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Original Article

Serum Levels of Uric Acid in Females of Polycystic Ovarian Syndrome with and without Insulin Resistance

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ABSTRACT

Females suffering from polycystic ovarian syndrome have marked insulin resistance, independent of obesity. These women also have multiple risk factors for cardiovascular diseases, such as dyslipidemia, insulin resistance and hypertension. Uric acid level has also been recognized recently as a risk factor for cardiovascular diseases, females with PCOS may have abnormal profile of uric acid. **Objectives:** To compare uric acid levels in females of polycystic ovarian syndrome with and without insulin resistance. **Methods:** Cross-sectional comparative study was conducted in Biochemistry Department of Islam Medical College, Sialkot. Patients were divided into 2 groups based on their insulin resistance. In group-A patients were taken with PCOS and in group-B patients were taken with PCOS without insulin resistance. A total of 108 cases (54 in each group) fulfilling the inclusion/exclusion criteria. In both groups uric acid level was measured by standard procedure. Data were entered and analyzed using SPSS version 22 accordingly. **Results:** The mean age for all the cases was 29.43 ± 4.08 years, while mean age in insulin resistance group was 29.33 ± 4.06 years and mean age in non-insulin resistance group was 29.52 ± 4.13 years. The mean uric acid in insulin resistance and non-insulin resistance group was 4.92 ± 0.89 mg/dl and 4.48 ± 0.95 mg/dl with significantly higher mean uric acid in insulin resistance group, p-value < 0.05. **Conclusion:** We conclude that females having PCOS with insulin resistance had higher mean uric acid levels. Females with insulin resistance must be prevented from hyperuricemia to minimize the further risk of insulin resistance.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a very diverse endocrine abnormality of the females. Anovulation, hyperandrogenism, infertility, and metabolic dysfunctions are the main characteristic features of this disease [1, 2]. Increased prevalence trend of insulin resistance and its related abnormalities has been noticed in female having PCOS [3]. In the process of atherosclerosis, chronic inflammation and endothelial dysfunction are major early defects. The exact etiology of PCOS is not known but different theories exist about the pathogenesis of PCOS. One of the major underlying causes of polycystic ovarian syndrome is relative insulin resistance [4, 5]. This relative insulin resistance leads to chronic hyperinsulinemia which leads to impaired growth of ovarian follicles, irregular metabolism of ovarian androgen and altered response of gonadotropins [6, 7]. An organic acid called uric acid (UA) is formed during the metabolism of purine nucleotides. Elevated serum uric acid (SUA) is intimately linked to metabolic diseases such metabolic syndrome, type 2 diabetes, insulin resistance, and obesity. Reproductive hormones have reportedly been shown to impact SUA levels [8]. Through mechanisms involving renal secretion

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clearance and reabsorption, estradiol (E2) may have an impact on the SUA level. The concentration of UA is positively correlated with follicle-stimulating hormone (FSH), while E2 and progesterone (P) levels are negatively correlated with the concentration of UA [9, 10]. Additionally, there was a correlation between a greater UA level and a higher likelihood of anovulation. The relationship between different endocrine hormone alterations in women and the SUA level is not well understood. According to various diagnostic criteria, 4–18% of women of reproductive age have polycystic ovarian syndrome (PCOS), a widespread endocrine and metabolic disorder. The reproductive hormones androgen, the luteinizing/follicle-stimulating hormone (LH/FSH) ratio, and estrogens are frequently disturbed in women with PCOS [11]. It is yet unclear if the hormonal imbalance in PCOS has an impact on the SUA level and the prevalence of hyperuricemia. Rare studies that evaluate the SUA level in PCOS are available, and those that do offer inconsistent findings [12]. Due to the variability of PCOS, we expected that these studies with limited sample sizes could not draw a firm conclusion. The objective of this study was to compare uric acid levels in females of polycystic ovarian syndrome with and without insulin resistance.

METHODS

This Cross-sectional comparative study was conducted in the Biochemistry Department of Islam Medical College, Sialkot in collaboration with Islam Teaching Hospital, Sialkot. A total of 108 females were taken in this study selected using non-probability purposive sampling. Patients were divided into 2 groups based on their insulin resistance. Group-A: In this group patients were taken with PCOS and insulin resistance. Group-B: In this group patients were taken with PCOS without insulin resistance. All patients in the age group of 20-40 years diagnosed with PCOS using Rotterdam criteria, visited in outpatient's department of Gynecology, Islam Teaching Hospital, Sialkot was the inclusion criteria. The subjects having hypertension, coronary heart disease, diabetes mellitus, cushing's syndrome, renal diseases, liver cirrhosis, inflammatory intestinal diseases and malabsorption syndromes were excluded. Subjects on vitamin supplementation, diuretic medications and with history of alcohol and smoking were also not included. HOMA-IR (Homeostatic Model Assessment-Insulin Resistance) was used for the determination of the Insulin resistance. Blood glucose level was measured by the enzymatic colorimetric method. Serum uric acid was measured by the enzymatic colorimetric method. Serum insulin level was determined by the ELISA (Enzyme-Linked Immunosorbent Assay).

