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ORIGINAL ARTICLE

Association Between Insulin Resistance and Hyperandrogenism in Women with PCOS. A Cross-Sectional Clinical Study

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders that is typified by both reproductive and metabolic dysfunctions with hyperandrogenism and insulin resistance being the major manifestations. A combination of these two factors is central to disease manifestation and progression.

Objectives: To assess the relationship between biochemical and clinical hyperandrogenism and insulin resistance in PCOS women.

Methods: This cross-sectional clinical study included one hundred women diagnosed with PCOS. Clinical hyperandrogenism was assessed using the modified Ferriman–Gallwey (mFG) score, while biochemical hyperandrogenism was evaluated by measuring serum total testosterone, sex hormone-binding globulin (SHBG), and calculating the free androgen index (FAI). Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Participants were stratified into insulin-resistant and non–insulin-resistant groups based on a predefined HOMA-IR cutoff. Associations between insulin resistance and androgen parameters were analyzed using correlation analyses, group comparisons, and multivariable linear regression.

Results: Insulin-resistant women reported much higher mFG scores, high total testosterone and FAI and lower SHBG levels than non-insulin-resistant participants (P value < 0.05). The clinical and biochemical markers of hyperandrogenism were significantly and negatively correlated with HOMA-IR, whereas SHBG had a positive correlation with HOMA-IR. Insulin resistance was observed to be a predictive independent variable of high androgen levels even after controlling the age and body mass index.

Conclusion: hyperandrogenism in PCOS women has a close relationship with insulin resistance, which is an independent isomer of androgen overproduction. Insulin resistance can be characterized and managed early in the life of the affected individuals and this may enhance their metabolic, as well as reproductive outcomes**.**

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, Hyperandrogenism, HOMA-IR, Testosterone, DHEA-S.

INTRODUCTION

Polycystic ovary syndrome (PCOS) has been one of the most prevalent endocrine ailments in women who are of reproductive age and a cause of menstrual disruptions, anovulatory infertility, and clinical hyperandrogenism [1]. PCOS normally manifests itself clinically through oligomenorrhea or amenorrhea, hirsutism, acne, androgenic alopecia as well as polycystic ovarian morphology on an ultrasound. In addition to reproductive phenotypes, it is becoming more accepted that PCOS is a systemic metabolic syndrome since numerous of these women present the signs of insulin resistance, compensatory hyperinsulinemia, dyslipidemia, central adiposity, and an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus [2]. Metabolic phenotype can be found even in women with normal body mass index, although excess weight can usually aggravate the severity of both metabolic and androgen-related characteristics [3].

Insulin resistance has been regarded as a key pathophysiologic agent in PCOS. A scenario arises in which when the peripheral tissue including skeletal muscle and adipose tissue becomes unresponsive to insulin, the pancreas secretes more insulin to achieve glucose homeostasis [4]. The direct and indirect effects that this chronic hyperinsulinemia has on ovarian steroidogenesis. Insulin has the potential of stimulating ovarian theca cell production and boosting luteinizing hormone (LH)-mediated production of androgens resulting in high levels of circulating androgens. Furthermore, insulin reduces the production in the liver of sex hormone-binding globulin (SHBG) that raises the amount of free (biologically active) testosterone [5]. Thus, insulin resistance can be a source of hyperandrogenism via several mechanisms and hyperandrogenism can accumulate effects on adipose tissue functionality, inflammation and lipid metabolism, potentially entering into a self-perpetuating loop [6].

Another clinical and biochemical characteristic exhibited by several women with PCOS is hyperandrogenism, which is strongly correlated with hirsutism and acne, the most troubling of them all. Nonetheless, the extent of the androgen surplus and the manifestation of the clinical syndrome differ significantly in different individuals owing to their differences in ethnicity, body composition, age and assay methods of estimation of hormones. On the same note, insulin resistance in PCOS exists on a continuum between subtle impairment that can only be unearthed using surrogate indices to passing glucose intolerance [7]. Due to this heterogeneity, it is significant to figure out the extent of insulin resistance-hyperandrogenism association within a specific clinical group to use it as a risk factor and as a guide to prioritize the mode of therapy like lifestyle modification, insulin-sensitizing medications, and anti-androgen treatment [8].

Despite a considerable number of studies that indicate a connection between insulin resistance and androgen excess, the degree of association as well as its uniformity varies depending on the population and the study design [9]. The differences in the diagnostic criteria of PCOS, different indices to measure insulin resistance (e.g., HOMA-IR), and the different markers to measure androgen status (total testosterone, free testosterone, free androgen index, DHEAS, SHBG) may affect results [10]. Furthermore, demographic variables that are local, including obesity trends, food consumption, and access to early clinical help, might alter the observed relation in the practical environment. A dedicated cross-sectional study on a clinically selected population with PCOS can be useful in terms of evidence on the metabolic-reproductive connection and can serve to guide systems of combined care [11].

