EVALUATION OF GLYCATED ALBUMIN AND HbA1c LEVELS WITH BODY MASS INDEX IN POLYCYSTIC OVARIAN SYNDROME CASES

Suresh Babu Kondaveeti

1Associate Professor, Department of Biochemistry, NIMS Medical College, NIMS University, Jaipur, Rajasthan, India.

BACKGROUND
Polycystic ovarian syndrome (PCOS) is a highly prevalent endocrine-metabolic disorder that implies various severe consequences to female health, including alarming rates of infertility. Although its exact etiology remains elusive, it is known to feature several hormonal disturbances including hyperandrogenemia, Insulin Resistance (IR) and hyperinsulinemia.

Hyperinsulinemia was noted in 60% to 80% of PCOS cases and plays a central role in the development of further complications. The prevalence of obesity in PCOS ranges from 48% to 85%.

The aim of the study is to evaluate Glycated Albumin (GA) and HbA1c levels with Body Mass Index (BMI) in Polycystic Ovarian Syndrome (PCOS) cases.

MATERIALS AND METHODS
This case-control study performed at NIMS Hospital, NIMS University, Jaipur includes 60 PCOS patients and 60 age matched healthy controls of any age. Fasting venous blood samples were obtained for analysis of fasting blood glucose, GA and HbA1c.

RESULTS
GA and HbA1c levels are higher in cases (16 ± 2.85), (6.4 ± 0.20) than in controls (14 ± 0.75), (5.45 ± 0.10). Out of 60 cases, 28 are pre-diabetic range (GA < 16-18%, HbA1c 5.75 ± 6.40%), 20 are in diabetic range (GA >18%, HbA1c >6.40) and 12 are in non-diabetic range (GA <14%, HbA1c <5.8%). BMI of PCOS cases (25.45 ± 3.4 kg/m²) was significantly higher than controls (21.25 ± 2.8 kg/m²). Both GA and HbA1c shows significant correlation with BMI.

CONCLUSION
From the above study we concluded that BMI associated with glycemic index in PCOS.

KEYWORDS
Glycated Albumin, HbA1c, Body Mass Index, Polycystic ovarian syndrome.

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BACKGROUND
Polycystic Ovarian Syndrome (PCOS), it is a common endocrine disorder affecting 4–12% of women. The consensus definition of PCOS recognizes obesity as an association and not a diagnostic criterion, as only 40–50% of women with PCOS are overweight.1 Other causes of menstrual disturbance and hyperandrogenism must be excluded by appropriate endocrine investigations. The World Health Organization defines normal weight for adults as a body mass index (BMI) of 18.5–24.99 kg/m², overweight with a BMI of 25 kg/m² or more, and obese with a BMI of 30 kg/m² or more.2 Insulin suppresses the secretion of sex hormone-binding globulin by the liver, leading to increased levels of free circulating testosterone. Women with PCOS are more insulin resistant than weight-matched women who do not have the syndrome.3 Insulin resistance (IR) is seen in approximately 10–15% of slim and 20–40% of obese women with PCOS, and women with PCOS are at increased risk of developing type II diabetes, the more overweight an individual the greater the degree of IR.4 Hyperinsulinemia was noted in 60% to 75% of PCOS cases and played a central role in the development of further complications. In spite of hyperinsulinemia, there is an increased prevalence of insulin resistance (IR) in PCOS patients which can lead to increased glucose tolerance and type 2 diabetic mellitus (T2DM). Increased insulin leads to increased androgen production from the ovarian thecal cells and this hyperandrogenemia is responsible for androgenic obesity.5 GA and HbA1c parameters are routinely measured to check the glycemic control over a proceeding 3-12 week of time. They are used as indicators for the state of glycemic control, progression of the disease and development of complications in diabetic cases.6,8

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Corresponding Author:
Dr. Suresh Babu Kondaveeti, Associate Professor,
Department of Biochemistry,
NIMS University, Jaipur,
Rajasthan, India.
E-mail: sureshbabu_kondaveeti@yahoo.com
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MATERIALS AND METHODS
The present case control study was conducted in NIMS Medical college& hospital, NIMS University, Jaipur, Rajasthan. After getting written consent from the cases and controls, detailed history were obtained and recorded in their respective proforma. They were subjected to physical examination and anthropometric measurements as per protocol followed by systemic examination, urine pregnancy test was done to rule out pregnancy, ultrasonography of abdomen and pelvis were performed in all subjects of this study.

