ORIGINAL ARTICLE

RELATIONSHIP BETWEEN SERUM LIPOPROTEIN LEVELS AND INSULIN RESISTANCE IN NON-OBESE WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Background: To investigate the association between serum lipoprotein levels and insulin resistance in women with polycystic ovarian syndrome (PCOS). **Methods:** Twenty-five PCOS patients and twenty-five age-matched controls were enrolled in the study. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), fasting glucose (FBG), fasting insulin (FINS), serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C) levels were estimated. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to calculate the insulin resistance. **Results:** The mean arterial pressure, TAG, LDL-C, serum insulin, HOMA-IR and serum LH levels were significantly higher in PCOS patients as compared to healthy controls, whereas no significant differences in BMI, fasting glucose, serum cholesterol, HDL-C and FSH levels were observed between PCOS patients and controls. **Conclusion:** Serum lipoprotein ratio significantly correlates with insulin resistance and can be used as the marker of insulin resistance in PCOS patients.

Keywords: Polycystic ovary syndrome, lipoproteins, insulin resistance
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INTRODUCTION

The generally accepted clinical definition of polycystic ovary syndrome also known as Stein-Leventhal syndrome, implies on association of hyperandrogenism with chronic anovulation in women without a specific underlying disease of the adrenal or the pituitary gland.[1] Polycystic Ovary Sy ndrome (PCOS), is an endocrine disorder that affects 5–10% of women.[2] It was first described in medical literature in 1935 when Stein and Leventhal wrote about a group of women without menstrual periods and who had large ovaries with multiple cysts. It occurs among all races and geographical areas and is the most common hormonal disorder among women of reproductive age and is a leading cause of infertility.[3] In PCOS, the hormones including LH and insulin that signal the ovary, are out of balance, resulting in an ovarian dysfunction.[4]

PCOS is defined when two out of the following three features were present[5]:

- oligo- or anovulation
- clinical and/or biochemical signs of hyperandrogenism, and
- polycystic ovaries

Typical symptoms of PCOS include menstrual irregularity, excess hair growth on face, chest or abdomen due to increased androgen production, obesity and insulin resistance.[6,7] Patients with PCOS are also at risk for type 2 diabetes (T2DM), CVD, and hyperestrogen-related cancers. There is also a high risk of spontaneous abortion observed in women with PCOS.[8] However, there is a lot of variation in this disorder and symptoms can range from mild menstrual irregularity to complete lack of menstrual periods with failure of ovulation and severe abnormal hair growth.[9]

A high prevalence of insulin resistance and hyperinsulinemia in women with PCOS has been reported previously.[10] Insulin resistance is defined as the impaired ability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as compared to in a normal population. More severe degrees of insulin resistance are common in obese women with PCOS.[11] There are various mechanisms of insulin resistance. Factors leading to insulin resistance include among others a decrease in insulin binding due to autoantibodies to insulin receptors, post receptor defects, and a decrease in insulin receptor sites in target tissues are all involved in insulin resistance.[12] Insulin resistance is often associated with acanthosis nigricans.[13]

Insulin resistance is closely related to lipid disorders, and other risk factors of coronary artery disease even if the glucose metabolism is normal. Using biguanides or thiazolidinediones (TZDs) to treat insulin resistance in PCOS patients has achieved satisfactory clinical effects.

Increased serum concentrations of LDL-Cholesterol (LDL-C) are atherogenic whereas increased HDL-Cholesterol (HDL-C) is considered cardioprotective. Increased serum concentrations of triglycerides (TGs) have also been recognised as a risk factor for cardiovascular disease.

The aim of this research was to study the correlation between serum lipoprotein levels and insulin resistance in PCOS to provide new ideas for evaluation and treatment of PCOS with insulin resistance.

MATERIAL AND METHODS

This study included 25 patients with PCOS and 25 age-matched controls. All subjects were non-obese with a BMI<30. They were divided into two groups; Group 1 included 25 women of age 20–39 years with PCOS. Group 2 included 25 women without PCOS of similar age group. This was a case-control study. Consent was obtained from each subject by using an appropriately designed form. The protocol was approved by the Ethical Review Committee, University of Health Sciences, Lahore.

The following exclusion criteria were used in the selection of patients and controls; age less than 20 and more than 39 years, BMI of less than 18 and more than 30, pregnancy, diabetes, hypothyroidism, hyper-prolactinemia (>25 ηg/ml), Cushing's syndrome, non-classical congenital adrenal hyperplasia, and current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, anti-androgens, ovulation induction agents, anti-diabetic and anti-obesity drugs, any other hormonal drugs, women with clinical and/or biochemical hyper-androgenism alone, patients with history of any neoplasia or using anti-hypertensives. These factors were ruled out by using an appropriate questionnaire, status record, and physical examination.

The diagnosis of polycystic ovarian syndrome was made on the basis of combination of clinical, transvaginal ultrasound and biochemical criteria. A complete physical examination was performed on all subjects which included measurement of height, weight, heart rate, systolic (SBP) and diastolic (DBP) blood pressure. The mean blood pressure and body mass index (BMI) were calculated and recorded.

Five ml fasting blood samples were collected by venipuncture after complete aseptic measures from each subject and stored in two types of tubes. Two ml in grey top tubes containing EDTA for glucose estimation and 3 ml in red top plain tubes without additives or anti-coagulants. The blood was centrifuged at 3,000 rpm for 10–15 minutes. Serum was separated, glucose levels were measured and remaining serum sample was aliquoted and stored at -80 ºC until analysed.

