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Metabolic Syndrome Associated with Polycystic Ovary Syndrome in Some Nigerian Women

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a group of symptoms associated with endocrine disorders in women of reproductive age. Women with this syndrome is at increased risk of metabolic syndrome. This study described the metabolic syndrome and its associated components among women with PCOS in Nigerian populace.

Methods: A total of 90 participants (50 PCOS and 40 controls) were recruited for the study. The diagnosis of PCOS was established using the criteria defined by International PCOS guidelines 2018. Demographic, anthropometric, and clinico-pathological data, including blood pressure, were obtained for each participant. Metabolic syndrome was diagnosed using the 2005 revised National Cholesterol Education Program Adult Treatment Panel-III (revised NCEP ATP_III) guidelines. Fasting blood glucose, insulin, total cholesterol, HDL, LDL, and triglycerides were evaluated with conventional spectrophotometric methods.

Results: The prevalence of metabolic syndrome in PCOS women was 24%, with an odds ratio of 5.211, while the prevalence of 5.7% was observed in the control group. The prevalence of central obesity (waist circumference >88cm), FBS ≥100 mg/dl, HDL <50 mg/dl, triglycerides ≥150 mg/dl, and blood pressure ≥130/85 mmHg in PCOS women was 60%, 22%, 54%, 12%, and 20%, respectively. The most frequently observed individual components of metabolic syndrome were increased waist circumference and decreased HDL cholesterol.

Conclusion: Metabolic syndrome and its components, especially obesity, are a major risk factor of PCOS in our population. Routine screening and modulating individual contributors of metabolic syndrome may support PCOS management.

Keywords: Polycystic Ovarian Syndrome, Metabolic Syndrome, Risk Factors.

1.0 INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a group of symptoms associated with endocrine disorders and has been described as the main endocrine disorder in women [1]. The global prevalence of PCOS has been reported to range from 6% to 10% [2]. There is a reported 5.6% prevalence rate in Chinese women and a 2.2% prevalence in Nigeria [3, 4]. Different diagnostic criteria are believed to have contributed to the variation in the prevalence of PCOS reported across various populations. The criteria for Diagnosing PCOS have been provided by four scientific bodies: the National Institutes of Health [5]; the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine [6]; the Androgen Excess and PCOS Society (AES) [7], and the International PCOS Guidelines [8]. The clinical manifestations of PCOS include hyperandrogenism, oligomenorrhea or amenorrhea, hirsutism, and chronic anovulation. The PCOS women are at increased risk of developing metabolic syndrome [9]. Metabolic syndrome (MS) is a cluster of clinical risk factors for the development of cardiovascular diseases (CVD) and diabetes, and these factors include abdominal obesity, dyslipidemia, glucose metabolic disorders, especially insulin resistance with or without glucose intolerance and elevated blood pressure [10,11]. Though different definitions of metabolic syndrome criteria exist, the concept of clustering of risks leading to diabetes and cardiovascular disease (CVD) is well accepted. Several expert groups: the World Health Organization [WHO], the American Association of Clinical Endocrinologists [AACE], International Diabetes Foundation (IDF), and National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) have published diagnostic criteria for the identification and clinical diagnosis of metabolic syndrome. These criteria have emerged based on each group's relative importance to certain risk factors associated with metabolic syndrome. A prevalence of 33.6% was reported in PCOS women in Brazil [12].

Similarly, a prevalence of 22.7% was reported in Iranian women with PCOS [13]. The metabolic syndrome (MS) and the polycystic ovary syndrome (PCOS) seem to be intertwined even though they are separate disorders. This relationship could be partly attributed to observed common features like insulin resistance, obesity, and risk of cardiovascular disease. Obesity has been reported to amplify hyperandrogenism in PCOS, resulting in

increased total testosterone, free androgen index, and decreased sex hormone-binding globulin (SHBG) [14]. Also, the androgen excess observed in PCOS has been suggested to directly influence adipocyte function [15]. While the contribution of these individual parameters continues to attract interest in both MS and PCOS, the metabolic syndrome continues to drive the twin global epidemics of type 2 diabetes and cardiovascular disease. However, there is an overwhelming medical and economic imperative to identify the risk of developing metabolic syndrome in individuals with PCOS.

