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PON1, Adiponectin and Visfatin: Predictors of CVD in women with PCOS

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Abstract

Background: One of the main causes of female infertility is polycystic ovarian syndrome (PCOS). Adipokines, such as visfatin and adiponectin, are released by adipose tissue. Visfatin mimics the effects of insulin. Visfatin mimics the actions of insulin by binding to the insulin receptor at a different site than insulin. Adiponectin is a Protein produced almost exclusively by adipocytes. Exerts strong insulin-sensitizing, anti-atherogenic, anti-inflammatory, and anti-diabetic effects. However, low levels are associated with obesity, IR, metabolic syndrome, T2DM, and CVD. Serum paraoxonase 1 (PON1) level is an antioxidant associated with HDL complex. Diminished activity of PON1 enzyme and increased levels of malondialdehyde (MDA) has been reported in variety of diseases involving oxidative stress. The CRP Elevated serum levels of CRP reflects chronic inflammation

Objective: To compare the serum levels of PON1,Visfatin ,Adiponectin , MDA and CRP in obese and normal women with PCOS with their respective controls.

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Materials and methods: Case-control study was carried out at the Biochemistry Department, Koppal Institute of Medical Sciences, Koppal, India from July 2015 to March 2018. It included 100 women with PCOS (50- obese and 50 normal) and 100 control subjects (50- obese and 50 normal), aged 18 to 40 years. Visfatin, Adiponectin, PON 1, CRP and Malonaldehyde (MDA) were estimated.

Results: Serum levels of PON1 and Adiponectin were significantly decreased and Visfatin and MDA levels were increased in women with PCOS irrespective of BMI compared to their respective controls with a p value of <0.001, suggesting a significant inverse correlation between PON1 activity and Adiponectin and Visfatin,CRP and MDA concentrations in women with PCOS irrespective of BMI.

Conclusions: Women with PCOS have increased oxidative stress irrespective of BMI indicated by decreased serum PON1 and Adiponectin and increased levels of serum MDA, CRP and Visfatin. PCOS women should be evaluated for oxidative stress and antioxidant, which can be beneficial in preventing coronary vascular diseases. Hence they can serve as markers in women with PCOS.

Key words: Polycystic ovarian syndrome, Visfatin, Adiponectin, CRP, MDA and PON 1.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine metabolic disorder characterized by oligo- or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovary disease (PCO). It occurs in 5 to 10 percent of women of reproductive age.[1] Patients with PCOS are at increased risk for the development of diabetes mellitus, hypertension and atherosclerotic heart disease. Women with PCOS have oxidative stress (OS) which plays a key role in the pathogenesis of cardiovascular disease (CVD). Malonaldehyde (MDA) produced during the decomposition of polyunsaturated fatty acids, is one of the stable end products of lipid peroxidation that can serve as a good biomarker.[2,3]

Paraoxonases enzyme is synthesized by liver and is associated with high-density lipoproteins (HDL). It plays an important role in protection against oxidative damage and lipid peroxidation, contribution to innate immunity, detoxification of reactive molecules, bioactivation of drugs, modulation of endoplasmic reticulum, stress and regulation of cell proliferation and apoptosis.[4].It possess anti-atherogenic and anti-inflammatory properties, resulting from its ability

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to destroy modified phospholipids and to prevent accumulation of oxidized lipids in lipoproteins.[1].Lower serum PON1 activity is observed in patients with cardiovascular diseases.[5]

Visceral adipose tissue releases various adipokines such as leptin, adiponectin, resistin, vaspin [6] and visfatin, which have influences on IR. [7] Visfatin exhibits insulin-like activity and has been shown to activate the insulin receptor in various insulin-sensitive cell types in vitro, stimulate glucose uptake into adipocytes and muscle cells, and suppress glucose release from hepatocytes in vitro.[8,9] Adiponectin, a protein produced almost exclusively by adipocytes, is considered to exert insulin sensitizing, anti-atherogenic, anti-inflammatory and anti-diabetic action in high levels and Low levels are associated with obesity, insulin resistance, metabolic syndrome, T2DM, and CVD. [10,11]

A study done by Kelly CCJ et al, showed that low grade chronic inflammation as reflected by increased C-reactive protein concentrations independently predicts those at risk for coronary heart disease and type 2 diabetes.The probable cause of rise in hs-CRP in obese individuals is due to an increase in the secretion of cytokines from adipose tissue [12].

