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Research Article

STUDY OF GLYCATED HEMOGLOBIN LEVELS IN POLYCYSTIC OVARY SYNDROME

RENUKA P*, SHAKTHIYA T, VINODHINI VM

Department of Biochemistry, SRM Medical College Hospital & Research Centre, Kattankulathur, Kancheepuram - 603 203, Tamil Nadu, India. Email: rpangaluri@gmail.com

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ABSTRACT

Objective: Polycystic ovarian syndrome (PCOS) is often accompanied by insulin resistance, obesity, and cardiometabolic risk factors. Androgen excess-PCOS recommends oral glucose tolerance test or glycated hemoglobin (HbA_{1C}) to evaluate dysglycemia in PCOS subjects. We undertook this study to evaluate the prevalence of elevated HbA_{1C} levels in PCOS women.

Methods: The study was carried out among 100 PCOS patients from SRM Hospital, 100 healthy individuals were included as controls. Fasting glucose, HbA_{1C}, Insulin and Homeostasis Model Assessment-Insulin Resistance Index were estimated.

Results: Patients with polycystic ovary syndrome showed a significant increase in HbA_{1C} levels (5.799±1.022; 4.96±0.625, p=0.001) when compared to the control group.

Conclusion: We found elevated HbA_{1C} levels in PCOS women categorizing 26% as prediabetes and 28% as having type 2 diabetes mellitus.

Keywords: Glycated hemoglobin, Polycystic ovarian syndrome, Pre-diabetes, Type 2 diabetes mellitus.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a metabolic disorder with obesity-related cardiovascular risk factors, infertility, dyslipidemia, and pro-atherogenic lipid alterations increasing the susceptibility to cardiovascular disease [1]. PCOS subjects are at high risk of developing insulin resistance, dysglycemia and type 2 diabetes mellitus (T2DM). In 2010, a consensus statement by Androgen Excess Society recommended that a 2 h oral glucose tolerance test (OGTT) should be performed in PCOS women with a body mass index (BMI) >30 kg/m^2, alternatively in lean women or overweight PCOS women with advanced age (>40 years), a personal history of gestational diabetes mellitus or family history of T2DM [2].

American Diabetes Association (ADA) recommended the usage of glycated hemoglobin (HbA_{1C}) levels for making a diagnosis of prediabetes and diabetes keeping in view that fasting is not required for estimation of HbA_{1C} and it also gives a time-averaged estimate of blood glucose over the preceding 8–12 weeks [3].

Based on ADA recommendation, HbA_{1C} is endorsed by androgen excess PCOS (AE-PCOS) for assessment of dysglycemia in PCOS women. Hence, the current study was undertaken to determine the prevalence of elevated HbA_{1C} levels in PCOS subjects.

METHODS

The study protocol was reviewed and approved by the Ethics committee of SRM Medical College Hospital and Research Centre (vide letter No.740/IEC/2015) and informed written consent was obtained from all the participants at the time of enrollment in the study.

The cross-sectional study was carried out among 100 PCOS patients attending infertility Outpatient Department at SRM Medical College Hospital and Research Centre. 100 healthy age-matched women were included as controls. PCOS subjects were selected based on Rotterdam criteria [4]:

Out of the three criteria, two are required for diagnosis:

- Hyperandrogenism
- Clinical (hirsutism or less commonly male pattern alopecia) or
- Biochemical (raised free androgen index or free testosterone).
- Oligo/anovulation·
- Polycystic ovaries on ultrasound.

Subjects were excluded from the study if they had thyroid or other endocrine disorders or taking steroids, insulin-sensitizing drugs.