Thus, the proposed cross-sectional clinical study will test the hypothesis of correlation between insulin resistance and

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hyperandrogenism in women with PCOS. Through measurement of insulin resistance with routine biochemical measurements and measurement of hyperandrogenism with clinical scoring and hormone measurements, the study aims to define whether an increased insulin resistance level is strongly connected to the increased androgen excess in the study group and also to determine how insulin resistance level can be conditioned by body mass index and other clinical factors.

MATERIALS AND METHODS

This cross-sectional clinical study was conducted at Category-D Hospital, Munda, Lower Dir, Khyber Pakhtunkhwa, Pakistan, and the Department of Obstetrics & Gynaecology, KRL Hospital, Islamabad, Pakistan. The study included 100 women of reproductive age who presented to the gynecology outpatient departments of the participating centers and were diagnosed with polycystic ovary syndrome (PCOS) during the study period from may 2022 till may 2023.

Diagnosis of PCOS was established according to standard diagnostic criteria, requiring the presence of at least two of the following: oligo- or anovulation, clinical and/or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on pelvic ultrasonography, after exclusion of other endocrine disorders. Women who were pregnant or lactating, had diabetes mellitus, thyroid dysfunction, hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, androgen-secreting tumors, chronic systemic illness, or had used hormonal therapy or insulin-sensitizing drugs within the preceding months were excluded from the study.

A detailed clinical history was obtained from all participants, followed by a thorough physical examination. Anthropometric measurements were recorded, and body mass index (BMI) was calculated using the standard formula. Clinical hyperandrogenism was assessed using the modified Ferriman–Gallwey (mFG) scoring system, with additional documentation of acne and androgenic alopecia. Pelvic ultrasonography was performed to evaluate ovarian morphology.

After an overnight fast, venous blood samples were collected to measure fasting plasma glucose, fasting insulin, total testosterone, and sex hormone-binding globulin (SHBG). Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), while biochemical hyperandrogenism was evaluated using serum total testosterone and the free androgen index (FAI). Participants were stratified into insulin-resistant and non-insulin-resistant groups based on a predefined HOMA-IR cutoff value.

Data were entered and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were presented as frequencies and percentages. Group comparisons were performed using suitable parametric or non-parametric tests. Correlation analyses were carried out to determine associations between insulin resistance and androgen parameters, and multivariable linear regression analysis was used to identify independent predictors of androgen levels after adjusting for potential confounders. A p-value of less than 0.05 was considered statistically significant. Ethical approval was obtained from the relevant institutional review committees, and written informed consent was taken from all participants prior to enrollment.

RESULTS

The analyzed population involved 100 women having PCOS. The average age of the participants was 25.8 (4.6) years and the average body mass index was 27.4 (3.9) kg/m 2. According to the preset HOMA-IR cutoff, 62 and 38 individuals were identified as insulin-resistant and non-insulin resistant respectively as shown in table 1. Biochemical hyperandrogenism (mFG score 64) and clinical hyperandrogenism (mFG score 68) were found in 64 and 68 percent respectively as shown in table 2. The clinical and biochemical hyperandrogenism and a low level of SHBG were much higher among the women who were insulin-resistant than among the non-insulin-resistant women as shown in table 3.The correlation between HOMA-IR and clinical and biochemical indicators of hyperandrogenism was moderate and positive, whereas on the other hand, there was a negative significant correlation between HOMA-IR and SHBG as shown in table 4.After adjustment for age and body mass index, insulin resistance remained an independent and significant predictor of elevated total testosterone levels.

Table 1. Baseline clinical and metabolic characteristics of the study population (n = 100)

Variable	Mean ± SD / Median (IQR)
Age (years)	25.8 ± 4.6
Body mass index (kg/m²)	27.4 ± 3.9
Fasting glucose (mg/dL)	94.2 ± 10.6
Fasting insulin (µIU/mL)	14.8 (10.2–19.6)
HOMA-IR	3.4 (2.5–4.6)
mFG score	12.1 ± 4.3

Table 2. Comparison of androgen parameters between insulin-resistant and non–insulin-resistant groups

