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HbA1c AND ITS ASSOCIATION WITH hs-CRP IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Medical Science

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ABSTRACT

Aim And Objective : The present study aims to assess the association of hs-CRP and HbA1c in women with PCOS.
Material And Methods : 50 woman with PCOS, according to Rotterdam criteria, clinical symptoms and laboratory result were studied, the hemoglobin A1c level and hs-CRP level were assessed by blood test.
Results: The mean age was 26±5.03 years. HbA1c mean concentration was 5.88±0.62% and hs-CRP mean was 4.61+3.72. Elevated HbA1c was observed in patients of PCOS as compared to control group. It is statistically significant.
Conclusion: Chronic low-grade inflammation is a common feature of insulin resistant states, including obesity, PCOS, and type 2 diabetes. Serum hs-CRP levels are raised in PCOS women as compared to healthy women reflecting association of low grade chronic inflammation with PCOS patients. In present study it was observed that raised hs-CRP is associated with increased levels of HbA1c in patients with PCOS suggesting of degree of inflammation.

KEYWORDS

Blood sugar level, Hemoglobin A1C, hs-CRP, PCOS.

INTRODUCTION-

Polycystic ovary syndrome (PCOS) is also known as hyperandr ogenic anovulation or Stein-Leventhal syndrome. PCOS is one of the main causes of endocrine-dependent infertility, with a prevalence of 2.2-26% women of reproductive years.[1] Small fluid-filled sacs develop on the ovaries. PCOS is not only a reproductive problem but it is a complex reproductive, metabolic, cardiovascular complications.

This disorder is associated with **anovulation** (ovaries do not release an Oocyte during a menstrual cycle), **hirsutism** (coarse, dark, terminal hair distributed in male pattern), **Obesity** (an excessive amount of body fat), **multiple cysts** in the ovaries, increased excess production of female sex hormones from ovary with insulin resistance and over activity of androgens. [2] PCOS is associated with mainly abdominal obesity and insulin resistance. It is a combination of genetic and environmental factors. [3]

The symptoms of the polycystic ovary syndrome usually begin around menarche, [4] but onset after puberty may also occur as a result of environmental modifiers such as weight gain. Premature Pubarche, the result of early secretion of adrenal steroids, may be a harbinger of the syndrome. [5] In addition, an aberrant intrauterine environment has been implicated in the conditions pathogenesis, particularly its metabolic components. [6]

The women with PCOS always have some aberration in gonadotropin secretion as compared with women who have normal menstrual cycles. [7] However, since gonadotropin concentrations vary over the menstrual cycle and are released in a pulsatile fashion into the circulation, measurement of luteinizing hormone and follicle-stimulating hormone provides little diagnostic sensitivity. Thus, in routine clinical practice, abnormal gonadotropin levels (an elevated level of luteinizing hormone or an elevated ratio of luteinizing hormone to follicle-stimulating hormone) need not be recorded to diagnose the polycystic ovary syndrome.

The women with PCOS have insulin resistance. Insulin interacts with LH within the theca cells of polycystic ovaries to cause activation of key enzyme (p450c17α) in the biosynthesis of ovarian androgens such as testosterone, liver through suppression of hepatic synthesis of sex-hormone-binding globin (SHBG). [8] Increased levels of luteinizing hormone (LH), serum testosterone and decreased levels of sex hormone- binding globulin (SHBG), these correlate with hyperinsulinemia and obesity. [9]

Increased cardiovascular risk factors, insulin total cholesterol, low-density lipoprotein (LDL), triglycerides and blood pressure and lower high-density lipoprotein (HDL) have been reported among PCOS patients. [10] the well-documented presence of increased risk factors has led to suggestions that women with PCOS are at higher risk of cardiovascular diseases.