2.0 METHODOLOGY

A total of 90 participants (50 PCOS and 40 controls) were recruited for the study. PCOS diagnosis was established using the criteria as defined by International PCOS guidelines 2018, requiring the presence of any two of (1) Oligomenorrhea – and/or anovulation, (2) Clinical and/or biochemical signs of hyperandrogenism, and (3) Polycystic ovary morphology (presence of 12 or more follicles in each ovary, 2-9 mm in diameter and/or increased ovarian volume >10mL). Apparently, healthy women with no PCOS were recruited as controls. Ethical approval was obtained from the institutional Health Research and Ethics Committee prior to the commencement of the study (CMUL/HREC/05/19/527).

General demographic and clinicopathological details were obtained from the participants. Anthropometric data such as height, weight, waist circumference, and hip circumference were measured, and the body mass index (BMI) was calculated as weight (kg)/height² (m²), while the weight hip ratio (WHR) was calculated as the measurements of the waistline/hipline ratio. Fasting blood glucose, total cholesterol, HDL, LDL, and triglycerides were analyzed by photometry method using Roche Cobas C111 clinical Chemistry analyzer. Insulin was assayed using electrochemiluminescence (ECL) technology (Roche Diagnostics, Switzerland).

Metabolic syndrome was assessed using the 2005 revised National Cholesterol Education Program Adult Treatment Panel-III (revised NCEP ATP_III) guidelines which recommended the presence of at least any three of the following: (1) abdominal obesity given as waist circumference [> 88 cm (> 35 in)], (2) triglycerides ≥ 150 mg/dL, (3) HDL cholesterol < 50 mg/d, (4) systolic/diastolic blood pressure $\geq 130/85$ mmHg, and (5) fasting plasma glucose ≥ 100 mg/dL [16].

2.1 Statistical Analysis

Statistical data analysis was performed using IBM SPSS version 25 (IBM Illinois, USA). Data were analyzed using student's t-test, Mann-Whitney U, Chi-Square, and Logistic regression, where appropriate. A p-value < 0.05 was considered statistically significant.

3.0 RESULTS

Table 1 shows the demographic and anthropometric characteristics of the PCOS and controls. The mean weight, BMI, waist circumference, and waist-hip ratio were higher in PCOS (77.70 ± 15.7 , 29.57 ± 6.0 , 0.93 ± 0.1 and 0.87 ± 0.1 , respectively) compared to the controls (68.43 ± 11.5 , 26.19 ± 4.4 , 0.87 ± 0.1 and 0.83 ± 0.1 , respectively) $p < 0.05$.

Table 1. Comparison of Demographic and Anthropometric Parameters in the Study Population

Parameter	PCOS Mean $\pm$ SD	Control Mean $\pm$ SD	t-value	p-value
Age (Years)	29.44 $\pm$ 5.0	30.83 $\pm$ 4.0	-1.367	0.175
Age at menarche (Years)	13.15 $\pm$ 2.2	14.13 $\pm$ 2.3	-1.131	0.264
Weight (Kg)	77.70 $\pm$ 15.7	68.43 $\pm$ 11.5	2.942	0.004*
Height (m)	1.62 $\pm$ 0.1	1.72 $\pm$ 0.6	-1.124	0.264
BMI (Kg/m ²)	29.57 $\pm$ 6.0	26.19 $\pm$ 4.4	2.810	0.006*
Waist circumference (m)	0.93 $\pm$ 0.1	0.87 $\pm$ 0.1	2.666	0.026*
Hip-circumference (m)	1.07 $\pm$ 0.1	1.04 $\pm$ 0.1	1.369	0.175
Waist hip ratio	0.87 $\pm$ 0.1	0.83 $\pm$ 0.1	2.304	0.024*

*Difference is statistically significant, $p < 0.05$

Table 2. Comparison of Biochemical Data in Cases and Control Groups

Parameter	PCOS Mean $\pm$ SD	Control Mean $\pm$ SD	t-value	p-value
Cholesterol (mg/dl)	178.56 $\pm$ 43.9	175.21 $\pm$ 28.7	0.396	0.693
HDL (mg/dl)	49.52 $\pm$ 11.6	56.73 $\pm$ 13.3	-2.653	0.010*
LDL (mg/dl)	112.34 $\pm$ 41.0	108.53 $\pm$ 25.6	0.486	0.628
Triglyceride (mg/dl)	95.02 $\pm$ 39.2	78.02 $\pm$ 35.9	2.011	0.048*
Glucose (mg/dl)	89.82 $\pm$ 23.1	86.10 $\pm$ 13.3	0.856	0.394
	Median (Q1-Q3)	Median (Q1-Q3)	U-value	p-value
Insulin (uU/ml)	13.59(9.4-21.1)	8.63(5.1-30.3)	-1.079	0.281

*Difference is statistically significant, $p < 0.05$

Table 2 shows the biochemical analysis in the PCOS and controls; the mean HDL was lower in PCOS (49.52 ± 11.6) compared to the controls (56.73 ± 13.3) $p < 0.05$, and the mean triglycerides were higher in PCOS (95.02 ± 39.2) compared to the controls (78.02 ± 35.9) $p < 0.05$. Figure 1 shows the occurrence of metabolic syndrome in the PCOS and controls, indicating a prevalence of 24% and 5.7%, respectively.