$$\text{HOMA} - \text{IR} = \frac{\text{Fasting insulin (µlU/ml)} \times \text{Fasting glucose (mg/dL)}}{405}$$

All data were entered and analysed using SPSS version 220.. Qualitative data like gender were presented in form of frequency (%). The quantitative data like age and uric acid were presented in form of mean ± S.D. Independent sample *t* test was used to compare uric acid level in both study groups. p-value ≤ 0.05 was considered as significant.

RESULTS

The mean age of cases was 29.43 ± 4.08 years. The mean age in insulin resistance group was 29.33 ± 4.06 years and mean age in non-insulin resistance group was 29.52 ± 4.13 years. The median age in both groups was same (Table 1).

Age (years)	No. of cases	Mean ± S.D	Median	IQR
Insulin resistance	54	29.33 ± 4.06	28.50	7.00
Non-insulin resistance	54	29.52 ± 4.13	28.00	5.25
Total	108	29.43 ± 4.08	28.00	6.00

Table 1: Comparison of Age (years) in both study groups

The mean weight in insulin resistance and non-insulin group was 78.04 ± 11.36 (kg) and 75.91 ± 11.32 (kg) respectively, the mean height in insulin resistance and non-insulin group was 1.56 ± 0.08 and 1.60 ± 0.09 m. The mean BMI in insulin resistance and non-insulin group was 32.04 ± 4.08 and 29.79 ± 3.78 respectively. The mean weight was insignificant in both groups, p-value > 0.05 while mean BMI in insulin resistance group was significantly higher than non-insulin group, p-value < 0.05 (Table 2).

Parameter		No. of cases	Mean ± S.D	t-test (p-value)
Weight (kg)	Insulin resistance	54	78.04 ± 11.36	0.235 (0.331)
	Non-insulin resistance	54	75.91 ± 11.32	
	Total	108	76.97 ± 11.34	
Height (m)	Insulin resistance	54	1.56 ± 0.08	0.976 (0.031)
	Non-insulin resistance	54	1.60 ± 0.09	
	Total	108	1.58 ± 0.09	
BMI	Insulin resistance	54	32.04 ± 4.08	2.97 (0.004)
	Non-insulin resistance	54	29.79 ± 3.78	
	Total	108	30.91 ± .07	

Table 2: Comparison of Weight (kg), Height (m) and BMI in both study groups

The mean Uric acid in insulin resistance and non-insulin group was 4.92 ± 0.89 mg/dl and 4.48 ± 0.95 mg/dl with significantly higher mean uric acid in insulin resistance group, p-value < 0.05 (Table 3).

Variables	Insulin resistance	Non-insulin resistance	Total
No. of cases	54	54	108
Mean ± S.D	4.92 ± 0.89	4.48 ± 0.95	4.70
Minimum	3.20	2.60	2.60
Maximum	6.91	6.84	6.91
p-value	<0.05	0.521	0.552

