Prevalence of Abnormal Glucose Metabolism and Dyslipidemia Across Different Categories of Body Mass Index Among Women with Polycystic Ovarian Syndrome

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Background: Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies among reproductive aged women. It is associated with metabolic problems such as obesity, insulin resistance and dyslipidemia. Obesity in itself is associated with insulin resistance and dyslipidemia. However, it remains unclear whether lean and obese PCOS women share the same metabolic profiles.
Objective: The aim of this study was to identify the prevalence of abnormal glucose metabolism and dyslipidemia across different categories of body mass index among women with PCOS
Methods: A retrospective cross – sectional study included 160 PCOS patients covering the years 2015 to 2017 was performed. Fisher's exact test, one-way analysis of variance using Fisher-Hayter multiple comparisons procedure and independent-test were used to compare the prevalence of disease among the different categories of body mass index (i.e. non-obese, overweight and obese).
Results: Among obese patients, the prevalence of pre-diabetes was 39.33% (35/89) and Type II diabetes mellitus was 8.99% (8/89). Among overweight, pre-diabetes patients were at 16.67% (5/30), while diabetics were only 6.67% (2). Among the non-obese population, only 17.07% (7/41) were classified as pre-diabetics while only 2.44% (1/41) were considered diabetic. For the prevalence of dyslipidemia, overweight and obese patients had the most proportion of affected individuals, at 90% (27/30) and 87.64% (78/89), respectively.
Conclusion: Abnormal glucose metabolism and dyslipidemia are more prevalent among obese and overweight women compared to non-obese PCOS patients.

Key words: polycystic ovarian syndrome, body mass index, insulin resistance, dyslipidemia

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies among women of reproductive age.[1,2] It affects about 5-20% of women worldwide.[3] The Philippine Society for Reproductive Medicine recommends the use of the Rotterdam criteria in diagnosing PCOS among Filipino women.[4] Following this criteria, a diagnosis of PCOS is made when a woman presents with at least two of the three characteristic features of PCOS namely: oligo-anovulation, clinical and/or biochemical signs of androgen excess, and polycystic ovarian morphology.[3]

The diagnosis of PCOS is primarily clinical requiring emphasis on history and physical examination. Menstrual irregularities is the common complaint, which easily allows the clinician to identify oligo-anovulation. Clinical signs of androgen excess may present as hirsutism or acne.

The severity of hirsutism is clinically determined by using the Modified Ferriman Gallwey (MFG) scoring system. This system scores the amount of hair in nine androgen-sensitive body areas.[4] The firm threshold value of hirsutism is still debated but ranges between MFG scores of 6 to 9 among Caucasians.[5] Population-based studies have suggested ethnic-specific cutoffs. In Thailand, an MFG score of ≥3 is hirsute, while in China, the accepted score for hirsutism is ≥5.[6,7] In an unpublished local study, a cut-off score of 3 is suggested among Filipinos.[8] The last diagnostic feature of PCOS is the polycystic ovarian morphology (PCOM). This feature is identified by ultrasound when there are a total of 12 or more follicles measuring 2 – 9 mm in diameter in both ovaries.[5]

Although most women with PCOS consult for menstrual irregularities, it must be highlighted that PCOS should be recognized as a complex syndrome with associated metabolic risks.[9] The etiology of PCOS is both genetic and lifestyle-related.[3] Ultimately, the pathophysiology of this condition is still an enigma. However, insulin resistance and compensatory hyperinsulinemia are said to play important roles in the pathophysiology of PCOS.[5]

Abnormal glucose metabolism is a common feature in women with the disease.[5] About 50–70% of women with the condition show insulin resistance of varying intensities.[10] In the Philippines, a study conducted among thirty-seven PCOS women showed a 93.3% prevalence of insulin resistance using the homeostasis assessment model.[11]

The mechanism for impaired insulin action in PCOS is unclear. It is postulated that there is a post-receptor defect in insulin signaling with increased serine phosphorylation. This leads to decreased expression of an insulin sensitive glucose transport protein (GLUT 4), resulting to abnormal glucose metabolism.[12] Apart from dysglycemia, hyperinsulinemia also aggravates androgen excess by increasing free testosterone actions by reducing the synthesis of sex hormone binding globulin.[13]

