Indian Journal of Clinical Biochemistry, 2008 / 23 (3) 262-266

CORRELATION BETWEEN SERUM LIPID PROFILE AND CAROTID INTIMA-MEDIA THICKNESS IN POLYCYSTIC OVARIAN SYNDROME

Sarama Saha, Chandan Sarkar, Subhash Chandra Biswas* and R Karim**

*Departments of Biochemistry, *Obstericts & Gynaecology and **Radiodiagnosis, Institute of Post Graduate Medical Education and Research, Kolkata – 700 020, W.B*

ABSTRACT

Abnormal lipid profile is often found in women with Polycystic Ovary Syndrome. To assess the impact of abnormal lipid profile on atherosclerosis in young Polycystic Ovary Syndrome women, carotid intima-media thickness as judged by B-mode ultrasonography were done in 30 young (18-35 yrs) Polycystic Ovary Syndrome women and in similarly age-matched 30 apparently healthy controls. Compared to controls, young Polycystic Ovary Syndrome women had significantly elevated serum total cholesterol, triglyceride and LDL-C levels and carotid intima-media thickness. HDL-C level did not differ significantly between two groups of women. In Polycystic Ovary Syndrome women carotid intima-media thickness was positively correlated with serum total cholesterol, triglyceride and LDL-C and negatively correlated with serum HDL-C. Our study suggests that even young Polycystic Ovary Syndrome women are prone to atherosclerosis from early age.

KEY WORDS

Lipid Profile, Polycystic Ovary Syndrome, Carotid Intima-media thickness.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a disorder characterized by chronic anovulation, androgen excess, insulin resistance and often presence of obesity. In the early follicular phase of the menstrual cycle, PCOS women have increased serum LH and low or low normal serum FSH levels, with an increased ratio of LH to FSH. The increased LH secretion stimulates excess androgen production by the thecal cells of the ovary. The androgen by inhibiting production of sex hormone binding globulin (SHBG) causes excess free androgen level which is responsible for hirsutism.

Insulin resistance is an important feature of PCOS and the increase in androgens in PCOS is preceded by altered insulin action. Hyperinsulinemia by inhibiting hepatic synthesis of SHBG can cause hyperandrogenism. In addition, excessive insulin can bind insulin like growth factor – 1 (IGF – 1) receptors in the ovary (1) leading to increased androgen production by thecal cells. In the fibroblasts of 50% PCOS patients (PCOS-Ser), there is decreased insulin dependent receptor autophosphorylation of tyrosine residue and increased constitutive insulin receptor serine phosphorylation (2). It has been earlier shown that phosphorylation of serine or threonine residue of insulin receptor diminishes signal transduction (3). Hence, it could be the molecular mechanism of insulin resistance in PCOS patients.

It has been hypothesized that serine phosphorylation of adrenal and ovarian $P_{450\ c17}$ in PCOS patients increases adrenal and ovarian 17,20 lyase activity producing hyperandrogenism (4). Thus hyperandrogenism and insulin resistance may be related by a common mechanism.

It has been shown that women of PCOS have increased coronary heart disease risk factors including abnormal lipid profile (5). Hyperinsulinemia is often associated with dyslipidemia. It has also been shown that increased greater carotid artery intima-media thickness (IMT) as judged by B-mode ultrasonography is an indicator of generalized atherosclerosis and is a risk factor for myocardial infarction and stroke (6,7). Therefore we thought it prudent to correlate serum lipid profile and carotid intima-media thickness in PCOS.

Address for Correspondence :

Dr. Chandan Sarkar
Department of Biochemistry,
Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata – 700 020
E-mail : csarkar2347@rediffmail.com

Previously Guzick et al (8) and Talbott et al (9) assessed presence of subclinical atherosclerosis sonographically by measuring carotid IMT. These investigators found increased carotid IMT in middle aged women with PCOS compared to normal women of same age group. However, Talbott et al (9) could not find any difference of statistical significance of carotid IMT between PCOS cases and controls in the age group 30 – 44 years. We have seen PCOS cases among females of teens and twenties. We decided to study the carotid IMT and lipid profile mainly among patients of this age group (18-35 years).

MATERIALS AND METHODS

The study was carried out on 30 PCOS women and 30 apparently normal healthy women in the department of Biochemistry, IPGME&R, Kolkata in collaboration with department of Gynaecology & Obstetrics of the same institute from February 2005 to June 2006. Women with PCOS were recruited from the Gynaecology & Obstetrics OPD of IPGME&R, Kolkata. Criteria for diagnosis of PCOS were as per Talbott et al (9) and were history of chronic oligomenorrhoea or amenorrhea with (a) hirsutism (clinical feature of hyperandrogenism) or (b) LH/FSH ratio > 2 or (c) elevated serum total testosterone concentration >2 nmol/l. Apparently normal non-pregnant women of same age group were recruited from female staff of IPGME&R, Kolkata. These women did not have hirsutism and their menstrual cycles were normal and LH/FSH ratio <2. In addition, USG showed multiple cysts in ovaries in 76.66% of PCOS women but not in any normal menstruating women. The study was approved by local ethical committee and informed consent was taken from each participant.

