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HbA1c in Polycystic Ovary Syndrome as the Cardiac Risk Assessment

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Abstract

Objective: Polycystic ovary syndrome (PCOS) is an endocrine disorder associated with hyperandrogenism marked with hirsutism and ovarian dysfunction. These conditions may lead to the risk of insulin resistance (IR), type 2 diabetes, obesity, and cardiovascular disease. These conditions are related to PCOS complications hence our aim was to study and investigate the relationship between high-sensitivity C - reactive protein (hs-CPR) level and glycosylated hemoglobin (HbA1c) level in PCOS patients.

Materials and Methods: Female patients visiting the obstetrics and gynecology outpatient department (OPD), aged between 19 and 45 years with a body mass index (BMI) of 25 to 29 kg/m^2. The individuals fulfilling the National Institute of Health (NIH) criteria for PCOS; including amenorrhea or oligomenorrhea and had been clinically diagnosed with hyperandrogenism were served as subjects.

Results: Two hundred and ten individuals with HbA1c of 5.4% have a higher risk of cardiovascular disorders. The study showed the association between increased cardiac risk as measured by hs-CRP and patients with normal HbA1c values with a sensitivity of 77.2% and specificity of 75.99%. The HbA1c cutoff value can be used in the PCOS patients to assess the cardiac risk due to association of HbA1c cut off value with false positivity rate of 15.24%.

Conclusion: In PCOS patients with chronic low-grade inflammation, IR, and the degree of inflammation associated with HbA1c value was observed.

Keywords: HbA1c, Polycystic ovary syndrome, hs-CRP, Cardiovascular disorder

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Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder associated with hyperandrogenism marked with hirsutism and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology (PCOM)). PCOS symptoms are typically marked with hirsutism, amenorrhea (no menstruation), chronic anovulation and infertility, obesity and enlarged cystic ovaries. The prevalence of PCOS is most common in women of reproductive age (1).

The clinical manifestation of PCOS affects the whole life of a woman; starting from puberty and continuing during the reproductive years. The PCOS patients are prone to increased risk of cardiovascular disease, hypertension, diabetes and other metabolic disorders, specifically carbohydrate and lipid metabolism. PCOS affects the fertile period of women with an increased prevalence of gestational complications, such as miscarriage, gestational diabetes and preeclampsia (2). The gonadotropin-releasing hormone triggers the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) which is essential for distinct phases of the menstrual cycle. In PCOS, due to lack of these hormones either ovum is not formed or ova cannot come out of the follicle. This results in irregularity in the cycle or amenorrhea. (3) Early diagnosis is crucial to decrease the risk of complications due to PCOS (2).

High blood sugar levels may provide a crucial breakthrough in the pathogenesis of PCOS and related complications. The early diagnosis, weight & diet control and changing lifestyle may prevent the development of PCOS related complications such as infertility, subfertility, atherosclerosis and diabetes. (4) PCOS etiology is unknown and hence considered a multifactorial disorder with various genetic, metabolic, endocrine and environmental abnormalities (2). Due to the large diabetic population, India is closely related to PCOS and metabolic syndrome or its associated complications. Genetically women are susceptible to developing PCOS. The final expression of the PCOS phenotype depends upon the interaction of environmental factors (obesity) with the genetic factors that result in metabolic and menstrual disturbances. Irrespective of the geographic origin of individuals, a rapidly increasing prevalence of polycystic ovarian syndrome, excess body fat, negative body fat patterning, hypertriglyceridemia, and obesity- related diseases, such as diabetes and cardiovascular disease (4). Hence, it is necessary to diagnose PCOS early in Indian women so that primary preventive strategies can be initiated earlier.

As hyperandrogenism, menstrual irregularities and insulin resistance (IR) as the key features of PCOS, the clinicians may recommend testing blood pressure, menstrual cycle duration and ultrasound for follicle count, mean ovarian volume, endocrine parameters tests (sex hormone binding globulin, testosterone, free androgen index (FAI), Follicle Stimulating Hormone, Anti Müllerian Hormone, Prolactin, thyroid function tests), lipid profiles and Glucose tolerance test (GTT) (3). The study from Vu et.al. (2016) stated that high-sensitivity C - reactive protein (hs-CRP) is a better marker for predicting cardiovascular diseases in patients with PCOS (5). hs-CRP is a helpful biomarker for inflammation in cardiovascular diseases and chronic low-grade inflammation in PCOS. Dietary modification and medications may decrease the risk of cardiovascular disease and serum CRP. There are studies available that support the risk of cardiovascular diseases due to elevated hs-CRP (>2 mg/L) (4). It is well documented that glycosylated hemoglobin (HbA1c) is a known marker for IR and cardiovascular diseases. These conditions are related to PCOS complications hence this study aims to investigate the association between hs-CPR level and HbA1c level in patients with PCOS (6).