The aim of the present study was to compare serum levels of PON1 activity, Adiponectin, Visfatin, CRP and MDA in obese and normal women with PCOS with their respective controls.

MATERIALS AND METHODS

A case control study was conducted on 100 diagnosed PCOS patients (50- obese (BMI >30) and 50 normal (BMI <25) and 100 controls (50-obese and 50 normal) in the age group of 18-40 years. Fasting blood sample of 5.0 ml was obtained from each participant. Serum CRP, visfatin adiponectin and were measured by Enzyme-linked immunosorbant assay (ELISA). Serum malonaldehyde (MDA) was determined by thiobarbituric acid reactive substances (TBARS). Ethical approval was obtained from the Ethics Committee of the college. Informed consent was obtained from the participants. Physical examination of each subject was carried out. The height and weight of all individuals were measured. Body mass index (BMI) was calculated as kg/m2. Diagnosis of PCOS was done according to the Rotterdam ESHRE revised consensus 2003. Women suffering from any known diseases like diabetes mellitus, thyroid disease, malignancy, hypertension, cardiovascular diseases, renal failure, Cushing's syndrome, prolactinoma and

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history of taking any other medication such as lipid lowering drug, oral contraceptives pills, ovulation induction, antiobesity drugs antidiabetic and antihypertensive drugs within 6 months were excluded. The control group was composed of female volunteers without concomitant disease, aged 18-40 years, BMI < 25 and BMI >30, who had regular menstrual cycles and no signs of clinical and biochemical hyperandrogenism.

PON 1 was determined by using p-nitro phenol acetate as substrate and the increase in absorbance at 412 nm due to formation of p-nitro phenol was read (14&15). PON1 activity was assessed by the rate of enzymatic hydrolysis of 1.0 mmol/l paraoxon (*O*,*O*-diethyl-*O*-*p*-nitrophenylphosphate; Sigma Chemical Co.) to *p*-nitrophenol in 1 mmol/l CaCl2 and 2 mmol/l NaCl The amount of *p*-nitrophenol generated was monitored with a continuously recording spectrophotometer (UV-1601 Shimadzu) by the increase in absorbance at 412 nm and 25□C. The amount of *p*-nitrophenol generated was calculated from the molar absorbtivity at pH 8.0, which was 17 000/mol/cm. One unit of PON1 activity is defined as 1 nmol of 4-nitrophenol formed per minute, under the above assay condition (Gan *et al.*, 1991; Mackness *et al.*, 1991) in 0.1 mol/l Tris–HCl (pH 8.0) at a final concentration of 1.2 mmol/l.

Statistical Analysis Statistical analysis:

All the experimental data were expressed as mean±SE. The data were analyzed by one-way analysis of variance (ANOVA) followed by Student Newman Keul's multiple comparison tests. $p<0.05$ was considered statistically significant. SigmaPlot13 was used for statistical analysis and for plotting the graph (Systat Software, USA).

RESULTS

The levels of Paraoxonase in control subjects (Con-Normal, Con-Obese) and PCOS (PCOS-Normal, PCOS-Obese) and were 201.4 ± 0.9, 189.1 ± 10.5, 172.0 ± 6.4 and 156.5± 9.6 respectively. All the groups showed significant difference.

Serum levels of Visfatin were increased in obese women with PCOS 22.99±1.39 and non-obese women with PCOS 13.93±1.21 when compared to their controls 6.91±1.11 and 7.19± 1.13 respectively with a p value of <0.001.

Serum levels of Adiponectin were decreased in obese women with PCOS 6.99±0.50 and non-obese women with PCOS 8.21±0.45 when compared to their controls 10.79±0.71and 13.84±0.61 respectively with a p value of <0.001.