Total cholesterol (TC) and Triglyceride (TG) were estimated by enzymatic methods (10,11). HDL-Cholesterol (HDL-C) was estimated by phosphotungstic acid precipitation followed by enzymatic analysis in supernatant fraction (12). LDL-Cholesterol (LDL-C) was estimated using Friedwald equation [TC – (HDL-C + TG/5)] (13). Fasting Serum FSH, LH, TSH, Prolactin and Insulin levels were estimated by ELISA. Fasting serum testosterone levels were measured (in 5 PCOS women) by chemiluminiscence immunoassay. Serum fasting Glucose was estimated by GOD-POD method. All parameters were measured from morning blood samples collected after twelve hours fasting. In oligomenorrheic PCOS subjects and in apparently normal women LH and FSH were estimated in the early follicular phase (Second or third day of menstruation).

Anthropological indices like age, blood pressure, BMI (body mass index), waist-hip ratio were measured in each subject. In addition, fasting glucose/insulin ratio and HOMA-IR score [fasting glucose (mmol/L) X fasting insulin (μU/ml)/22.5] (14) were also calculated in each participant.

Sonologist performed duplex carotid scanning of the right and left common carotid artery, carotid bulb and the first 1.5 cm of the internal and external carotid artery using a Toshiba Scanner (Corevision) equipped with a 7-10 MHz linear transducer (Mechanical index 0.4, Thermal Index 0.6). Average of measurement of each location was taken to produce an overall measure of carotid IMT (mean carotid IMT).

Statistical significance between cases and controls were estimated using two-tailed unpaired *t* test. P value < 0.05 was considered significant. Correlation analysis between carotid IMT and parameters of lipid profile were done using Pearson Correlation Coefficient.

RESULTS

Table 1 shows the anthropological indices of normal controls and PCOS subjects. Age, systolic pressure, diastolic pressure, waist-hip ratio, height were not statistically different in PCOS cases and controls (P > 0.05). However, weight of the PCOS patients were higher (61.12 ± 11.79 kg vs 53.65 ± 8.03 kg, P = 0.034) than that of controls. As a result PCOS subjects had higher BMI than that of controls (25.75 ± 4.58 vs 21.97 ± 2.99, P = 0.006).

Table 2 shows different hormone profile. Prolactin, TSH were not significantly different (P > 0.05) in both PCOS cases and controls. However, FSH/LH ratio was significnalty higher in PCOS cases than in controls (2.75 ± 0.83 vs 1.90 ± 0.21, P < 0.001). Similarly fasting serum insulin concentration was higher in PCOS cases than in controls (18.74 ± 2.70 vs 13.03 ± 1.40, P < 0.001). Fasting glucose and HOMA-IR scores were lower in controls than in cases but fasting glucose/insulin ratio were higher in controls than in cases.

Table 3 shows lipid profile and carotid IMT values of PCOS cases and controls. Serum TC, TG, LDL-C and mean carotid IMT were significantly higher in PCOS cases compared to controls (P < 0.05). However, HDL-C concentrations were not statistically different between two groups.

DISCUSSION

We estimated serum TSH and Prolactin levels to rule out hypothyroidism and hyperprolactinemia as possible causes of dyslipidemia (15, 16) among clinically diagnosed PCOS

Table 1 : Anthropological Indices of Normal Controls and PCOS Subjects (Values are mean ± SD)

Parameter	Control	PCOS Women	P Value
Age (years)	28.70 ± 7.06	26.11 ± 4.23	0.31
Systolic Pressure (mm Hg)	119.00 ± 11.01	120.87 ± 11.26	0.71
Diastolic Pressure (mm Hg)	75.00 ± 5.27	77.67 ± 8.24	0.25
Weight (kg)	53.65 ± 8.03	61.12 ± 11.79	0.034 *
Height (Metre)	1.56 ± 0.07	1.54 ± 0.06	0.36
BMI (Kg/m^2)	21.97 ± 2.99	25.75 ± 4.58	0.006 *
Waist-hip ratio	0.90 ± 0.03	0.90 ± 0.04	0.52

*P < 0.05.