4 ml of venous blood was collected from all subjects after 12 h overnight fasting for plasma glucose and HbA_{1C} in appropriate vacutainers. The samples were processed on the same day. Plasma glucose was analyzed in the Beckman Coulter (California, USA) AU480 chemistry autoanalyzer using kits procured from the same company. HbA_{1C} was measured by high-performance liquid chromatography method using Biorad D-10 (USA) analyzer, and free thyroxine, free triiodothyronine, thyroid-stimulating hormone, insulin, and prolactin were measured using FEIA technique in TOSOH AIA 360 (Japan) hormone analyzer. Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR) was calculated using the formula:

Fasting insulin (μIU/ml)×Fasting glucose (mg/dl)/405

BMI was calculated using the formula: Weight (kg)/Height^2 (m^2)

World Health Organization (WHO) recommendations were utilized to classify patients into underweight if BMI ≤18 kg/m^2, normal weight if BMI 18–22.9 kg/m^2, overweight if BMI was 23–24.9 kg/m^2 and obese if BMI ≥25 kg/m^2.

The ADA in 2010 [5] suggested the utility of HbA_{1C} for the diagnosis of prediabetes and diabetes mellitus using the following criteria:

Normal	4.3–5.6%
Prediabetes	5.7–6.4%
Diabetes mellitus	≥6.5%

Statistical analysis

All the data were expressed as the mean and standard deviation. The statistical significance for PCOS and healthy subjects was analyzed using independent Student's *t*-test. Pearson's correlation analysis was done to study the association between HbA_{1C} and BMI in PCOS patients.

RESULTS

The basic characteristics and mean distribution of biochemical parameters in the cases and controls are depicted in Table 1.

The mean levels of fasting plasma glucose, insulin, HOMA-IR were found to be significantly elevated in the PCOS patients compared to controls.

Patients with polycystic ovary syndrome showed a significant increase in levels of HbA_{1C} (5.799±1.022; 4.96 ±0.625, *p<0.001) when compared to the control group.

HbA_{1C} levels in PCOS patients were found to correlate positively with BMI, fasting blood sugar (0.556, p<0.001) and Insulin (r=0.221, p=0.027) which are depicted in Table 2.

DISCUSSION

In our study, we observed that 54% of PCOS subjects had elevated HbA_{1C} levels. These statistics are much higher than those reported by a Korean study (31%) [6]. In a study conducted on Turkish patients with PCOS, only 7.6% showed HbA_{1C} values more than 5.6% [7]. About 8.6% of Danish PCOS subjects had more than 6% HbA_{1C} [8].

There was a significant difference in mean HbA_{1C} levels between patients with PCOS and controls (5.79±1.02 vs. 4.96±0.62). This finding is in concurrence with a Korean study which reported mean elevated HbA_{1C} levels (5.55 ± 0.34 and 5.31 ± 0.24) between PCOS patients and controls. In their study, a significant association was demonstrated between PCOS and elevated HbA_{1C} following adjustments for cardiovascular risk factors such as alcohol, BMI, hypertension, smoking, high-sensitivity C-reactive protein, and dyslipidemia, on performing a multivariate regression analysis. They showed that the odds of having increased HbA_{1C} was 6.67 times higher in Korean PCOS patients [6].

We found significantly higher BMI among PCOS patients which correlated positively with the HbA_{1C} levels. Our findings are supported by Legro *et al.* [9] who observed that as BMI increased in PCOS patients, there was an increased prevalence of glucose intolerance. They also showed an independent association between increased risk of T2DM and high baseline levels of fasting plasma glucose, BMI and response to glycemic load. A prospective, randomized study performed in North India on PCOS women showed that Myo-inositol and metformin were effective in decreasing their BMI, thereby improving insulin sensitivity [10].

Table 1: Mean distribution of biochemical parameters in PCOS cases and controls

Parameter	Controls	Patients	p value
BMI (kg/m^2)	21.486±1.823	23.207±4.293	0.0003*
HbA1C (%)	4.96±0.625	5.799±1.022	<0.001*
FBS (mg/dl)	87.91±11.31	93.51±16.67	0.006*
Insulin (µU/ml)	6.373±2.144	7.3745±3.7954	0.022*
HOMA-IR	1.376±0.4879	1.687±1.0069	0.006*

Values are expressed in mean±standard deviation. The values are statistically significant if the *P*<0.05*. PCOS: Polycystic ovarian syndrome, BMI: Body mass index, HbA_{1C}: Glycated hemoglobin, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index, FBS: Fasting blood sugar