Hyperandrogenism is a significant feature of PCOS, as it is the consequence of androgen excess such as hirsutism and ovulatory dysfunction that cause women to seek consult.[14] Androgen excess in PCOS originates from the ovaries and adrenal glands.[15] There is enhanced androgen synthesis by follicular theca cells and an increased peripheral conversion of testosterone to the most potent androgen, 5α–dihydrotestosterone.[3,13,15] It has been said that hyperandrogenic PCOS phenotypes are more inclined to have metabolic syndrome and insulin resistance when compared with non-hyperandrogenic phenotypes.[16]

These factors of insulin resistance and resultant hyperandrogenemia result in a catastrophic cycle as hyperandrogenemia per se affects insulin sensitivity. Testosterone modifies lipolytic activity in visceral adipose tissue favoring release of free fatty acids (FFA) into circulation. This increase in FFA availability causes functional and structural changes in hepatocytes and skeletal myocytes, with the accumulation of metabolites, which promote serine phosphorylation, again resulting to abnormal glucose metabolism.[17]

Alterations in glucose and lipid metabolism are intertwined. The atherogenic lipoprotein profile found in PCOS is likely related to insulin resistance. In insulin-resistant states, there is increased lipolysis and fatty acid release from adipose tissue. Furthermore, androgens are involved in the regulation of lipoprotein lipase and hepatic lipase activity. Women with PCOS have increased levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and decreased levels of high-density lipoprotein cholesterol (HDL-C).[18,19,20] Approximately 70% of women with PCOS have at least one biochemical marker of dyslipidemia.[21]

Overweight or obesity affects approximately 60–80% of PCOS patients. Obesity in itself is associated with insulin resistance and dyslipidemia, independent of PCOS. The association of adiposity with type 2 diabetes mellitus and cardiometabolic risk is well established and has been implicated as the basis of increased cardiometabolic risk in PCOS.[22] Some studies argue that fat distribution, mainly abdominal obesity has more impact on glucose metabolism than total body weight.[23]

On the other hand, non-obese or overweight PCOS women, have also been noted to have a change in body composition with an increase in abdominal fat distribution, which in turn correlates with risk factors such as insulin resistance.[21,24] Evidence suggests that lean women with PCOS have increased levels of pro-inflammatory cytokines in

the blood, which can promote atherosclerosis and cardiovascular disease predisposing them to a greater risk of glucose intolerance and abnormalities in lipid profile.[25]

In addition, some studies suggest that metabolic disturbances occur among PCOS women regardless of body mass index (BMI). In a study conducted by Kar comparing the anthropometric, clinical, and metabolic profiles of different PCOS phenotypes, the author found that among 410 subjects, there was a 13% prevalence of metabolic syndrome among lean PCOS patients and that a significant number of lean women had abnormal waist circumference and waist to hip ratio.[1] In Korea, in a total of 837 females with PCOS aged 15–40, it was found that metabolic syndrome was associated with non-obese hyperandrogenic women with PCOS.[26]

It is agreed, that in all PCOS women, the risk for cardiovascular disease should be assessed.[27] Several guidelines recommend comprehensive cardiovascular risk-factor screening at diagnosis and should be repeated with a frequency stratified by metabolic risk.[3,28,29] Assessment should include family history, ethnic group, BMI, waist circumference, smoking status, blood pressure, glycemic status (oral glucose tolerance test and lipid profile).[28,29] The gold standard for assessment of insulin resistance is the euglycemic and hyperinsulinemic clamp. However, these methods are expensive and not readily available. Therefore, insulin sensitivity is measured by simpler methods, such as an oral glucose tolerance test.[30]

Since majority of studies evaluating the prevalence of glucose intolerance and dyslipidemia among PCOS patients are obese, more studies are needed to understand the metabolic risks in lean PCOS women.[31] Furthermore, the prevalence of obesity varies between different ethnic populations of women with PCOS as lifestyle characteristics within different geographic areas, as well as genetic predisposition to obesity within populations differ.[23] Together, these factors underscore the need for local data on this matter.

The aim of this study was to determine the prevalence of abnormal glucose metabolism and dyslipidemia across different categories of BMI among women with PCOS.