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In this study the authors try to explore whether the association of hs-CRP level with the HbA1c level in patients with IR and related metabolic disorders.

Materials and Methods

376 females were recruited prior to this cohort study and their demographic and clinical data utilized for the analysis. These patients were between the ages of 19 and 45 year from the Obstetrics & Gynecology OPD and having a body mass index (BMI) of 25 to 29 kg/m^2. The individuals fulfilling the National Institute of Health (NIH) criteria for PCOS; including amenorrhea or oligomenorrhea and had clinically diagnosed with hyperandrogenism were served as subjects (7).

The patients consuming insulin, oral contraceptives, sensitizers, anti-androgens, medications for weight loss and hyperlipidemia, cigarettes, two alcoholic drinks per week were excluded from the study. Also, the patients suffering from diabetes mellitus, thyroid disorders, and systemic illness were excluded from the study.

The patients were fasting for 12 hours before conducting tests. The testing conducted during follicular phase for menstruating women. Blood samples were collected for hs-CRP and HbA1c testing simultaneously. Latex-enhanced Immunoturbidimetric immunoassay was used for measuring hs-CRP on instrument XL-640, Fully Automated Biochemistry Analyzer, manufactured by Transasia Bio-Medicals Ltd, India. The cation exchange high performance liquid chromatography (HPLC) was used to determine HbA1c value on Hb-Vario, manufactured by Transasia Bio-Medicals Ltd, India (Erba Mannheim). The blood samples from the menstruating patients were collected during the follicular phase of the menstruating cycle, which helped in reducing the effects of hormonal changes on inflammatory parameters and metabolism.

For descriptive statistical analysis, SPSS version 20.0 for windows software was done. The descriptive statistical analysis for categorical variation included means, standard deviations, proportion, frequencies and logistic regression to find out the relationship between HbA1c and hs-CRP. Also, the area under the curve (AUC) used to assess the discrimination in this statistical model. The statistical significance was assessed by two-sided with a *P* less than 0.05 for all these tests.

Ethical considerations

This cohort study was approved by the Institutional Ethics Committee and conducted from February 2021 to April 2021 in a tertiary care hospital affiliated with a medical college in western India.

Ethical clearance for conducting the study was given with reference number RGMC/ CSMH/IEC/A/2021/01/186

Results

A total of 376 subjects were enrolled in the study. Out of 376, 27 individuals were excluded as per the exclusion criteria and the remaining 349 individuals were analyzed further in the study. The average age of patients was 31.0 (mean) ± 7.1 (SD) (Range: 19-45 years) years. The average BMI of the patients was 23.0 (± 2.5) (Range: 24- 27.9 kg/m^2).

The average HbA1c was 5.6% (± 0.50) (Range: 4.8- 6.4%). 205 (59%) individuals had normal HbA1c levels (HbA1c less than 5.7%), and 132 (38%) had pre- diabetes (HbA1c between 5.7 and 6.5).

255 individuals (73.2 %) had a hs-CRP value > 2 mg/L. To check the association between HbA1c cut off value, hs-CRP more than 2 mg/L, different HbA1c cut offs ranging from 5.1 to 5.7% and regression analysis of hs-CRP were taken in consideration (Table 1).

In Table 2, individuals are differentiated in these cut-off values against the increased hs-CRP (greater than 2 mg/l).

210 individuals had cut off HbA1c value of 5.4% and may have higher risk of cardiovascular disorders. These results are indicative of association of HbA1c value and hs-CPR values that are within normal ranges,

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and sensitivity 77.2% and specificity 75.99%. The HbA1c cutoff value can be used in the PCOS patients to assess the cardiac risk due to association of HbA1c cut off value with false positivity rate of 15.24% (Table 2).