Figure 1. Prevalence of Metabolic Syndrome among PCOS and Control Group

*Difference is statistically significant, $p < 0.05$

Figure 2. Occurrence of Individual Components of the Metabolic Syndrome in PCOS

Figure 2 shows the distribution of different components of metabolic syndrome in the PCOS study population. The most common individual features of the metabolic syndrome were higher waist circumference and reduced HDL cholesterol (60% and 54% of PCOS, respectively). The waist circumference exceeded 88.9 cm in 60%, HDL cholesterol was less than 50 mg/dl in 54%, triglycerides were 150 mg/dl or greater in 12%. Blood pressure was 130/85 mm Hg or greater in 20%, and fasting glucose

concentrations were 100 mg/dl or greater in 22% of the PCOS study population, respectively.

Figure 3 shows the comparative analysis of obesity in PCOS and control group; obesity was more pronounced in PCOS than controls ($X^2=8.036$, $p=0.005$). The old ratios of metabolic syndrome and its components are shown in Table 3, with metabolic syndrome, waist circumference, BMI, waist-hip ratio, and HDL, having an odds ratio of 5.211, 1.109, 1.093, 12.047, and 0.954, respectively.

Figure 3. Comparative Analysis of Obesity in PCOS and Control Group

*Difference is statistically significant, $p<0.05$

Table 3. Risk Analysis of Metabolic Syndrome and its Individual Parameters in PCOS

Parameter	Odd ratio	95% CI	p-value
Metabolic Syndrome	5.211	1.086-24.993	0.039*
Waist circumference (m)	1.109	1.010 – 1.219	0.030*
BMI (Kg/m ²)	1.093	1.003 – 1.190	0.041*
Waist hip ratio	12.047	2.011 – 74.57	0.030*
HDL (mg/dl)	0.954	0.919-0.990	0.014*
LDL (mg/dl)	1.002	0.990 – 1.015	0.695
Triglyceride (mg/dl)	1.013	1.000 – 1.026	0.054
Glucose (mg/dl)	1.014	0.989 – 1.040	0.282
Insulin (uU/ml)	1.009	0.986 – 1.034	0.437
Hypertension (mm Hg)	1.086	0.699-1.688	0.713

*Difference is statistically significant, $p<0.05$

4.0 DISCUSSION

Polycystic ovary syndrome (PCOS) and Metabolic syndrome (MS) are distinct disorders but related due to observed common features. The 24% metabolic syndrome prevalence in PCOS reported in this study was lower than the report from some other populations and higher in others. A prevalence of 33.6% was reported in PCOS women in Brazil [12], while 22.7% was reported in Iranian women with PCOS [13]. This disparity may be due to variation in individual factors implicated in these conditions in different populations. However, the high prevalence of metabolic syndrome observed in the PCOS compared to the controls suggests the underlying contribution of the various components of metabolic syndrome to the pathophysiology of PCOS in our study population. It is worth highlighting that the commonest features of metabolic syndrome observed in the PCOS participants in this study were markers of obesity and dyslipidemia. This finding is consistent with the role of visceral obesity, dyslipidemia, and insulin resistance in the pathophysiology of PCOS [17].

Patients with PCOS have been reported to have a high prevalence of upper-body obesity, as shown by increased waist circumference and the waist-hip ratio [18]. Obesity results from excess fat accumulation in the body leading to cardiovascular morbidities, insulin resistance, and even the development of type 2 diabetes. An elevated non-esterified fatty acid (NEFA), glycerol, hormones, and pro-inflammatory cytokines, are released from adipose tissues in obese patients [19]. The secretion of cytokines (e.g., leptin, TNF- α) and an elevated plasma NEFA level produce obesity-induced inflammation that could affect glucose metabolism and insulin sensitivity, resulting in type 2 diabetes [20]. Insulin resistance resulting from obesity could cause elevated fasting blood glucose, the

major underlying factor in diabetes mellitus. Thus, obesity, defined either by body mass or fat distribution and its associated insulin resistance, is an important risk factor in PCOS.