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There were higher levels of serum CRP in obese women with PCOS (12.14±1.26) and non-obese women with PCOS (8.78±1.38) compared to their controls respectively (7.79±3.12 and 3.04±1.99) with a p value of <0.001.

The levels of MDA in control subjects (Con-Normal, Con-Obese) and PCOS (PCOS-Normal, PCOS-Obese) and were 1.9 ± 0.4, 3.9 ± 0.4, 5.5 ± 0.3 and 7.1± 0.5 respectively. All the groups showed significant difference.

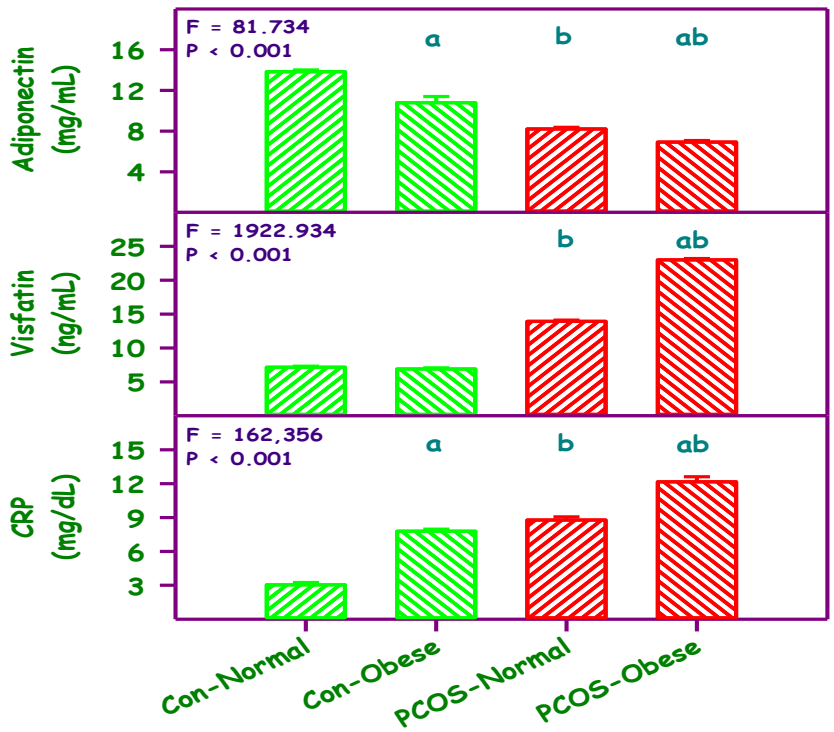

Figure 1: Comparison of serum adiponectin, visfatin and CRP in control (con) and PCOS women. Con-normal, con-obese, PCOS-normal and PCOS-obese.

The values are mean ± SE (n = 50 each)

The 'F' and 'P' values are by one way ANOVA with Student Newman Keul's multiple comparison test.

a Significantly different from the respective normal and obese groups.

b Significantly different from the respective control and PCOS groups.

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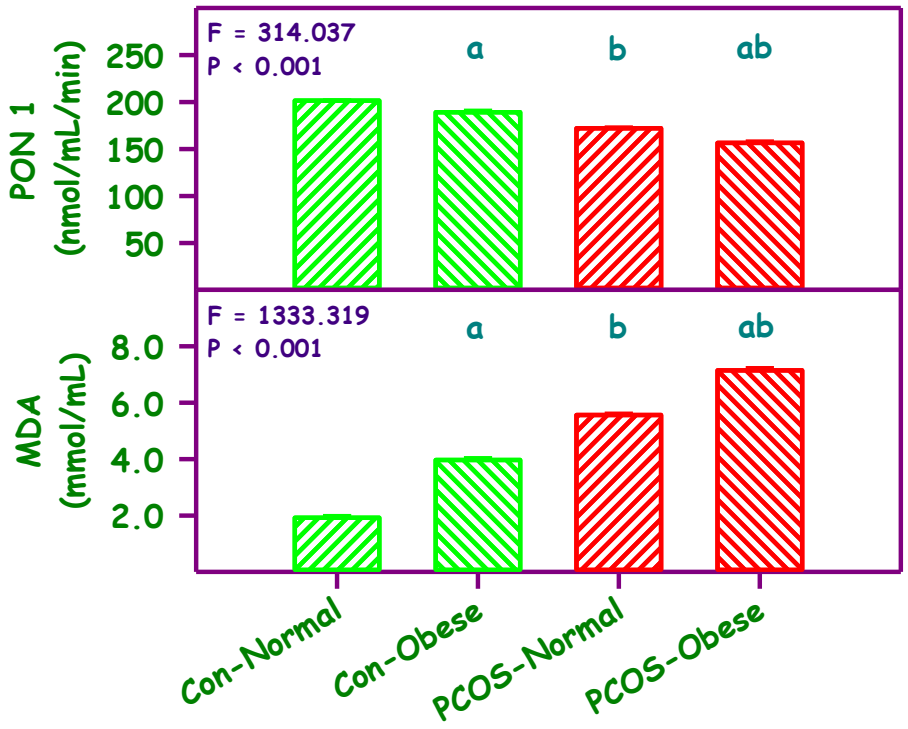