Methods

Study Design and Duration

This is a cross – sectional study done from January 2015 to December 2017. A three - year chart review was performed among PCOS patients referred to the Reproductive Endocrinology and Infertility Outpatient Clinic of UP-PGH.

Study Site

The study was conducted among PCOS women seen in the Reproductive Endocrinology and Infertility Outpatient Clinic of UP-PGH as this clinic serves as a referral center for women diagnosed with PCOS.

Study Population

Inclusion Criteria

1. PCOS patients as diagnosed based on the Rotterdam criteria
2. Reproductive age (18-40)
3. Available baseline glucose testing such as: Fasting blood sugar, 75- gram OGTT or HbA1c and lipid profile
4. Consulting at the Reproductive Endocrinology and Infertility Outpatient Clinic during the period of January 2015-December 2017

Exclusion Criteria

1. Ongoing pregnancy or breastfeeding
2. Diagnosed with type 1 diabetes mellitus
3. Having medical conditions with known effects on lipid profile such as thyroid disease and familial lipid disorders
4. Patients diagnosed with conditions that may present with hyperandrogenism such as androgen secreting tumors, Cushing disease, congenital and non-classical adrenal hyperplasia
5. PCOS patients with incomplete data such as height, weight, baseline glucose testing and lipid profile

Sample Size

A total of 160 PCOS women were included in this study. A cross-sectional study of independent exposed and unexposed groups with a ratio of 2:1 was considered – since there were more women with PCOS who were either overweight or obese. Prior research suggests that the likelihood of insulin resistance or dyslipidemia was around 75% among women with PCOS, thus there was a need to study 146 women to reject the null hypothesis that the exposure rates for both exposure groups are equal with a power of 80% and the Type I error probability associated with such test of the null hypothesis is 95%. An additional oversampling of 10% was included to account for incomplete data

Description of Study Procedures

The protocol for this research was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) for review and approval. Upon approved, the list of new PCOS patients seen in the past three years was retrieved from the Reproductive Endocrinology and Infertility Outpatient Department logbooks. After identification, the primary investigator performed chart retrieval from the UP-PGH medical records. Upon tabulation, patients' names were substituted with a code number. Also retrieved from the chart were age, BMI, results of their baseline 75 gram OGTT or HbA1c, and lipid profile. The data were encoded in a Microsoft excel sheet and submitted for data analysis.

Data Analysis

After data collection, the information was encoded in an electronic spreadsheet and data were processed using the software Stata 13. Baseline characteristics of the population such as age, body mass index and serum parameters for the diagnostic procedures were expressed using mean and standard deviation, and their ranges; while frequency and percentage were used for the presence of diabetes, prediabetes, dyslipidemia and categorized values of the body mass index.

The categorized BMIs of the women in the study population were compared across the presence of normal or abnormal lipid profile values, normal or elevated glucose testing levels; and a diagnosis of diabetes mellitus – using Fisher's exact test. One-way analysis of variance with Fisher-Hayter standardized difference as multiple comparisons procedure was also performed to determine association of actual values of fasting blood glucose, lipid profile and 75-gram OGTT results across ranks of the body mass index. As a result of limited numbers, glycosylated hemoglobin levels were compared across ranks of the body mass index using independent t-test.

The prevalence of insulin resistance, dyslipidemia, overweight and obesity among women with PCOS, and their 95% interval estimates, were also computed. Trend analysis for proportions was performed as well to determine if there is a pattern in the prevalence of abnormal 75-gram OGTT and lipid profile results across the classification of body mass index scores. The level of significance for all sets of analysis was set at a p-value less than 0.05 using two-tailed comparisons.

Results

A total of one hundred sixty (160) women with polycystic ovarian syndrome were included in this study. The average age of the participants was 27 ± 5.87 years old with more than half of the sample less than twenty six years old suggesting a relatively young population of participants in the study,. The youngest patient was 18 years old. By BMI, it can be noted that more than half of the participants were considered obese (n: 89, 55.63%), followed by non-obese women (n: 41, 25.63%) and overweight women (n: 30, 18.75%). The summary of the clinical characteristics is shown in Table I.