cases. However as data of Table 2 shows, both of these hormones were within normal limits (TSH: 0.4 –6μIU/ml and Prolactin: 3 – 23 ng/ml) and were not statistically different. This rule out their deficiencies as possible causes of dyslipidemia in PCOS cases and indicates pathophysiology of PCOS was responsible for dyslipidemia in concerned subjects. The findings of elevated TC, TG and LDL-C were in agreement with those of Mattson et al (17), Wild et al (18) and Talbott et al (19). However, contrary to their findings of decreased HDL-C in PCOS women, in our study PCOS women did not have statistically different HDL-C levels compared to controls (47.60 ± 6.06 vs 43.10 ± 8.46, P = 0.081). This may be due to the fact that our study group is of younger age group than theirs. In our study all women were below 40 years and maximum were in their twenties. Only 3 out of 30 PCOS cases (10%) and 5 out of 30 controls (16.67%) were above 29 years Though mean age ± SD were comparable in both groups, percent of women in their thirties were more in controls. However, this difference was not translated in their carotid IMT or lipid profile (Table 3). Rather the reverse (i.e., PCOS women had statistically higher mean carotid IMT and adverse lipid profile values compared to normal controls) pattern was seen. This points to the fact that dyslipidemia is a feature of PCOS and this dyslipidemia was translated in Carotid IMT among PCOS women in our study. Bonithon-Kopp et al (20) suggested a mean carotid IMT > 0.75 mm as a measure of subclinical atherosclerosis. In our study 16.67% of PCOS cases met the criteria against none in the control group. 10% of PCOS women approached (0.7 mm) this value. Furthermore that dyslipidemia was translated into increased IMT in PCOS cases, was also corroborated by association study. Carotid IMT was positively correlated with TC, TG, LDL-C and negatively correlated with HDL-C in both PCOS cases (r=-0.30) and controls (r=-0.37). However, the degree of association varied in PCOS cases compared to controls. In controls, mean carotid IMT was positively correlated more with TG (r = 0.54) than TC (r = 0.22) or LDL-C (r = 0.17). But in PCOS cases mean carotid IMT was more positively correlated with TC (r = 0.46), LDL-C (r = 0.43) than TG (0.41). This suggested that Cholesterol particularly LDL-C fraction increase was responsible for atherosclerosis and increased mean carotid IMT among PCOS women. Our study has been supported by the findings of Vryonidou et al (21), who found significantly higher carotid IMT (0.58 vs 0.47 mm, P < 0.001) among young women with PCOS (17-35 yrs) as compared to healthy controls.

Increased fasting insulin and fasting glucose/insulin ratio are

Table 2 : Hormone Profile & Metabolic indices of Nomal Controls and PCOS Subjects (Values are mean±SD)

Parameter	Control	PCOS Women	P Value
TSH (μIu/ml)	2.63 ± 1.09	2.30 ± 0.96	0.40
Prolactin (ng/ml)	17.16 ± 4.88	19.38 ± 7.59	0.25
Insulin (μU/ml)	13.03 ± 1.40	18.74 ± 2.70	<0.001 *
FSH / LH	1.90 ± 0.21	2.75 ± 0.83	< 0.001 *
Fasting Glucose/Insulin ratio	6.15 ± 0.57	4.65 ± 0.68	<0.001*
HOMA-IR	2.57 ± 0.37	3.96 ± 0.62	<0.001*
Glucose (mg/dl)	79.50 ± 4.57	85.60 ± 6.47	0.002*

*P < 0.05.

Table 3 : Serum Lipid Profile and Carotid IMT of Nomal Controls and PCOS Women (Values are mean±SD)

Parameter	Control	PCOS Women	P Value
Total Cholesterol (mg/dl)	135.20 ± 30.05	172.13 ± 33.56	0.005 *
Triglyceride (mg/dl)	111.20 ± 34.32	163.32 ± 54.14	< 0.001 *
LDL-C (mg/dl)	65.36 ± 28.29.01	96.41 ± 29.56	0.014 *
HDL-C (mg/dl)	47.60 ± 6.06	43.10 ± 8.46	0.079
VLDL-C (mg/dl)	22.24 ± 6.86	32.65 ± 11.36	< 0.001 *
Carotid IMT (mm)	0.44 ± 0.05	0.63 ± 0.19	<0.001 *

*P < 0.05.

measures of insulin resistance in obese PCOS women (22). In our study, compared to normal controls, PCOS women had increased BMI, fasting serum insulin and fasting glucose/ insulin ratio (Table 1 and Table 2). HOMA-IR scores for insulin resistance were significantly higher in PCOS patients than normal range values (2.1-2.7). Also , Acanthosis nigricans, a peripheral indicator of insulin resistance was present in 3 (10%) PCOS women. These findings of insulin resistance were supported by previous study (23). Fasting hyperinsulinemia is often associated with dyslipidemia (Syndrome X). Epidemiological studies have also shown that in middle aged and elderly people, hyperinsulinemia with other adverse cardiovascular risk factors, is associated with increased Carotid IMT (24). Thus it appears that in our study hyperinsulinemia and dyslipidemia (increased TC, TG and LDL-C) were responsible for increased Carotid IMT.

Hyperinsulinemia is often associated with increased BMI and insulin stimulates cholesterol transport into arteriolar smooth muscle cells and enhances the cholesterol synthesis and proliferation of these cells (25). Epidemiological studies has shown that women with PCOS are at high risk of cardiovascular or cerebrovascular disease (26). Thus our study points to the idea that chronic exposure to adverse cardiovascular risk factors among PCOS from early age can lead to premature subclinical athrosclerosis. It is to be noted that except two PCOS patients, none in the cohort were hypertensive and the mean systolic and diastolic BP of the two groups (PCOS women and control women) were within normal limit and were not statistically different. Thus, we recommend routine serum fasting insulin estimation in PCOS women and if hyperinsulinemia is present, use of insulin lowering drugs even in young PCOS women should be encouraged. Simultaneously, if BMI is increased, they should be encouraged to undergo life-style modifications through diet & physical exercise.

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