Serum FSH, LH and insulin levels were determined by ELISA using commercially available kits (Monobind Inc, Lake Forest, CA, USA) with an automated EIA analyzer (CODA, Bio-Rad Laboratories, Hercules, CA, USA).[14]

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula[15]:

HOMA-IR=

Fasting insulin (μU/ml)×Fasting glucose (mmol/l)/22.5

Serum levels of glucose were determined by GOD/PAP method, triacylglycerides (TAG's) by GPO-PAP method, cholesterol (Enzyme Endpoint Method), HDL-C and LDL-C were measured by automatic chemistry analyzer.[14]

Data were analysed using student's *t*-test in SPSS-16, and $p<0.05$ was considered statistically significant.

RESULTS

The mean BMI values of the patients with PCOS and controls were not significantly different in the two age matched groups.

The mean arterial pressure, on the other hand, was significantly higher ($p<0.001$) in subjects with PCOS as compared to their age matched controls. PCOS patients had significantly higher ($p<0.005$) triacylglycerides (TAG) levels and LDL-C levels ($p<0.05$) as compared to their age matched controls whereas no difference in serum cholesterol and HDL-C levels was observed between the two groups.

No significant differences in fasting glucose levels were observed between PCOS patients and controls whereas PCOS patients had significantly higher ($p<0.05$) fasting insulin level. Insulin resistance as assessed by HOMA-IR was significantly higher in patients with PCOS as compared to respective controls.

Serum FSH levels between patients and their age matched controls were not significantly different whereas serum LH levels were significantly higher ($p<0.05$) in PCOS patients as compared to their respective control group. No significant differences were noted in LH/FSH ratio among PCOS and control groups (Table-1).

Table-1: Test parameters in control and PCOS

Parameters	Controls	PCOS
BMI (Kg/m^2)	21.8±1.02	23.3±0.67
MAP (mm Hg)	81.6±1.6	92.6±1.4*
Triglyceride (mg/dl)	121±8.64	155±8.33*
Cholesterol (mg/dl)	143±4.77	162±8.34*
HDL (mg/dl)	45.2±2.08	39.8±1.79*
LDL (mg/dl)	140±11.1	186±10.7*
Fasting glucose (mg/dl)	94.7±3.26	86.7±3.25
Fasting insulin (μIU/ml)	13.01±1.1	32.4±5.94*
LH (mIU/ml)	4.94±0.65	9.42±1.62*
FSH (mIU/ml)	6.76±1.28	6.57±0.55
LH/FSH ratio	1.45±0.41	1.71±0.33
HOMA-IR	3.0±0.3	7.26±1.45*

*$p<0.05$

DISCUSSION

In the present study conducted on premenopausal women, we found significant difference in lipid profile and insulin resistance between PCOS patients and their age-matched controls.

In our study, MAP was higher in women with PCOS compared to their age-matched controls. These findings confirm previous observations which demonstrate similar differences in blood pressure between controls and PCOS cases.[16–18] Serum TAG levels were shown to be significantly higher as

compared to their age matched controls. The mean cholesterol levels were within the normal range (<200 mg/dl). Peak estradiol levels during the follicular phase of menstrual cycle, and progesterone during the luteal phase were lower among the PCOS cases due to oligoovulation. If the increase in LDL-C is related to lower estradiol levels across time, the lack of change in ovarian function might possibly explain the slow rate of increase in LDL-C with age among PCOS cases versus controls. The non-significant increase in TC among controls with increasing age may be due to a general decline in ovarian function and is most likely the explanation for the difference in total cholesterol in relation to age among PCOS cases and controls.[19]

The PCOS has previously been complicated with insulin resistance that may lead to hyper-insulinemia and T2DM.[20] In our study, fasting insulin levels of PCOS patients were significantly higher than their age-matched controls.[21] Previously, based on observation that obese women with PCOS develop greater degree of insulin resistance has been interpreted as due to increase in body mass.[22] This possibility was ruled out in the present study by including non-obese PCOS and their age-matched controls. Hyper-insulinemia stimulates ovarian cytochrome P450c17 α activity in non-obese women with PCOS, thereby increasing serum androgen concentrations[23] and as a consequence, decreasing serum sex hormone-binding globulin (SHBG) concentration[24]. Hyperinsulinemia has also been reported to stimulate adrenal P450c17 α activity of some affected women.[25] In this study, fasting glucose levels in PCOS patients and controls were within the normal range but insulin levels were significantly raised in women with PCOS compared to controls. These observations indicate a tendency towards insulin resistance that is compensated by increased secretion of insulin sufficient to keep glucose levels in the normal range in these patients.

The present study supports the view of hyper-insulinemia and insulin sensitivity as salient features of the syndrome even in absence of obesity. In our study, mean LH levels were higher in PCOS group compared to their age-matched controls which, whereas no significant difference was observed between FSH levels. Patients with hyperinsulinemia and excess of LH have been regarded to constitute a distinct subgroup with increased adrenal androgenic activity.[26]

CONCLUSION

Serum lipoprotein ratios had significant positive correlation with insulin resistance in PCOS patients, which could be used as a simple, reliable, and economic indicator to evaluate insulin resistance. Thus, it had important clinical significance for diagnosis and treatment options of PCOS.

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