Table 3: Comparison of Uric acid levels in both study groups

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DISCUSSION

Polycystic ovarian syndrome (PCOS) is a widespread female endocrinopathy that affect around 5% females of reproductive age group. In the women of reproductive age group, PCOS is a very commonly found hormonal disorder [13]. According to Paradisi *et al.*, and different studies, the prevalence of PCOS has increased in the sub continental region during the recent past, in Indian Kashmiri women it is 37.3% and Pakistani women it is 20.7% [14, 15]. The mean age of cases was 29.43 ± 4.08 years. The mean age in insulin resistance group was 29.33 ± 4.06 years and mean age in non-insulin resistance group was 29.52 ± 4.13 years. The median age in both groups was same (Table 1). Cardiovascular risk factors are associated with PCOS as demonstrated by different studies. Common clinical features of PCOS which include hyperandrogenism, oligo/amenorrhea, insulin resistance and obesity [16]. Increased prevalence trend of insulin resistance and its related abnormalities has been noticed in female having PCOS. In the process of atherosclerosis, chronic inflammation and endothelial dysfunction are major early defects. Tzeng *et al.*, and Leustean *et al.*, also describe the relationship between elevated urid acid serum levels that reflect low-grade chronic inflammation. The metabolic disturbances associated with PCOS like insulin resistance, hyperandrogenism, and hypertension may adversely accelerate the cardiovascular risk profile in these women [17, 18]. Polycystic ovarian syndrome is not only a reproductive abnormality but also known as a very important metabolic disorder, having increased risk of diabetes mellitus and cardiovascular diseases. Women suffering from PCOS also have insulin resistance, independent of obesity. The mean weight in insulin resistance and non-insulin group was 78.04 ± 11.36 (kg) and 75.91 ± 11.32 (kg) respectively, the mean height in insulin resistance and non-insulin group was 1.56 ± 0.08 and 1.60 ± 0.09 m. The mean BMI in insulin resistance and non-insulin group was 32.04 ± 4.08 and 29.79 ± 3.78 respectively. The mean weight was insignificant in both groups, p-value > 0.05 while mean BMI in insulin resistance group was significantly higher than non-insulin group, p-value < 0.05 (Table 2). Studies have shown that uric acid has inflammatory, proliferative and oxidative actions at endothelial level, thus increasing the cardiovascular risk. Studies have been reported for inverse correlation in patient with metabolic syndrome between insulin sensitivity and uric acid and this shows the inherent feature of hyperuricemia as metabolic syndrome. These studies and data result in the consideration to use uric acid as diagnostic marker for identification of insulin resistance and metabolic syndrome. Two groups of Forty-two young women similar age, one with PCOS and other as control were designed to study relationship between lipoprotein level, uric acid and insulin resistance in obese and non-obese patients with PCOS. The key conclusions of the study revealed that HOMA-IR and Plasma uric acid levels were greater in patients with PCOS than in healthy women as compared with obese PCOS, non-obese PCOS subjects which shows higher TG, insulin, HOMA-IR and uric acid levels. Study also revealed no correlation among HOMA-IR, plasma uric acid and serum androgen. Hence there is an increased level of uric acid in PCOS as also describe by Luque-Ramírez *et al.*, [19, 20]. Serum uric acid elevated level may also exert pro-oxidant, proinflammatory, and proliferative role at the endothelial lining, increase cardiovascular risk leading to endothelial injury. In women suffering from PCOS both classical and non-classical risk markers for cardiovascular diseases are present and uric acid is considered among them. Relationship between obesity, insulin resistance and uric acid in obese and non-obese patients having PCOS was also explored by Zhang *et al.*,. They include thirty-eight obese and overweight women with PCOS and thirty control with same age group. Study didn't show and statistically significant finding and difference in uric acid levels between women with control and PCOS but contrary shows significant with obese PCOS patients having higher level of uric acid. Obese PCOS patient also had comparatively higher levels of HOMA-IR than overweight PCOS patients. However, a statically significant positive correlation was reported by the author between HOMA-IR and level of uric acid, BMI, insulin levels and waist circumference in PCOS group. The mean Uric acid in insulin resistance and non-insulin group was 4.92 ± 0.89 mg/dl and 4.48 ± 0.95 mg/dl with significantly higher mean uric acid in insulin resistance group, p-value < 0.05. In a recent study for the evaluation of traditional and non-traditional cardiovascular risk factors in women with PCOS, 40 diagnosed patients of PCOS and 40 healthy age and BMI matched controls were studied. Author has reported statistically significant raised levels of HOMA-IR, homocysteine, uric acid and CRP in patients of PCOS as compared to the control group. Women with PCOS are usually insulin resistant and exhibit hyperinsulinism. There is an inhibitory role of raised level of insulin on excretion of uric acid from kidney. This can be the explanation of raised levels of uric acid (though within the reference range) in patients with PCOS as compared to healthy control group. Uric acid level in PCOS women may also rise due to hepatic induction of purine metabolism by androgen. Moreover, as uric acid appeared as an early indicator of cardiovascular risk, hence, early interventions such as screening and treatment to lower down uric acid have been associated with prevention of cardiovascular outcomes. In a study of forty women with PCOS and forty non-hyperandrogenic

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women, levels of serum uric acid were measured [21, 22]. The study was further carried out by Krysiak *et al.*, and El-Eshmawy *et al.*, on thirty-four women with PCOS who were given either metformin or an oral contraceptive having ethyl estradiol with cyproterone acetate for 6 months. There was significant decrease in uric acid level in patients of PCOS due to correction of androgen levels with anti-androgenic contraceptive pill [23, 24]. In current study the mean uric acid in insulin resistance and non-insulin resistant group was 4.92 ± 0.89 mg/dl and 4.48 ± 0.95 mg/dl with significantly higher mean uric acid in insulin resistance group, p-value < 0.05.

CONCLUSIONS

We conclude that females having PCOS with insulin resistance had higher mean uric acid levels. Females with insulin resistance must be prevented from hyperuricemia to minimize the further risk as elevated levels of uric acid have been associated positively with insulin levels in a many clinical situations.

Conflicts of Interest

The authors declare no conflict of interest

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