PCOS is pro-inflammatory conditions and its low grade chronic inflammation cause ovarian dysfunction metabolic derangements. [2] Most women with PCOS have insulin resistance and the prevalence of the metabolic complications such as dyslipidemia, prediabetes or non-insulin dependent diabetes mellitus (DM2) and coronary artery disease is increased. [11]

Circulating C-reactive protein (CRP) is an acute phase protein secreted from the liver, which is stimulated by interleukin-6, originating from the adipose tissue it is considered to estimate low grade chronic inflammations. [12] Low-grade inflammation, reflected by elevated levels of circulating high-sensitive C-reactive protein (hs-CRP), has been suggested to be related to insulin resistance and cardiovascular diseases development. [13]

High sensitive C-reactive protein (hs-CRP) is a marker of low grade chronic inflammation synthesized by liver. low grade chronic inflammation is a key process in the development of atherosclerosis and high hs-CRP levels is cardiovascular risk factor. [14]

According to Americans Heart Association (AHA) guidelines, hs-CRP is a global indicator of future vascular events in adults without any previous history of cardiovascular disease, with acceptable precision levels down to below 0.3mg/L. Few studies have demonstrated an association between insulin resistance and increased hs-CRP levels. [15] Insulin resistance is a common manifestation in PCOS, which is strongly associated with risk of metabolic syndrome and type 2 diabetes.

Glycated Hemoglobin (HbA1c) is considered a maker of glycemic index over is period of 2-3 months elevated HbA1c levels indicate the risk of type 2 diabetes or prediabetes. [16] Glycated hemoglobin is produced by a ketoamine reaction between glucose and N-terminal valine of both β-chains of the hemoglobin molecule. The major form of glycated hemoglobin is HbA1c.

Increased HbA1c concentrations have been associated with other risk factors for cardiovascular diseases (CVD) and the presence of metabolic syndrome. Previous studies have suggested that in patients with or without PCOS, an increase of 1% in the absolute HbA1c concentration is associated with a 10-20% increase in CVD risk. [17]
This study was done to evaluate the diagnostic role of hs-CRP and its

association with HbA1c in patients with PCOS.

MATERIALS AND METHODS

The study was conducted in Department of Biochemistry in association with Department of obstetrics and gynecology of Mahatma Gandhi Medical College &Hospital, Jaipur. Patients diagnosed for PCOS, visiting the Outpatient Department (OPD) of obstetrics and gynecology fulfilling the inclusion criteria were enrolled for the study. 100 age matched healthy subjects constituted the control group. The study was conducted subject to approval from the **Institutional Ethics Committee** (IEC). Written and informed consent was obtained from all participants prior enrollment into the study.

Total 50 subjects fulfilling the inclusion criteria were taken for study. The control group consisted of fifty (n=50) age matched healthy females.

Patients diagnosed with PCOS based on Rotterdam criteria and ages between 18 to 45 years were included in the study. Pregnant and menopausal women were excluded from the study. Patients with Systemic inflammatory diseases, recent and chronic infections, were also excluded from the study. Blood samples for all subjects (patient and control group) were collected using standard aseptic technique and analyzed for following investigations, Blood Sugar HbA1c, hs-CRP. Parameters were estimated by fully automated analyzer VITROS 5600.

The results obtained presented as mean + SD and subjected to statistical analysis. A p-value of < 0.05 shall be considered as statistically significant.

Statistical Analysis

Result obtained for various parameter were presented as mean+SD among the two groups i.e. PCOS patients (n=50) and control group (n=50). The result of patients group was compared with those of control group by applying student's t-test. HbA1c and its association with hs-CRP in patients with polycystic ovary syndrome. ANOVA test was also applied. A p-value of ≤ 0.05 was considered as significant for all statistical tests.

RESULTS AND DISCUSSION

The study population consisted of 100 subjects (50 PCOS patients, 50 controls). Patients were taken from out- patient department of obstetrics and gynecology, Mahatma Gandhi Medical College and Hospital, Jaipur. Patients were selected based on the predefined inclusion and exclusion criteria and after obtaining informed consent. Blood sample was collected and analyzed for estimation of HbA1c, hs-CRP. Data of both controls and cases were analyzed statistically. P value of < 0.05 was found statistically significant.

Mean age of presentation with PCOS is 26±5.03 years, as shown in table (1).

