Assessment of glycated hemoglobin and uric acid level in polycystic ovarian syndrome in a Tertiary Care Institute of Marathwada region

Sunita M. Aghade[1,*], Jayashree S. Bavikar[2]

[1]Assistant Professor, Dept. of Biochemistry, JIIU's Indian Institute of Medical Science and Research, Warudi, Maharashtra, [2]Associate Professor, Dept. of Biochemistry, Government Medical College, Aurangabad, Maharashtra, India

***Corresponding Author:**
Email: aghadesunita@gmail.com

Abstract

Introduction: The Polycystic Ovary Syndrome (PCOS) is one of the most common reproductive endocrine disorders, affecting 5–10% of women in the reproductive age. Insulin resistance is the hallmark of this disorder. PCOS has been epidemiologically linked to an increased risk for type 2 diabetes mellitus and cardiovascular diseases. The present study was planned to study glycated hemoglobin (HbA1c) and uric acid level in patients of PCOS.

Materials and Methods: The study comprised of 60 women with PCOS as cases and 60 healthy females as controls. HbA1c and uric acid level were measured in all participants.

Results: Glycated hemoglobin and serum uric acid were significantly increased in PCOS group and showed positive correlation with body mass index and waist: hip ratio. The prevalence of raised HbA1c was 40% in PCOS women.

Conclusion: In our study we found significant alterations in HbA1c and uric acid level in cases of PCOS. Early identification of these changes and timely intervention can reduce morbidity due to type 2 diabetes mellitus and cardiovascular diseases in PCOS. This will help to redefine the paradigms of PCOS care in India.

Keywords: Cardiovascular Disease, HbA1c, PCOS, Type 2 Diabetes Mellitus, Uric Acid.

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Introduction

Polycystic Ovarian Syndrome (PCOS) is a heterogeneous, polygenic, multifactorial, gynecological disorder. It is a complex endocrinopathy; affecting 5–10% women of reproductive age group. The diagnostic criteria for PCOS include chronic anovulation, hyperandrogenism and polycystic ovaries.[1] It is the leading cause of anovulatory infertility. PCOS is associated with various long term complications such as reproductive (infertility and pregnancy complications), cosmetic (acne, hirsuitism, acanthosis nigricance) and psychological (depression, anxiety). These women are at an increased risk of developing serious metabolic sequelae (obesity, metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases).[2]

Insulin resistance (IR) occurs in around 50% to 80% of PCOS women whether obese or non-obese and is the fundamental disturbance in this disorder.[1] Insulin resistance, androgen excess and abdominal adiposity which is frequently observed in PCOS, is linked to an increased risk of type 2 diabetes mellitus (T2DM).[3] PCOS has been identified as a significant non-modifiable risk factor for T2DM and the risk of developing diabetes is 7 times increased than general population.[1,2] Approximately, 25% to 30% of PCOS women will show impaired glucose tolerance at a younger age (by 30 years) and 8% of affected women will develop type 2 diabetes annually.[4] Thus, women with PCOS are regarded as a reservoir of future diabetes.

Diabetes and its complications are a major cause of death and disability and impose tremendous burden on health care system. Therefore, PCOS women should be routinely screened for impaired glucose tolerance and diabetes mellitus.[5] Current screening recommendations in PCOS include, fasting plasma glucose and 2-hour oral glucose tolerance test (OGTT) particularly in obese and high risk patients.[3] However, OGTT is inconvenient, time consuming and the patient has to be assessed while fasting. In contrast, Glycated Hemoglobin (HbA_{1c}) is a single blood test, does not require fasting, and has less day-to-day variability during stress and illness. It is the best index of chronic glycemic status, and reflects average blood glucose level over the previous 10-12 weeks. By using this simple test, the rate of periodic monitoring of PCOS women for development of prediabetes and diabetes might improve in near future.[6]

