and insulin resistance. Adiponectin could be used as a biomarker to distinguish the patients at a higher risk of diabetes and cardiovascular morbidity. Their findings indicate that adiponectin stands out as an independent factor that associates with insulin resistance among their patient population. The current study showed nearly the same results [21]. A similar finding of this study had been reported by **Mirza et al.** who concluded that serum adiponectin levels are independently associated with PCOS and are only partly explained by IR. The association of PCOS with low adiponectin level remained consistent and statistically significant after adjustment for BMI [22].

CONCLUSION

It could be concluded that PCOS was found to correlate with low adiponectin levels, independently of BMI. The findings in this study also indicate that circulating adiponectin levels could be treated as a biomarker of insulin resistance and that the adipocytokine and metabolic biomarker levels are significantly correlated. The relationships between adiponectin and insulin resistance and sensitivity, metabolic syndrome, and BMI in women with PCOS suggest that adiponectin potentially could serve as a marker for disease risk and provide opportunity for earlier intervention if knowledge is successfully translated from laboratory to clinical practice.

LIMITATIONS OF THE STUDY

The limitations of this study lie in the relatively small number of subjects in each group, affecting the statistical power.

RECOMMENDATIONS

Further research is required before adiponectin can be used as a biomarker for PCOS in clinical practice. The relevant "dose" for risk and where adiponectin falls in the pathway for the disease are essential pieces of knowledge for determining the range of utility. Differing adiponectin levels in women diagnosed with PCOS compared with "healthy" controls suggest biomarker application, especially as noted for prepubescent girls. Determination of "normal" ranges of adiponectin in the population and/or standardization of ranges for given ages or BMIs is essential, as is a delineation of what level of adiponectin is reflective of imminent or actual disease. These standards would be extremely valuable if it turned out that adiponectin could serve as a marker for risk prior to the development of the disorder. Such early detection would, in turn, aid in the development of treatment modalities to prevent PCOS, itself, or at least some of the negative consequences of the disorder. An understanding of the underlying biological mechanism/mechanisms of PCOS would enable development of new treatment options.

REFERENCES

1. **Costello M and Ledger W (2012):** Evidence-based lifestyle and pharmacological management of infertility in women with polycystic ovary syndrome.Womens Health (Lond Engl),8(3): 277-290.
2. **Rotterdam ESHRE/ASRM- (2004):** Sponsored PCOS Consensus Workshop Group:Revised consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril., 81:119
3. **Lerchbaum E and Obermayer-Pietsch B (2012):** Mechanisms in endocrinology: Vitamin D and fertility: a systematic review. Eur J Endocrinol., 166(5): 765-778.
4. **Rouzi and Ardawi (2009):** Serum calcitropic hormones in Saudi women with polycystic ovary syndrome: a prospective study. Fertil Steril.,92: 106.
5. **Celik C, Tasdemir N, Abali R (2014):** Progression to impaired glucose tolerance or type 2 diabetes mellitus in polycystic ovary syndrome: a controlled follow-up study. Fertil Steril.,101:1123–1128.
6. **Cho L, Randeva H, Atkin S (2007):** Cardiometabolic aspects of polycystic ovary syndrome. Vasc Health Risk Manag., 3:5.
7. **Gulcelik N, Aral Y, Serter R (2006):** Adiponectin is an independent determinant of insulin resistance in

women with polycystic ovary syndrome. Gynecol Enocrinol., 511:522.

8. **Wang Y, Zhu J and DeLuca H (2012):** Where is the vitamin D receptor? Arch Biochem Biophys., 523(1):123-133.
9. **Dalamaga M , Diakopoulos K , Mantzoros (2012):** the CS . At The Role of with Adiponectin in Cancer: A Review of Current Evidence [J]. Endocr Rev. , 33 (4): 547 - 594 .
10. **Yilmaz M1, Bukan N, Demirci H, Oztürk C, Kan E, Ayvaz G, Arslan M (2009):** Serum resistin and adiponectin levels in women with polycystic ovary syndrome. Gynecol Endocrinol., 246-252
11. **Matsuzawa Y (2005).** Adiponectin: Identification, physiology and clinical relevance in metabolic and vascular disease. Atherosclerosis Supplements, 6: 7-14.
12. **Mattu H and Randeva H (2013):** Role of adipokines in cardiovascular disease. J Endocrinol., 216(1): T17-36.
13. **Svendsen P, Christiansen M, Hedley P et al. (2012):** Adipose expression of adipocytokines in women with polycystic ovary syndrome. Fertil Steril., 98: 235–341.
14. **Galic S, Oakhill JS, Steinberg GR (2010):** Adipose tissue as an endocrine organ. Mol. Cell. Endocrinol., 316: 129-139.
15. **Pittas A G, Joseph N A & Greenberg A S (2004):** Adipocytokines and insulin resistance. Journal of Clinical Endocrinology and Metabolism, 89: 447-452.
16. **Trujillo M, Scherer P (2005):** Adiponectin – journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med.,257:167–175.
17. **BIOMATIK**: life Science Products and Services; Enzyme-Linked Immunosorbent Assay kit for Adiponectin (ADP); www.biomatik.com
18. **Chin CI, Hsu MI, Lin SH, Chang YCI, Hsu CS and Tzeng CR (2015):** Adiponectin and leptin in overweight/obese and lean women with polycystic ovary syndrome. Gynecological Endocrinology, 31(4): 264-268.
19. **Orio F, Palomba S, Zullo F (2004):** Are serum adiponectin levels really reduced in obese women with polycystic ovary syndrome? Human Reproduction; 19: 215–216.
20. **Ardawi MS and Rouzi AA (2005):** Plasma adiponectin and insulin resistance in women with polycystic ovary syndrome. Fertility and Sterility; 83: 1708–1716.
21. **Niafar M, Nader ND (2015):** Adiponectin as serum biomarker of insulin resistance in patients with polycystic ovarian syndrome. Gynecol Endocrinol.,31(6):473-476.
22. **Mirza SS, Shafique K, Shaikh AR, Khan NA and Qureshi MA (2014):** Association between circulating adiponectin levels and polycystic ovarian syndrome. Journal of Ovarian Research, 7(1): 18.