Insulin is a polypeptide hormone secreted by the β-cells of the pancreas. Its main action is to regulate glucose metabolism. Insulin stimulates peripheral glucose uptake in fat and muscle tissues. [20] Hyperglycemia occurs later as pancreatic β-cells fail to secrete enough insulin to compensate for the insulin resistance. Hyperinsulinemia is thought to be the result of insulin resistance. Insulin resistance leads to decreased disposal of glucose into muscle, and postprandial hyperglycemia. Later, deficient insulin action results in increased hepatic output and fasting and all-day hyperglycemia. Insulin resistance is associated with obesity, a sedentary lifestyle and caloric excess. [21]

The study has presented that sugar levels of PCOS patients is higher than control groups [91±10.52]. It is not statistically significant as shown in table (2).

Glycated hemoglobin (HbA1c) is a better indicator of glycemia than glucose concentration at a single point of time. Measurement of HbA1c is commonly used for prediabetes and type 2 DM. HbA1c does not require fasting blood glucose over the preceding 3-12 weeks. Elevated HbA1c concentrations have been associated with other risk factors for cardiovascular disease (CVD) and the presence of metabolic syndrome in several other non-PCOS clinical conditions and populations. [17] In the present study, elevated HbA1c was observed in patients of PCOS as compared to control group (p valve 0.000). It is statistically significant as shown in table no (3). According to the American Diabetes Association (ADA) guidelines, the value of HbA1c between 5.7%-6.4% is considered as prediabetes and value above 6.4% is considered as diabetes.

Insulin resistance is associated with elevated levels of plasma hs-CRP, hyperinsulinemia and cardiovascular autonomic dysfunction. Many studies have reported that Serum hs-CRP, a sensitive marker of chronic low-grade inflammation and a mediator of atherosclerotic disease, is increased in women with PCOS but there are other reports which have negated these associations. [22] hs-CRP is an acute phase reactant produced predominantly by hepatocytes under the influence of cytokines such as interleukin (IL-6) and tumor necrosis factor-alpha. Adipose tissue is a known source of IL-6 and TNF-α which stimulates hs-CRP synthesis in the liver. [23] hs-CRP also play a functional role by promoting the uptake of lipids into foamy macrophages with atherosclerotic plaques. [24] Elevated CRP levels are independent of obesity in PCOS and indicate inflammatory process and its estimation helps in diagnosis of PCOS. [25] In the current study, hs-CRP levels were found to be higher in patients of PCOS than control group (4.61+3.72). It is statistically significant (p valve 0.000) as shown in table (4).

Chronic low grade inflammation indicated by an increased CRP levels predicted the risk of coronary heart disease and Type 2 DM in PCOS women, in a study done by Boulman et al 2004. [26]hs- CRP levels were divided into three groups <1, 1-3 and >3 mg/L corresponding low, moderate and high risk for future cardiac vascular events. Tosi et al 2009 also reported that out of total 116 patients, 46.5% patients had hs-CRP levels >3 mg/L. [27]In the present study, out of the total 50 patients, 54% patients had hs-CRP levels >3mg/L, 30% patients had hs-CRP level 1-3mg/L and 16% patients had hs- CRP levels <1 mg/L which are shown in table (5.1).

Inflammation is considered as a key feature of atherosclerotic plaques, and a strong relationship exists between systemic inflammation activity and the occurrence of atherothrombotic events like myocardial infraction. [28] The patients were further distributed into three groups based on hs-CRP levels. 8 patients had the level of hs-CRP <1.0mg/L their mean was 0.54±0.22, 15 patients had hs-CRP 1.0-3.0 mg/L their mean was 1.99±0.59 and 27 patients had hs-CRP >3.0 mg/L their mean was 7.36+3.21. It is shown in table (5.2).