Table 2: The Pearson's correlation analysis between HbA_{1C} (5.799±1.022) and BMI, FBS, insulin, HOMA-IR in PCOS patients

Parameter	Mean±SD	r value	p value
BMI (kg/m^2)	23.207±4.293	r=0.259	p=0.0092*
FBS (mg/dl)	93.51±16.67	r=0.556	p=0.0001*
Insulin (µU/ml)	7.3745±3.7954	r=0.221	p=0.027*
HOMA-IR	1.687±1.0069	r=0.343	p=0.0047*

The values are statistically significant if the *P* value is<0.05*. PCOS: Polycystic ovarian syndrome, BMI: Body mass index, HbA_{1C}: Glycated hemoglobin, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index, FBS: Fasting blood sugar, SD: Standard deviation

Fasting glucose levels between 100 mg/dL and 125 mg/dL were used for defining prediabetes. Based on this we found that 27% of PCOS women were having a prediabetic state and 17% of PCOS subjects came under T2DM (≥126 mg/dL). ADA suggested that HbA_{1C} can be used for assessment of diabetes in PCOS women. The prevalence of prediabetes was 26%, and that of diabetes was 28% in PCOS subjects using HbA_{1C} for assessment of diabetes in our study. A study on 671 PCOS women from Austria showed a prevalence of 12.8% and 1.5% for prediabetes and T2DM, respectively [11]. Some studies have advocated PPBS as a better predictor of overall glycemic status [12].

We categorized PCOS subjects by BMI as non-obese <25 kg/m^2) and obese (≥25 kg/m^2) according to the definition for Asians (WHO Western Pacific region, 2000) and the prevalence of elevated HbA_{1C} was analyzed. We found that 45% of non-obese PCOS subjects had HbA_{1C} ≥5.7 and the number of obese subjects with elevated HbA_{1C} was 10. The prevalence of pre-diabetes is found to be 35% among obese and 24% in non-obese PCOS cases. 50% of obese PCOS subjects and 23% of non-obese PCOS cases were diagnosed as T2DM based on the HbA_{1C} levels.

AE-PCOS Society suggested that OGTT must be performed in obese patients or in lean subjects over 40 years of age [13]. In view of our finding, we suggest that even young and non-obese subjects with PCOS need to be screened for type 2 diabetes to ensure early intervention. Comparison of diagnostic methods for identifying pre-diabetes and diabetes in PCOS subjects by Hurd *et al.* [14] showed that HbA_{1C} was effective in identifying 20% subjects with normal OGTT as having pre-diabetes and concluded that PCOS patients should be screened for glycemic status using HbA_{1C} or OGTT.

Elevated HbA_{1C} levels have been associated with risk factors for cardiovascular disease and the presence of metabolic syndrome in many clinical conditions. It has been observed that a 1% increase in the absolute HbA_{1C} concentration is associated with a 10–20% increase in cardiovascular risk [15].

In view of the high prevalence of cardiometabolic risk factors and risk of cardiovascular disease, early detection of pre-diabetes is of great importance in women with PCOS. A large percentage of PCOS subjects with pre-diabetes were shown to progress to type 2 diabetes in a few years [16]. The rate at which they progressed to develop T2DM was found to be 2–3% [17,18].

CONCLUSION

We found elevated HbA_{1C} levels in PCOS women categorizing 26% as pre-diabetes and 28% as having T2DM. We suggest that HbA_{1C} may be used as a screening tool for identifying pre-diabetes and T2DM among PCOS subjects due to its advantages such as convenient sampling (since fasting is not mandatory) and less variability due to illness or stress.

Further studies are necessary to assess whether HbA_{1C} is as effective as OGTT as a diagnostic tool for diabetes in patients with PCOS.

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CONFLICT OF INTEREST

All authors hereby declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTIONS

All authors have made substantial contribution to the work reported in the manuscript. Renuka. P: Conception and designing of the study, data analysis and interpretation, drafting of the article, critical revision of the article, final approval of the study to be published. Shakthiya. T: Data collection, data analysis and interpretation, drafting of the article Vinodhini VM: Drafting of the article, critical revision of the article, final approval of the study to be published.

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