Parameter	Insulin-Resistant (n = 62)	Non–Insulin-Resistant (n = 38)	p-value
mFG score	13.6 ± 4.1	9.8 ± 3.6	<0.001
Total testosterone (ng/dL)	72.4 ± 18.6	56.9 ± 14.2	<0.001
Free androgen index	8.2 (6.1–10.4)	5.6 (4.2–7.1)	0.002
SHBG (nmol/L)	28.6 ± 9.4	41.2 ± 11.3	<0.001

Table 3. Correlation between HOMA-IR and markers of hyperandrogenism

Parameter	Correlation coefficient (r)	p-value
mFG score	0.48	<0.001
Total testosterone	0.42	<0.001
Free androgen index	0.46	<0.001
SHBG	−0.51	<0.001

Table 4. Multivariable linear regression analysis predicting total testosterone levels

Variable	β coefficient	95% CI	p-value
HOMA-IR	0.37	0.21–0.54	<0.001
Age (years)	−0.08	−0.24–0.07	0.29
Body mass index (kg/m²)	0.19	0.03–0.36	0.02

DISCUSSION

This cross-sectional clinical trial proves that there was a strong relationship between insulin resistance and clinical and biochemical hyperandrogenism in women with polycystic ovary syndrome [12]. Insulin-resistant women reported a greater modified Ferriman Gallwey score, high total testosterone and free androgen index and lower sex hormone-binding globulin levels than did non-insulin-resistant participants. These results confirm the idea that insulin resistance is a key element to the endocrine changes recorded in PCOS [13]. The positive correlations between HOMA-IR and markers of androgen, as well as, the negative correlation between SHBG and other markers are supported by the established pathophysiological mechanisms. Hyperinsulinemia augments theca-cell androgen synthesis and augments steroidogenesis of luteinizing hormone estrus, suppressed hepatic SHBG synthesis at the same time [14]. This serves two-fold action by enhancing the bioavailability of the circulating androgens; therefore, exacerbating clinical manifestations including hirsutism. The intermediate strength of these associations indicates that insulin resistance is a significant, albeit not the exclusive, predictor of androgen excess and it demonstrates clinical heterogeneity of PCOS [15].

Moreover, there are also apparent androgen differences between insulin-resistant and non-insulin-resistant, which indicate the clinical significance of metabolic stratification among women with PCOS. The timely detection of insulin resistance can possibly guide clinicians to forecast the extent of hyperandrogenic effects and follow-up treatment based on it [16]. Women having higher HOMA-IR might be more benefited by medications that enhance the

sensitivity of insulin, i.e., structured lifestyle change, control of weight in addition to the insulin-sensitizing drug and traditional hormonal therapy [17]. In addition, the results support the idea of a multidisciplinary approach to PCOS treatment which integrates endocrine, metabolic, and reproductive evaluation, instead of prioritizing the gynecological symptoms. Understanding insulin resistance as a key element of modifiable factors could lead to the enhancement of long-term elements, i.e., lessening the threat of type 2 diabetes mellitus, cardiovascular illness, and enduring complications of persistent hyperandrogenism [18].

Multivariate regression analysis was additionally able to reveal that insulin resistance is a predictor of high blood levels of total testosterone when age and body mass index are controlled. This result has clinical implications as it shows that metabolic dysfunction is an additional cause of hyperandrogenism to the effect of obesity itself [19]. It also presents the reason why lean women with PCOS can potentially show a lot of androgen excess and justifies the reason why insulin resistance should be used to treat a wide range of PCOS phenotypes. Although it has strong points, the study has numerous limitations, such as cross-sectional design that does not allow conclusion making, and the use of surrogate indicators of insulin resistance [20]. Greater information on the temporal correlation between metabolic and hormonal dysfunction in PCOS would be given by longitudinal studies and more direct measures of insulin sensitivity.

CONCLUSION

Conclusively, insulin resistance is strongly associated with elevated clinical and biochemical hyperandrogenism in women with polycystic ovary syndrome and remains an independent predictor of androgen excess after adjustment for age and body mass index. These findings suggest that early identification and management of insulin resistance may improve both metabolic and reproductive outcomes in women with PCOS. Combined therapeutic approaches, including lifestyle modification and insulin-sensitizing therapy, may play a key role in reducing hyperandrogenic manifestations and lowering the risk of associated metabolic complications in affected women.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contributions:

S[1] conceived the study, collected data, and drafted the manuscript.
SA[2] supervised the research and critically reviewed the manuscript.
RN[3] contributed to data collection and clinical assessment.
NA[4] assisted in patient evaluation and data interpretation.
NJ[5] performed data analysis and contributed to results interpretation.
SNZ[6] provided methodological guidance and final manuscript review.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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