Discussion

After analyzing 349 individuals cut-off value 5.4% considered for a logistic regression analysis and discussion. This study is intended to find out HbA1c cutoff value that would be useful in estimating risk for associated to metabolic and cardiovascular disease risk due to PCOS. An HbA1c cutoff of 5.4% with a sensitivity of 77.2% and a specificity of 75.99% can be used as an early detection of increased inflammation, IR and cardiovascular disease. HbA1c can be used with hs-CRP as an inflammatory marker in PCOS patients. Simultaneous increase in both parameters may be indicative of higher risk of cardiovascular disease.

PCOS is a complicated disease and should be diagnosed in early stages and treated based on the patient's accurate diagnostic features. Clinicians with knowledge about the PCOS multiple complexities, pathophysiology, diagnosis, treatment, and comorbidities can treat emerging young adult women with PCOS (8). In PCOS, insulin resistance plays a critical role reproductive mechanism of women. Any alteration in IR may affect the anovulation and reproductive system of women. Hence it is essential to understand the pathophysiologic mechanism, pharmacogenetics evaluation of responders versus non-responders to metformin, the role of free fatty acid stimulation of androgens, and the role that insulin plays, and whether there are ethnic/genetic differences in PCOS presentations (9). Hence, taking HbA1c in diagnostic consideration in PCOS is essential, even in gestational diabetes mellitus during first trimester (10). Although HbA1c was not reported to be the most sensitive and specific screening tool for IR in patients with PCOS, it might be a good indicator of PCOS complications as well as consequences like cardiovascular diseases (6).

The hepatocytes influenced by tumor necrosis factor– alpha (TNF-alpha) and interleukin 6 (IL-6) produce CRP directly from adipose tissue. The key role of CRP is to promote lipid uptake into foamy macrophages within atherosclerotic plaques (11). As per the recent ACC/AHA guidelines, a CRP of more than 2 mg/l alarming for increased risk of cardiovascular disease. The increased levels of estrogen and progesterone can help in decreasing CRP levels during the menstrual

Table 1. The area under curve of HbA1c in prediction of hs-CRP more than 2 mg/L

Variables	AUC	HbA1c Cut off values						
		5.1%	5.2%	5.3%	5.4%	5.5%	5.6%	5.7%
HbA1c	0.6921	0.6985	0.7569	0.7899	0.7601	0.7106	0.675	0.5896
Correct (%)	0.7692	79.01%	81.79%	79.99%	75.99%	70.12%	35.23%	47.69%
Sensitivity (%)	0.8025	97.00%	93.26%	82.93%	77.20%	67.26%	41.23%	65.01%
Specificity (%)	0.7601	44.03%	63.22%	75.62%	76.02%	76.30%	26.31%	19.25%
False positive (%)	0.6992	24.56%	18.25%	12.99%	15.24%	17.54%	51.24%	43.12%
False negative (%)	0.6013	13.60%	16.85%	30.14%	37.99%	46.25%	82.15%	79.24%

Table 2. Individuals cut-off values against the increased hs-CRP (greater than 2 mg/l)

Variables	hs-CRP		
HbA1c %	**> 2.0 mg/L**	**< 2.0 mg/L**	**Total**
5.1	3 (30%)	7 (70%)	10 (100%)
5.2	2 (17%)	10 (83%)	12 (100%)
5.3	15 (58%)	11 (42%)	26 (100%)
5.4	50 (93%)	4 (7%)	54 (100%)
5.5	24 (62%)	15 (38%)	39 (100%)
5.6	24 (67%)	12 (33%)	36 (100%)
5.7	18 (64%)	10 (36%)	28 (100%)
5.7 - 6.4	84 (64%)	48 (36%)	132 (100%)
> 6.5	10 (83%)	2 (17%)	12 (100%)

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cycle. There are several studies available that say the hs-CRP is related to diabetes mellitus or cardiovascular disorders. In India, there are many women who are suffering from this PCOS, but very small reference data is available for it. The elevated hs-CRP is associated with PCOS along with the oxidative stress (12-14).

Conclusions

The correlation between HbA1c and the degree of inflammation in non-diabetic PCOS patients with chronic low-grade inflammation, obesity, and IR was found to be significant. In PCOS patients, a normal HbA1c value (5.4%) could be an indicator of increased hs-CRP and eventually cardio-vascular disorder. It is recommended to perform additional diagnostic tests to evaluate the cardiovascular disease risk factors and start suitable early treatment.

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Conflict of Interest

The authors declare that they have no conflicts of interests

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