Furthermore, abdominal fat is more lipolytic than subcutaneous fat, and it also does not respond easily to the antilipolytic action of insulin, thus making intra-abdominal fat more important in causing insulin resistance [21]. Insulin resistance with impairment of β -cell function leads to the development of diabetes. Insulin resistance in the muscle promotes glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in the insulin-resistant liver and diverting excess free fatty acids to the liver. As an alternative energy source to cells during insulin resistance, lipolysis occurs. This provides a high plasma level of NEFA which eventually causes lipotoxicity and a progressive loss of β -cell function.

Similarly, NEFA also decreases normal insulin release from β -cell with a marked impairment in glucose-stimulated insulin secretion and reduces insulin biosynthesis [19]. Thus, insulin resistance in adipose tissue is associated with decreased glucose uptake and increased release of free fatty acids (FFAs), which are converted in the liver to triglyceride-rich very-low-density lipoprotein (VLDL) particles. The delivery of an increased amount of FFAs to the liver and the increased release of FFAs during intrahepatic triglyceride lipolysis seems to regulate glucose production and insulin resistance. In parallel, increased FFA delivery to the liver increases the production of hepatic very-low-density lipoproteins, leading to increased concentration of plasma triglycerides. The latter effect increases the transfer of triglycerides from very-low-density lipoproteins to HDL, leading to an increased HDL clearance and decreased plasma HDL concentration [22]. In other words, FFA homeostasis seems to determine atherogenic dyslipidemia in metabolic syndrome and, consequently, in PCOS. This explains the high prevalence of dyslipidemia observed in our PCOS population in this study.

Elevated plasma small dense low-density lipoprotein (LDL) cholesterol, the most atherogenic subfraction of LDL, has been identified as a key feature in association with elevated triglyceride and low HDL cholesterol in susceptible individuals with greater abdominal fat accumulation (large waist circumference) [23]. The resulting hypertriglyceridemia drives the dyslipidemic triad by promoting the synthesis of small, easily oxidizable dense

LDL and enhanced clearance of HDL, which is believed to be highly atherogenic [10]. The major role of HDL is in reverse cholesterol transport (RCT), in which excess cholesterol is removed from the peripheral vessels and transported back to the liver for disposal [24], and in addition to this function, HDL-cholesterol has a direct action on different cell types which influence cardiovascular and metabolic health. Alteration in the regulation and function of HDL may contribute to increased cardiovascular mortality. Hence, the low HDL associated with metabolic syndrome may predispose PCOS patients to cardiovascular diseases.

Also, in the pathophysiologic spectrum of PCOS, androgen excess possibly acts as a triggering factor in the development of metabolic syndrome, playing a significant role beyond being involved in ovulatory dysfunction. Also, hyperandrogenism tends to amplify the adverse metabolic phenotype of PCOS in a dual-mode, through the aggravation of central adiposity and the perpetuation of insulin resistance [9]. Accumulation of excessive visceral adipose tissue (in the presence or absence of obesity) is associated with insulin resistance, hyperinsulinemia, and glucose intolerance. Insulin resistance typically increases with increasing body fat composition and is an important predisposing mechanism for developing metabolic syndrome. Furthermore, metabolic syndrome is known to be associated with diseases that are leading sources of morbidity and mortality, and such diseases include cardiovascular disorder, Type II diabetes, neurological disease, and nonalcoholic steatohepatitis [25]. Thus, metabolic syndrome comorbidity with PCOS will aggravate the complications resulting from PCOS. The associated metabolic syndrome diseases are usually chronic, causing life-long complications in PCOS that could become lethal.

With the metabolic syndrome driving the twin global epidemics of type 2 diabetes and cardiovascular disease, there is an overwhelming medical and economic imperative to identify risk of developing metabolic syndrome in PCOS individuals, so that early lifestyle interventions and treatment may prevent the development of complications such as diabetes and cardiovascular diseases in PCOS.

Metabolic syndrome and its individual components, especially obesity and dyslipidemia, are major risk factors of PCOS in our study population. Routine screening and modulating individual contributors of metabolic syn-

drome may support or improve PCOS management.

Conflicts of Interest

The authors declare no competing interests.

Authors' Contributions

DA collected data, contributed to data analysis and interpretation and manuscript writing. **TAS** contributed to data analysis and interpretation and made critical assessment of the study. **BI** contributed to data analysis tools, data analysis and interpretation and critical assessment of the study. **OM** contributed to study design, data analysis and interpretation and critical assessment of the study. **OA** conceived and designed the study, contributed to data analysis tools, analysis of data, manuscript writing and assembled the research team and lead proposal design. All authors approved the final copy of the manuscript

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