Elevated HbA_{1c} is also an independent risk factor for cardiovascular diseases (CVD). 1% increase in HbA_{1c} concentration is associated with 10-20% increase in CVD risk in PCOS group as well as in general population. Taking into account this potential association between HbA_{1c} and health consequences in PCOS patients, the current study aimed to estimate the prevalence of elevated HbA_{1c} in PCOS women in our institute.[7]

PCOS is characterized by increased activation of the inflammatory system stemming from insulin resistance, which predicts future cardiovascular risk.[8] IR elevates several pro-inflammatory mediators, which leads to endothelial dysfunction, reduced vasoreactivity, and subclinical atherosclerosis.[9] PCOS predisposes these women to a 50% increased risk for incident cardiovascular diseases. Various classic and non-classic cardiovascular risk markers cluster in PCOS women, such as abdominal adiposity, insulin resistance, chronic low-grade inflammation, increased oxidative stress and endothelial dysfunction.[10] A variety of circulating proatherogenic inflammatory mediators are independently increased in PCOS which predicts the early onset of adverse cardiovascular events.[8] Uric acid is one of these newly described non-classic cardiovascular risk marker.[11]

Uric Acid, an end product of purine metabolism; exerts proinflammatory, prooxidant and proliferative actions at the endothelial cell level. Raised uric acid levels are associated with increased risk of cardiovascular morbidity and mortality. In PCOS, androgens may increase serum uric acid levels by inducing the hepatic metabolism of purines.[11] In current study, we determined serum uric acid to identify PCOS women at risk of CVD.

PCOS women typically present to clinician early in life due to menstrual irregularity and androgen excess, when T2DM and CVD are rarely evident. These women represent an ideal population in which we can develop and implement strategies for prevention of these life threatening comorbidities; with the ultimate goal of reducing the enormous impact on health cost and improve the quality of life. In this view, we assessed HbA_{1c} and uric acid level in PCOS women to identify women at the risk of early onset of diabetes & cardiovascular disease.

Materials and Methods

After written and informed consent, 60 patients with a diagnosis of PCOS, between the age group 20–35 years were selected and compared with 60 healthy age matched controls. Study protocol was approved by the Institutional Ethical Committee. Baseline data including age, body mass index (BMI), and waist: hip ratio (W/H), systolic/diastolic blood pressure, medical history, clinical examinations and biochemical investigations were put in as part of the study design.

PCOS was diagnosed according to the Rotterdam criteria. Presence of two of the following three features confirmed the diagnosis: 1) clinical and/or biochemical signs of hyperandrogenism; 2) oligo- and/or anovulation; 3) polycystic ovaries (by ultrasound; presence of $\geq$ 12 follicles in each ovary measuring 2-9 mm in diameter).[3]

PCOS women did not take any medication like oral contraceptive pills, glucocorticoids, antiandrogens, anti-obesity drugs, lipid lowering drugs during the previous 6 months. Subjects with known diabetes were not included in this study. Patients with thyroid disorder, renal diseases, cardiovascular diseases, anemia, smoking and alcoholism were excluded from the study. Family history of PCOS, family history of diabetes, family history of infertility was the confounding factors in this study. We excluded such patients in our study.

Blood samples were collected from all participants and analyzed for HbA_{1c} and uric acid level. HbA_{1c} was measured by Ion Exchange Resin Method using commercial kits from ERBA diagnostics. There are certain limitations of this method: Levels are raised in anemia patients and fall during second trimester of pregnancy. Hemoglobinopathies, decreased red cell survival times, gross lipemia, turbidity will show incorrect results. Serum uric acid level was assessed by Uricase end point method. Fasting blood glucose level was analyzed by using Glucose Oxidase-Peroxidase (GOD-POD) method.

Detection Limit of various parameters is as follows: i) $HbA_{1c:}$ upto 18 %; ii) Serum Uric Acid upto 25 mg%; iii) Fasting Blood Glucose upto 500 mg%.