The glucose testing and lipid profile values of the study population can also be seen in table I. The average fasting blood glucose of the women appeared to be within the normal range (85.23 ± 17.68), The average results of their 75g OGTT were mostly in the normal range (first hour = 162.09 ± 53.48, second hour = 132.40 ± 46.28) – suggesting that most women appeared to have normal fasting blood glucose and glucose tolerance tests.

Only a tenth of the participants had the results for glycosylated hemoglobin levels, The average

results of this parameter were beyond normal range (5.6 ± 0.47).

Almost three-quarters of the women have desirable total cholesterol levels (n: 116, 72.50%), followed by borderline high level (n: 33, 20.63%) and less than one-tenth of them have elevated total cholesterol levels (n: 11, 6.88%).

For the triglyceride levels, more than half have normal serum levels (n: 109, 68.13%) Some reached borderline high (n: 34, 21.25%), and high levels (n: 17, 10.63%).

About 80% of the women have desirable levels of low-density lipoprotein levels, (n: 128, 80%), followed by those with borderline high levels (n: 26, 16.25%), and few having high to very high levels (n: 6, 3.75%).

In terms of high-density lipoprotein levels, less than half of the women have normal levels (n: 77, 48.13%).

Table 2 shows the overall prevalence of abnormal glucose metabolism and dyslipidemia in the study population. The prevalence of pre-diabetes among all the PCOS women in this study was 29.38% (n: 47, 95% CI: 22.85-36.87%) while it was 6.88% (n: 11, 95% CI: 3.76-12.01%) for diabetes mellitus. The disease burden was even higher for dyslipidemia with an estimated prevalence of 132 (82.5%) among women in this study with the estimate ranging from 75.82 to 87.65 percent.

Among overweight and obese women with PCOS, the prevalence of dyslipidemia appeared significantly higher - which was 88.24% [105/119] with a 95% confidence interval between 81.10 to 92.98 percent. At the same time, the burden of diabetes mellitus was also significantly higher among this group compared to non-obese women with PCOS – which was 8.40% [10/119] (95% CI: 4.47-14.94%).

Table 3 shows the comparison of serum marker levels according to BMI category. For fasting blood glucose, obese patients have significantly higher levels compared to non-obese women (F: 3.30, df: 157, 2; p: 0.04). There was no noted difference between overweight and obese women. A similar observation can be noted for both the first hour (F: 6.33, df: 157, 2; $p<0.01$), and second hour (F: 5.84, df: 157, 2; $p<0.01$) levels of the glucose tolerance test.

Using an independent t-test, the glycosylated hemoglobin levels across BMI categories, it was noted that women characterized as having obesity have higher levels of HbA1C than non-obese women (t: -1.99, df: 18, p: 0.06).

The triglyceride levels show that the serum levels of obese women were significantly higher compared to both non-obese and overweight women (F: 6.71, df: 157, 2; $p<0.01$) – while there was no noted difference between overweight and non-obese women.

Table 1. Clinical characteristics of study population.

Characteristics	Mean ± SD	Range
Age in years	27 ± 5.87	18 to 40
Body-mass index	25.89 ± 4.71	15.6 to 45
Fasting Blood Glucose	85.23 ± 17.68	60.71 to 185.71
75 g OGTT (n=160)		
1st hour	162.09 ± 53.48	66.07 to 407.14
2nd hour	132.40 ± 46.28	61.82 to 387.50
HbAIc in % (n=20)	5.6 ± 0.47	4.5 to 6.5
Lipid Profile		
Total cholesterol	176.25 ± 49.14	10.8 to 316.6
Triglycerides	130.71 ± 76.27	24.76 to 516.36
LDL-C	101.77 ± 35.58	40.4 to 203.85
HDL-C	52.81 ± 17.24	19 to 167.01

Table 2. Prevalence of abnormal glucose metabolism and dyslipidemia.