Figure 2: Comparison of MDA and paraoxinase 1 (PON 1) in control (con) and PCOS women. Con-normal, con-obese, PCOS-normal and PCOS-obese).

The values are mean ± SE (n = 50 each)

The 'F' and 'P' values are by one way ANOVA with Student Newman Keul's multiple comparison test.

a Significantly different from the respective normal and obese groups.

b Significantly different from the respective control and PCOS groups.

DISCUSSION

In the present study, visfatin levels were found to be significantly elevated in both obese and non obese women with PCOS as compared to their respective controls, showing a positive correlation between visfatin and indices of obesity (BMI). Similar observations were made by Chan et al, [13] Dikmem et al, [14] Sommer G et al, [15] and Yamam AD et al.[16]

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Visfatin activates its target cells by binding to the insulin receptor, at a site distinct from insulin, and exerts a variety of insulin-mimetic effects, including enhancing glucose uptake and increasing triglyceride synthesis.[7] High visfatin levels may suggest an impaired mechanism of visfatin signaling in target tissues in state of insulin resistance. They reflect a compensatory response to tissue-specific IR and hyperinsulinemia or an intrinsic dysregulation in visfatin biosynthesis. Visfatin are secreted from visceral adipose tissue more than subcutaneous one, so increased visceral adipose tissue is associated with increased production of visfatin. [17]

In the present study, adiponectin levels were found to be significantly reduced in both obese and non obese women with PCOS as compared to their respective controls, independent of insulin resistance, showing a negative correlation between adiponectin and indices of obesity (BMI). Similar observations were made by Vardhana et al,[18] svendsen et al,[19] Aroda et al,[20] Escobar-Morreale et al, [21]Glintborg et al.[22] However, Some studies have reported the converse Orio et al,[23] Panidis et al,[24] Spranger et al,[25] and inconsistent adiponectin levels were reported by Lewandowski et al.[26]

Adiponectin, a 247 amino acid polypeptide, secreted predominantly from adipose tissues, is inversely related with obesity, metabolic syndrome and insulin resistance.[27] Regulation of glucose and lipid metabolism via stimulation of fatty acid oxidation, suppression of hepatic glucose output and increased insulin sensitivity in liver and skeletal muscles are known to be key roles of adiponectin. Lean and obese women with PCOS have a higher trunk-to-peripheral fat ratio than respective women without PCOS. This effect may account for the lack of association between body weight and insulin sensitivity.[28] According to Susan[12] there may be an alternative explanation other than insulin resistance. High levels of androgen may also be the possible explanation.

The two adiponectin receptors (adipoR1& 2 have decreased expression in obesity. However, in women with PCOS these receptors are up regulated in both subcutaneous and visceral fat tissue. In all women, expression of adipoR1 is positively correlated with insulin, androgen index (testosterone/SHBG × 100), and testosterone in both types of fat and negatively correlated with SHBG. [29]

According to Sir-Petermann et al,[30]it is possible that the metabolic abnormalities of PCOS are present prior to hyperandrogenism and that adiponectin could be used as a susceptibility biomarker for girls at risk for development of PCOS.