Glycated hemoglobin value of 5.7% was considered as the cut-off value for 'elevated HbA_{1C}'. HbA_{1c} between 5.7–6.4% is considered as prediabetes and $HbA_{1c} \geq 6.5\%$ is considered as type 2 DM (American Diabetes Association, 2013).[3]

Statistical analysis

Data were analyzed using GRAPH PAD PRISM software, version 5. Data are interpreted as mean ± S.D. The differences between groups were assessed using student's unpaired t-tests.

Pearson's correlation coefficients were calculated to assess the correlation between the biochemical parameters. 'P' value < 0.05 was considered statistically significant.

Result

A description of demographic characteristics of the study and the control group is shown in Table 1. BMI and W/H ratio were significantly increased in PCOS group than control group. No significant difference was found in systolic and diastolic blood pressure. Biochemical parameters i.e., HbA_{1c}, uric acid and fasting blood glucose levels were significantly increased in PCOS group than in control group. (Table 2) HbA_{1c} and uric acid showed significant positive correlation with BMI and W/H ratio. (Table 3)

Out of 60 PCOS patients, HbA_{1c} level was increased in 24 patients (40%). 22 patients (37 %) had HbA_{1c} value between 5.7% and 6.4% (prediabetes) and 2 patients (3 %) had HbA_{1c} level of ≥ 6.5% (type 2 diabetes mellitus). In remaining 36 PCOS patients (60 %), the HbA_{1c} was < 5.7% (normal).

Table 1: Comparison of Demographic Characters in PCOS and Control Groups

S. N.	Clinical Parameters	Controls (60)	PCOS (60)	'P' value
1.	Age (years)	26.48 ± 6.12	25.91 ± 5.63	> 0.05
2.	BMI (Kg/m^2)	23.15 ± 3.72	27.33 ± 5.19	< 0.05*
3.	W/H ratio	0.79 ± 0.08	0.85 ± 0.11	< 0.05*
4.	Systolic Blood Pressure (mmHg)	118.82 ± 9.3	119.21 ± 7.04	> 0.05
5.	Diastolic Blood Pressure (mmHg)	78.42 ± 5.91	80.37 ± 7.63	> 0.05

Table 2: Comparison of Biochemical Parameters in PCOS and Control Groups

S. No.	Biochemical Parameters	Controls (60)	PCOS (60)	'P' value
1.	HbA_{1c} (%) Normal : 4.2–5.7 % Prediabetes : 5.7–6.4% Diabetes : ≥ 6.5%	4.97 ± 0.7	5.86 ± 1.07	< 0.001*
2.	Fasting Blood Glucose (mg %) Reference Range : 70-100 mg%	89.82 ± 7.34	102.65 ± 9.75	< 0.001*
3.	Uric Acid (mg %) Reference Range : 3-5.7 mg%	4.67 ± 0.86	6.90 ± 1.05	< 0.001*

Table 3: Correlation of HbA_{1c} and Uric Acid with BMI, W/H Ratio in PCOS Group

Biochemical parameters	BMI (Kg/m^2)	W/H ratio	'P' value
HbA_{1c} (%)	0.56	0.49	**< 0.01***
Uric Acid (mg %)	0.47	0.6	**< 0.01***

Discussion

PCOS is a chronic, reproductive, inflammatory disorder. Its manifestations usually begin in adolescence with evolution to include infertility and cardio-metabolic complications over a period of time.[2] PCOS should no longer be considered as purely gynecological disorder because of its predisposition to various cardiac and metabolic risk factors such as; obesity, glucose intolerance, atherogenic dyslipidemia and hypertension. A consequent increase in the long-term risk of type 2 diabetes mellitus and cardiovascular diseases signify that PCOS carries a tremendous health care burden.[12] So, PCOS originally started as a gynecological interest, has turn out to be a multisystem endocrinopathy over the years.