	Overall	Non-Obese	Overweight	Obese
Normal Glucose Testing (i.e. FBS, 75g OGTT, HbA1c)	102 (63.75%)	33 (80.49%)	23 (76.67%)	46 (51.69%)
Pre-diabetes Status	47 (29.38%)	7 (17.07%)	5 (16.67%)	35 (39.33%)
Impaired fasting glucose	6 (85.71%)	-	2 (40%)	7 (20%)
Impaired glucose tolerance	6 (85.71%)	6 (85.71%)	5 (100%)	32 (91.43%)
HbA1c between 5.5 – 6.4%	6 (85.71%)	1 (14.29%)	-	9 (25.71%)
Type II diabetes mellitus	11 (6.88%)	1 (2.44%)	2 (6.67%)	8 (8.99%)
Lipid profile				
Normal	28 (17.50%)	14 (34.15%)	3 (10%)	11 (12.36%)
Dyslipidemia	132 (82.50%)	27 (65.85%)	27 (90%)	78 (87.64%)

Table 3. Comparison of serum marker levels according to BMI.

	Non-Obese	Overweight	Obese	p-value
Fasting Blood Glucose	79.52 ± 7.03	84.88 ± 10.67	87.97 ± 21.95	0.04*
75 g OGTT				
1st hour	139.51 ± 34.71	160.13 ± 49.99	173.16 ± 58.60	0.01**
2nd hour	115.68 ± 30.30	126.15 ± 37.99	142.21 ± 52.31	0.01**
HbAIc	5.13 ± 0.71	-	5.68 ± 0.40	0.06
Lipid Profile				
Total Cholesterol	173.52 ± 55.80	182.91 ± 30.01	175.26 ± 51.29	0.49
Triglycerides	100.64 ± 65.39	117.14 ± 56.52	149.14 ± 81.77	0.01**
HDL-C	57 ± 13.95	49.85 ± 13.91	51.88 ± 19.30	0.17
LDL-C	92.58 ± 35.65	115.95 ± 29.59	101.23 ± 36.24	0.03*

For the levels of the low-density lipoproteins, overweight women had significantly higher levels compared to non-obese and obese women in the study (F: 3.89, df: 157, 2; p: 0.02). There were no significant differences noted for total cholesterol and high-density lipoprotein levels.

Table 4 shows the summary of glucose testing and lipid profile results according to BMI category. Based on the Fisher's exact test performed, there were significantly higher proportions of women with obesity who also have impaired fasting blood glucose levels (X^2: 5.85, p: 0.04). A similar pattern was noted for glucose tolerance with almost half of the women from the obese group demonstrating impaired glucose tolerance (X^2: 10.66, $p<0.01$).

It can be noted that there were more women with elevated levels of triglyceride among obese women compared with the other groups (X^2: 9.00, p: 0.01); while there were more overweight women with lower levels of high-density lipoproteins (X^2: 7.01, p: 0.03), and elevated levels of LDL (X^2: 5.67, p: 0.05) based on the Fisher's exact test.

There was no noted pattern among the glycosylated hemoglobin levels, which may be attributed to the limited number of women in the study who had results for this serum test. There were no noted differences in the proportions in terms of total cholesterol levels.

Discussion

The prevalence of obesity among PCOS patients is reported to be between 30-70%.[26] This proportion was also reflected in this study. In this study population, 89 (55.63%) were obese, 30

Table 4. Summary of glucose testing and lipid profile results according to BMI.

	Non-Obese	Overweight	Obese	p-value
Fasting Blood Glucose				
Normal	41 (100%)	28 (93.33%)	78 (87.64%)	
Impaired	-	2 (6.67%)	7 (7.87%)	0.04*
Diabetes mellitus	-	-	4 (4.49%)	
Glucose Tolerance				
Normal	34 (82.93%)	23 (76.67%)	50 (56.18%)	
Impaired	6 (14.63%)	5 (16.67%)	32 (35.96%)	0.01**
Diabetes mellitus	1 (2.44%)	2 (6.66%)	7 (7.87%)	
HBAIC				
Normal	2 (66.67%)	-	6 (35.29%)	
Pre-Diabetes	1 (33.33%)	-	9 (52.94%)	0.55
Diabetes mellitus	-	-	2 (11.76%)	
Lipid Profile				
Normal	14 (34.15%)	3 (10%)	11 (12.36%)	0.01**
Dyslipidemia	27 (65.85%)	27 (90%)	78 (87.64%)	
Total Cholesterol > 200	9 (21.95%)	10 (33.33%)	24 (26.97%)	0.56
Triglycerides ≥150 mg/dl	7 (17.07%)	7 (23.33%)	37 (41.57%)	0.01*
LDL ≥ 100 mg/dl	17 (41.46%)	21 (70%)	47 (52.81%)	0.05*
HDL <50 mg/dl	14 (34.15%)	18 (60%)	51 (57.30%)	0.03*

(18.25%) were overweight and 41 (25.63%) were non-obese.