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Serum levels of MDA was significantly elevated in both obese and non obese PCOS (P= <0.005). Similar observatios were made by various other studies. Mandal et al,[31] Zhang et al,[32] Palacio et al,[33] and Fenkci et al.[34]

MDA an oxidant marker correlates with the extent of lipid peroxidation. Free radicals in the body stay for a short duration before achieving stability by colliding with another molecule to either receive or donate an electron, in the process they generate another free radical (ROS). These ROS targets proteins, carbohydrates, nucleic acids and polyunsaturated fatty acids (PUFA), present in the cell membrane known as lipid peroxidation forming various end products. This process is opposed by antioxidant enzymes thus redox balance of cell. The imbalance between oxidants and antioxidants leads to Oxidative Stress. [35]

Serum levels of PON 1 an anti inflammatory marker was significantly decreased in both obese and non obese PCOS (P= <0.005). Similar observatios were made by various other studies. Karabulut AB et al,[36] Mandal B et al, [37] Zhang D et al,[38] Palacio JR et al, [39] and Fenkci V et al[40].

Oxidative stress and reduced serum paraoxonase lead to insulin resistance and type 2 diabetes mellitus.[41] LDL particles can be protected from free radical-induced oxidation by an HDL linked enzyme, paraoxonase 1 (PON1).[20] PON1 is inversely associated with atherosclerotic processes, in which ox-LDL plays a significant role. [42].

PON1 plays an important role in preventing oxidative stress and controlling inflammation, and the absolute or relative lack of PON1 lactonase activity contributes to PCOS.[1]

In our study there was increased serum levels of CRP in both obese and non obese PCOS patients compared to controls. Similar observations were made by Gonza´ lez F *et al*.[43]

Hepatocytes produce CRP, one of the markers of inflammation under the influence of pro-inflammatory cytokines like Tumor necrosis factor- α (TNF α) and interleukins 1 and 6. The significantly increased serum level of CRP indicates presence of low grade inflammation.[44]

Conclusion

Our findings conclude that Women with PCOS irrespective of obesity have increased oxidative stress and inflammation indicated by elevated levels of CRP, MDA and Visfatin. They have decreased antioxidants indicated by decreased levels of adiponectin and PON 1 irrespective of

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obesity. PCOS women should be evaluated for oxidative stress and antioxidant, which can be beneficial in preventing coronary vascular diseases. Detection of these markers can reduce the overall morbidity and enhances the prognosis of PCOS. Hence they can serve as markers in women with PCOS.

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Table 1: Comparison of serum adiponectin, visfatin, C-reactive protein (CRP), paraoxonase (PON 1) and MDA in control (con) and PCOS women.

S.NO	Parameter	Groups	Mean ± SE	Statistical analysis
1	Adiponectin (mg/mL)	Con-normal	13.8 ± 0.1	Figure 6.1
		Con-obese	10.7 ± 0.6	
		PCOS-normal	8.2 ± 0.1	
		PCOS- obese	6.9 ± 0.1	
2	Visfatin (ng/mL)	Con-normal	7.1 ± 0.1	Figure 6.1
		Con-obese	6.9 ± 0.1	
		PCOS-normal	13.9 ± 0.1	
		PCOS- obese	22.9 ± 0.1	
3	CRP (mg/dL)	Con-normal	3.0 ± 0.1	Figure 6.1
		Con-obese	7.7 ± 0.1	
		PCOS-normal	8.7 ± 0.2	
		PCOS- obese	12.1 ± 0.4	
4	PON 1 (mmol/Ml/min)	Con-normal	201.4 ± 0.1	Figure 6.2
		Con-obese	189.1 ± 1.4	
		PCOS-normal	172.0 ± 0.9	
		PCOS- obese	156.5 ± 1.3	
5	MDA (mmol/mL)	Con-normal	1.9 ± 0.0	Figure 6.2
		Con-obese	3.9 ± 0.0	
		PCOS-normal	5.5 ± 0.0	
		PCOS-obese	7.1 ± 0.0	
Values are expressed as Mean ± SE,(n=50 each)				