PCOS associated obesity is possible due to abnormalities in appetite- and weight- regulating hormones (leptin, ghrelin) and other adipocytokines. Raised TSH levels in PCOS also increased adipocytes proliferation, as well as increased pro-inflammatory markers. [29] Pro-inflammatory cytokines contributing to insulin resistance. The mechanism of Insulin-enhancing ovarian steroidogenesis is observed in PCOS. [30] A post insulin -receptor signaling defect comes from adipocytes and reduce in the abundance of the glucose transporter-4 despite there being no abnormalities in insulin receptor number. [31] Defects in insulin signaling receptors which results from accumulation of free fatty acids, excess glucose and other nutrients. Both glucose and free fatty acids acutely stimulate insulin secretion but chronic exposure to high levels of either nutrient leads to impairment of beta cell function. [32] β-cells dysfunction involves adverse effects of hyperglycemia and visceral lipid storage in persons with obesity and insulin resistance. We have already discussed that HbA1c is a better indicator of glycemic condition. Since, inflammation relates to insulin resistance and metabolic disorder seen in PCOS. In this study, an attempt was made to investigate whether the increase of hs-CRP level is associated with a certain cutoff of HbA1c.

The present study reported that hs-CRP has a direct association between HbA1c and hs-CRP levels. It is show in table (5.3).

Observations

Table 1: Comparison Of Age Between Control And Patient Group

Groups	Age(years)	t-value	P-value
Controls (n-50)	27.56±5.01	1.554	0.123
PCOS (n-50)	26±5.03		

Table 2:comparison Of Glucose (mg/dl) Between Control And Patient Group

Groups	Glucose (mg/dL)	t-value	P-value
Controls (n-50)	89.52±15.25	-0.588	0.558
PCOS (n-50)	91.06±10.52		

Table 3: comparison of hba1c (%) between control and patient group

Groups	HbA1c (%)	t-value	P-value
Controls (n-50)	5.37±0.54	-4.386	0.000
PCOS (n-50)	5.88±0.62		

Table 4: Comparison Of Hs-crp(mg/l) Between Control And Patient Group

Groups	hs-CRP (mg/L)	t-value	P-value
Controls (n-50)	1.20±0.71	-6.367	0.000
PCOS (n-50)	4.61±3.72		

Table 5.1: Distribution Of Subjects On The Basis Of Hs-crp Levels

hs-CRP Reference ranges	No. of patients/subjects Control groups	No. of patients/ subjects PCOS
Low range - <1 mg/L	21	8 (16%)
Average range – 1.0-3.0 mg/L	29	15 (30%)
High range - >3.0 mg/L	_	27 (54%)

Table 5.2: Comparison Of Hs-crp (mg/l) According To Their Distribution

hs-CRP Reference ranges (mg/L)	hs-CRP (mg/L)	F-Value	P-Value
Low range - <1.0 (n-8)	0.54±0.22	37.82	0.000
Average range – 1.0-3.0 (n-15)	1.99±0.59		
High range - >3.0 (n-27)	7.36±3.21		

Table 5.3: HBA1c Level In PCOS Patients Grouped According To hs-CRP Levels

hs-CRP Reference ranges (mg/L)	HbA1c(%)	F-Value	P-Value
Low range - <1.0 (n-8)	5.31±0.28	24.97	0.000
Average range – 1.0-3.0 (n-15)	5.46±0.26		
High range - >3.0 (n-27)	6.27±0.53		

SUMMARY AND CONCLUSION

Chronic low-grade inflammation is a common feature of insulin resistant states, including obesity, PCOS, and type 2 diabetes. Serum hs-CRP levels are raised in PCOS women as compared to healthy women reflecting association of low grade chronic inflammation with PCOS patients.

In present study it was observed that raised hs-CRP is associated with increased levels of HbA1c in patients with PCOS suggesting of degree of inflammation. HbA1c even in normal range, could be an indicator of elevated hs-CRP in PCOS patients. hs-CRP tests may be necessary in these women to assess the cardiovascular risk factor. Considering the value of hs-CRP in predicting risk for cardiovascular diseases and its association with insulin resistance, further research can be done using other marker of insulin resistance such as association of hs-CRP with uric acid, homocysteine and lipid profile in patients with PCOS.

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