The primary aim of this study was to assess the prevalence of abnormal glucose metabolism and dyslipidemia among different categories of body mass index. Metabolic derangements are prevalent among women with PCOS and current results show that these aberrations are more prevalent among overweight and obese PCOS women. These findings are similar with published data, wherein increasing BMI was found to worsen the metabolic problems in PCOS.[20]

Insulin resistance is a key feature of PCOS and this is manifested by abnormal glucose metabolism. The over-all prevalence of abnormal 75g OGTT and HbA1c in this study was only 36.26%, lower prevalence rate when compared to the findings of the local study of Yu-Mallen.[11] There was about a 93.3% prevalence of insulin resistance among the study subjects. This may be attributed to the fact that in their study, the measure of insulin resistance was the HOMA index, which is the gold standard for insulin resistance testing. This study was limited to fasting blood sugar, 75g OGTT and HbA1c, which are the more common tests performed in clinical practice, as recommended by the joint ASRM-ESHRE PCOS guidelines.

This study found a significantly higher percentage of pre-diabetes and diabetes mellitus among women with PCOS who are obese than the leaner subgroups. This underscores the established relationship of obesity and insulin resistance. In obesity, there is impaired suppression of hepatic glucose output and decreased insulin-stimulated glucose transport and metabolism in both adipocytes and skeletal muscle.[31]

Thirty-nine percent (39%) of the obese population were pre-diabetes and only 16-17% among the overweight and non-obese groups. Although non-obese women exhibit lower results for glucose testing, abnormal glucose metabolism is still present in this subgroup of PCOS women (17.07%).

Eighty-two percent of the study population had dyslipidemia. This is higher than the 70% prevalence in literature.[21] Lipid profile abnormalities were more prevalent among the obese and overweight phenotypes. Specifically, they had elevated triglycerides and LDL levels and decreased HDL levels – findings that are consistent with other studies involving PCOS women.[21] Castelo-Branco, et al.[9]

also noted an increase in total cholesterol levels. Furthermore, they observed that dyslipidemia was associated with obesity but not with non-obese and overweight PCOS patients, in spite of their use of the Western WHO criteria, which had higher cut-offs for BMI compared to the Asia-Pacific WHO criteria, which was used in this study. This shows a heightened burden of metabolic disease among the non-obese and overweight study groups.

Although not statistically significant compared to that of the obese women, it must be noted that among the 41 non-obese women included in this study, prevalence of dyslipidemia was 65.8%. This shows that the lean population of PCOS women is not spared from the metabolic sequelae that is inherent in the pathophysiology of this disease. In this subset of women, the most common marker for dyslipidemia is elevated LDL levels, followed by decreased HDL, increased total cholesterol and increased triglycerides, respectively. Elevated LDL and decreased HDL levels are known risk factors for the development of coronary artery disease, which is one of the major causes of death, worldwide.[31] These findings reinforce the need for cardiovascular risk assessment on all phenotypes of PCOS.

The true prevalence of insulin resistance and dyslipidemia among PCOS women is difficult to ascertain and compare as different centers use different laboratory parameters. Further studies with large population size and standard testing parameters should be done in order to improve knowledge on this matter. The clinical sequelae and implications of these metabolic derangements such as the development of cardiac disease, stroke and even death should be assessed among the obese and non-obese population as well.

Conclusion

Abnormal glucose metabolism and dyslipidemia are more prevalent among obese women compared to overweight and non-obese PCOS patients. Obesity may have an independent as well as an additive role on the development of metabolic complications of PCOS. However, non-obese PCOS women likewise present with adverse metabolic parameters, bringing to light the greater challenge in screening, monitoring and treating these patients. The fact that more than half of non-obese PCOS women are affected by dyslipidemia and about 20% have abnormal glucose metabolism urges clinicians to pay attention to this emerging population as the usual cornerstones of management such as weight loss and lifestyle modifications are usually applied to those with elevated BMI.

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