Inclusion Criteria
45 diagnosed cases of PCOS as per Rotterdam definition - the existence of the following three criteria to make the diagnosis of PCOS:
1. Oligo-ovulation or anovulation;
2. Clinical or biochemical signs of hyperandrogenism; and
3. Polycystic ovaries by ultrasonography

Exclusion Criteria
Any history suggestive of other potential causes, hyperandrogenism/oligo/amenorrhea (congenital adrenal hyperplasia, androgen secreting tumor), hypothyroidism, Cushing’s syndrome, hyperprolactinemia, other pituitary/adrenal dis- orders, other insulin resistance conditions (acromegaly), history of any drug intake and pregnancy.
45 age matched healthy females with regular menstrual cycle and not on any treatment were enrolled as controls.

Anthropometric Measurements
The weight and standing height of all study subjects were measured twice by using calibrated weighing scale and stadiometer with a fixed vertical backboard and an adjustable head piece respectively by two different examiners to avoid subjective error. BMI is expressed in the units of kg/m². BMI can be calculated by the present weight in kg divided by square of height in meters (Quetelet index). According to the World Health Organization, BMI can be graded into the categories listed in Table 1.

Sample Collection
Venous blood samples were collected from all the subjects after at least 8 hours fasting on the second day of menstruation. Blood specimens were collected into EDTA tubes for GA, HbA1c and in Serum Separator Tube for fasting glucose (FBG) and uric acid. All the biochemical analysis was performed using a Hitachi 902. The plasma glucose was estimated by GOD-POD method using a Olympus auto analyser In the fasting sample. In addition to plasma glucose, Glycated albumin and HbA1c were measured. Plasma GA levels were measured by an enzymatic method by using albumin specific protease, ketamine oxidase and an albumin assay reagent on a Hitachi Auto analyser (Lucica GA-L, Asahi Kasei Pharma Corp, Tokyo, Japan). HbA1c was estimated by high-performance liquid chromatography (Bio-Rad) according to International Federation of Clinical Chemistry (IFCC) and transferable to diabetes control and complications trial/national glycohaemoglobin standardization program (DCCT/NGSP).

Prolactin, total testosterone, luteinising hormone (LH) & follicular stimulating hormone (FSH) were estimated on the Advia Centaur’ CP immunoassay system by chemiluminescence method. Thyroid s m-ula ng hormone (TSH) was quantitated by immune radiometric assay by IRMA kit (IRMAK - 9).

Statistical Analysis
Unpaired ‘t’ test and two-tailed Pearson’s correlation were done between variables of PCOS cases and controls using the IBM SPSS version 20 statistical package. Data were considered to be significant if p <0.05 and highly significant with p <0.001.

RESULTS
Out of 60 PCOS cases, 20 cases had a history of sudden weight gain. Based on BMI divisions, 28 cases and 9 controls were overweight and obese (>25 kg/m²) with statistically significant difference between cases and controls (p=0.005). 18 cases with in the normal range of BMI and 3 cases were under weight.

We observed that 14 cases and 4 controls had FBG >100 mg/dl with nonsignificant p value >0.05. We also noted that GA and HbA1c parameters showed statistical significance (P=0.005) between cases (16+1.5% & 6.08+1.28%) and controls (14.24+0.25 & 5.34+0.54).

We have also noted from the data of GA and HbA1c, 25 cases were in pre-diabetic range (14.75+2.25 & 5.75+6.6), and 26 cases were in diabetic range (>18% & 7) according to ADA criteria.

The prevalence of T2DM is seen in 16 cases of PCOS and pre-diabetes seen in 22 PCOS cases of below normal BMI. But the prevalence of T2DM and pre-diabetes were seen in 6 and 16 overweight PCOS cases respectively.

There were 15 cases in pre-diabetic range with FBG 100-120 mg/dl. But in controls we noticed three cases in pre-diabetic range.