In our study, mean HbA_{1c} was elevated in PCOS patients and showed positive correlation with BMI and W/H ratio. The prevalence of raised HbA_{1c} in PCOS patients was 40% of which 37% were prediabetic and 3% were having diabetes. In a study by Sebastiao Medeiros et al; HbA_{1c} was raised in 38% PCOS patients; 35% with prediabetes and 3% with diabetes.[7] Jin Ju Kim et al found 31.2% prevalence of raised HbA_{1c} in PCOS women.[13] de Medeiros SF et al, found that HbA_{1c} was raised in 46 % of PCOS women.[14]

PCOS women demonstrate an expeditious progression from prediabetic phase to diabetes mellitus and the risk of early onset of diabetes mellitus is increased in these young women.[5] As diabetes by itself is a risk factor for CVD and other comorbidities; it is very important to detect

a disturbed glucose metabolism at an early stage in these young women. This will help to implement lifestyle interventions and medical therapies as soon as possible in order to prevent progression to diabetes.[3] Assessing HbA_{1c} level periodically may be a useful novel approach for screening of prediabetes and diabetes in this young, high risk PCOS population.[13]

PCOS is a proinflammatory state.[8] Insulin resistance and consequent hyperglycemia in PCOS leads to the inflammation by producing various inflammatory mediators.[15] Chronic low grade inflammation in PCOS results in endothelial dysfunction and facilitates the initiation of an early atherosclerotic process. Serum inflammatory biomarkers are being increasingly recognized as early predictors of atherosclerosis and cardiovascular diseases. Uric acid is one of this newly described inflammatory risk factor for CVD.[11]

In our study, uric acid levels were significantly increased in PCOS women and showed positive correlation with BMI and W/H ratio. Other studies by N. Swetha et al,[5] Ramzi J. et al,[16] Guddanti Rajeswari et al[17] also found similar findings. They concluded that uric acid can be used as non-classic cardiovascular risk marker in PCOS patients for early prediction of disease.

Increased uric acid levels in PCOS women can be explained by the inhibitory effect of hyper insulinism on renal excretion of uric acid.[11] Endothelial dysfunction and chronic inflammation in PCOS also contributes to elevated uric acid level.[17] Studies have shown that, decrement in serum uric acid concentration of high-risk patients improved the endothelial function and resulted in reduced cardiovascular morbidity and mortality.[18] As PCOS women have 50% increased risk for cardiovascular complications, serum uric acid can be used for early detection of high risk patients.

About 60%-70% of PCOS women present with central obesity. Obesity is linked with insulin resistance and increased risk of diabetes, hypertension, dyslipidemia, endothelial dysfunction and heart disease.[18] In this study, HbA_{1c} and uric acid showed positive correlation with BMI and W/H ratio in PCOS women. This indicates that obesity also plays an important role in this disorder.

Until now, management of PCOS is typically focused on the specific symptoms such as menstrual irregularity and infertility. However, looking into the intricate nature of the syndrome, a large number of complications will have to be addressed in the near future. PCOS has a long prodromal phase with noticeable abnormalities throughout the life cycle of affected women. Accordingly, adolescent girls with PCOS should be evaluated and treated in a manner analogous to adult PCOS. This will ensure quality health in adulthood, restore self esteem and will reduce the healthcare burden. Lifestyle interventions (diet and exercise) should be robustly encouraged in PCOS, which will improve reproductive outcome as well cut down the risk of diabetes mellitus & cardiovascular diseases.

The limitation of this study is that we enrolled only a small number of women attending tertiary care centre. This may have resulted in selection bias and limited the generalization to the community. Further long-term prospective studies are needed in large cohort to understand the potential role of HbA_{1c} and uric acid for early prediction of abnormal glucose tolerance and cardiovascular events in PCOS women.

Conclusion

In our study, significantly increased HbA_{1c} and uric acid levels correlating with BMI and W/H ratio are found in PCOS patients. These parameters are associated with untoward healthcare outcome in terms of type 2 diabetes mellitus and cardiovascular diseases. Use of these simple biochemical variables might prove worthwhile in early perception of adverse health consequences in PCOS. This will help to redefine the paradigms of PCOS care in India.

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