Two tailed Pearson’s correlation between parameters.
Our study showed that GA and HbA1c had positive correlation with BMI (r = 0.432, 0.408 p=.0018 & .001)

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<tbody>
<tr>
<td>1.</td>
<td>FBG (mg/dl)</td>
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<td>91.45±2.25</td>
<td>0.354</td>
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<td>2.</td>
<td>HbA1c (%)</td>
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<td>3.</td>
<td>GA (%)</td>
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Table 1. Anthropometric Parameters Description

*Significant difference, **Highly significant difference

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Table 2. t and p Values of Various Parameters

*Significant difference, **Highly significant difference
The DISCUSSION

The present study represents the first of its kind to investigate the relation between BMI and GA and HbA1c levels in PCOS cases. Our results showed strongest association between BMI and GA and HbA1c levels in PCOS cases.

GA and HbA1c in circulation are indicators of blood glucose control. GA is used as short term glycemic index over the past 3 weeks or more whereas, HbA1c widely used as long term glycemic index to monitor blood glucose over the past 8 weeks or more. GA and HbA1c both undergo permanent non-enzymatic glycation in line with the surrounding glucose concentration. The formation of HbA1c may be affected by anaemia, so, in our study we avoided the PCOS cases with anaemia.

Lerchbaum et al reported that the prevalence of obesity was 24.8% and overweight was 21.8% among PCOS women. Gomathi et al found that 54% of the women with PCOS were overweight or obese with respect to WHO classification of BMI grading. Randeva et al re-viewed that excess triglycerides enter into cells and activate proteins kinase C-β and C-β, ultimately reducing the glucose uptake. This leads to compensatory hyperinsulinemia which can stimulate excess fat deposition by hypertrophy and hyperplasia of adipose cells in the excess calorie environment. This is further aggravating IR by increasing obesity as a vicious cycle. This abnormal fat accumulation increases IR causing glucose intolerance and T2DM.

The prevalence of obesity in the PCOS population ranges from 38% to 87%. It has been re-ported that in obese PCOS women, the prevalence of IR was higher than obese women with normal menstrual cycle in the control group. Previous studies have indicated that obesity is negatively associated with GA and GA/A1c ratio. However, the underlying mechanisms of this relationship remain to be answered, and they were not fully evaluated in subjects with PCOS.

On the other hand, other studies have suggested that the negative association of obesity with GA is due to abnormal albumin concentrations in obese subjects. However, Nishimura et al indicated that obese children had higher serum albumin than non-obese children. Based on these unclear answers for the mechanism of the association between BMI and GA/A1c ratio, we tried to explain this mechanism with respect to BMI in PCOS cases, a representative parameter for obesity, and insulin secretory function. In accordance with the increase of BMI, insulin secretory function might be also increased to overcome the insulin resistance.

As OGTT (Oral glucose tolerance test) is time consuming one, GA or HbA1c along with FBG have been suggested as screening tools for pre-diabetes and type 2 diabetes. Now a days HbA1c has been replacing for its screening role in diabetes we tried GA in our study as superior screening tool for dysglycaemia assessment in PCOS cases. High levels of LH lead to bulk stromal growth leads to increased ovarian volume. And high circulating LH levels stimulates ovarian thecal cells to produce more androgens leading to hyperandrogenemia in turn leads to increased male pattern of fat accumulation both subcutaneously and around viscera which in turn leads to obesity with increased BMI. Trans, high saturated fat diet, less poly unsaturated fatty acid (PUFA) intake, high fructose intake, low fat and high carbohydrate diet, sedentary life style, leptin resistance contribute high triglycerides and VLDL levels in the circulation which can alter plasma membrane composition resulting in malfunctioning of insulin receptors.

The prevalence of IR maximum in obese PCOS cases compared to normally menstruating obese women. IR had a
key role in pathogenesis of PCOS. Though obesity is prevalent in PCOS women in our study only 22 cases are obese. Hyperinsulinemia causes direct hypothalamic effects which lead to increased appetite and gonadotropin secretion results high LG secretion in PCOS which leads to excessive androgen production in ovaries. Kumar et al also observed higher BMI in women with PCOS than in controls. In our present study our results showed that 28 cases had increased BMI and increased GA and HbA1c levels. 8 cases had normal BMI with increased GA and HbA1c levels. Among controls 3 women were having increased GA and HbA1c levels with increased BMI and 2 women with normal BMI but increased GA and HbA1c levels.

CONCLUSION
Our findings suggest that BMI strongly Associated glycaemic parameters such as GA and HbA1c in PCOS women.

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REFERENCES


