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DEALING WITH INSULIN RESISTANCE AMONG POLYCYSTIC OVARIAN SYNDROME PATIENT

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ABSTRACT

Background: Insulin resistance is a key factor in the pathophysiology of PCOS and is associated with various metabolic complications, including type II diabetes, obesity, and cardiovascular diseases.

Objective: The objective of this study is to evaluate effectiveness of multimodal treatment for managing insulin resistance in patients with Polycystic Ovarian Syndrome

Methodology: It is a randomized control study conducted at Sandeman Provincial Hospital Quetta from 1st May 2023 to 30th April 2024. 100 participants received tablet Metformin 500mg thrice a day along with a low calorie diet and exercise plan. Participant were treated for 3 months and their BMI, caloric intake, serum FSH, LH, testosterone, fasting blood glucose and fasting insulin levels were measured. The data analysis was conducted using the Statistical Package for Social Sciences version 24.00. The p value of ≤ 0.5 was considered significant.

Result: The average age of participants was 26.78±6.54years. There was reduction in BMI from 30.13±5.41 to 26.2±2.9, Homeostasis Model Assessment of Insulin Resistance decreased significantly from 4.2±0.8 to 2.1±0.5, with FSH increasing from 5.1±1.7U/L to 7.9±2.8U/L(P = 0.02) and LH decreasing from 9.2±5.5U/L to 6.5±1.7U/L(P= 0.02), indicating improved ovarian function and hormonal balance. Total testosterone levels also decreased from 76.3±12.4 pg/ml to 63.8±9.7pg/ml. menstrual regularity and ovulation restoration was observed in 71% and 59% of participants respectively.

Conclusion: Comprehensive management strategies integrating dietary adjustments, regular physical activity, and pharmacological treatment are foundational in enhancing insulin sensitivity and mitigating risks such as menstrual irregularities and hyper-androgenism in patients with Polycystic Ovarian Syndrome.

Keywords: Poly-cystic Ovarian Syndrome, PCOS, Insulin Resistance, Lifestyle Modification, Lipid Profile.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a complex, multifaceted endocrine disorder that affects a significant proportion of women of reproductive age worldwide. The prevalence of polycystic ovary syndrome (PCOS) is estimated to be between 4%-20% of women of reproductive age worldwide, with a pooled mean prevalence of 21.27% using different diagnostic criteria [1]. It is a disease that is most common in females aged 12-25 years with a combination of symptoms and clinical signs, including menstrual irregularities, hyper-androgenism, and polycystic ovaries [2]. 75% of women with polycystic ovary syndrome suffer infertility due to anovulation [3]. Research indicates that women who have PCOS are at increased risk for spontaneous abortions due to ovarian hyper-stimulation syndrome, gestational diabetes; pregnancy-induced hypertension (PIH); pre-term delivery [4]. Insulin resistance (IR) is common among many patients with this gynaecological disorder. The result of this condition is high levels of glucose circulating in the blood due to impaired cellular response to insulin.

The pathophysiology of PCOS involves a key role for insulin resistance. Specifically, insulin resistance was observed in up to 60.7% and 24.5% of women diagnosed with polycystic ovary syndrome (PCOS) when using HOMA-IR cutoffs of 1.82 and 3.16 respectively [5]. It has been found that studies show that being obese puts you at risk of developing insulin resistance. According to Sharif et al., a randomized control study notes a remarkable increase in the occurrence rate of insulin resistance among overweight polycystic ovary syndrome cases compared with those with healthy body weights (2.47 ± 0.40 vs 2.30 ± 0.43) [6]. Nonetheless, the exact underlying mechanisms for PCOS-induced IR are complex and multi-factorial.

Research has been done suggesting that insulin resistance in PCOS may be genetic. Different genetic polymorphisms that are connected to insulin signaling pathways like changes in the gene of insulin receptor and other genes influencing glucose metabolism have been found to increase insulin resistance in PCOS patients [7]. RP11-151A6.4 is a hub lncRNA that has been associated with insulin resistance, androgen excess and adipose dysfunction in women with polycystic ovary syndrome [8]. Gut microbiota disbiosis can as well result in insulin resistance, which is majorly associated with Polycystic Ovary Syndrome onset. Inflammation markers like TNF-α, IL-6 and CRP are elevated in females having PCOS at times. Therefore, persistent low level internal inflammation due to these reasons may interfere with the signaling of insulin leading to less sensitivity towards it thereby increasing possibilities of acquiring diabetes. [9].

It can be difficult to diagnose insulin resistance in patients with PCOS because there are no standardized diagnostic criteria. This condition can be accurately assessed through standard methods like the Quantitative Insulin Sensitivity Check Index (QUICKI), the Matsuda index, and the Homeostasis Model Assessment of insulin resistance (HOMA-IR). These diagnostic tests are considered sensitive but imperfect since they show overlap along the detection threshold. In the diagnosis of insulin resistance, euglycemic hyper-insulinemic clamp technique still stands as the golden standard [10]. Alleviating symptoms of insulin resistance through dietary and pharmacological modifications is important in warding off chronic complications like type II diabetes and cardiovascular diseases. Management of insulin resistance normally involves a low glycemic index diet, resistance training exercises and the use of drugs have led to significant improvements; they include metformin, pioglitazone and rosiglitazone.. Moreover, myo-Inositol and D-chiro-Inositol have shown promising results in managing PCOS symptoms, including menstrual irregularities and ovulatory dysfunction [11].

There are certain gaps in the literature. Different studies often use different criteria, such as the Rotterdam criteria, NIH criteria, or Androgen Excess and PCOS Society criteria, leading to inconsistent results and making it challenging to compare findings across studies. Most studies on insulin resistance in PCOS are cross-sectional, providing a snapshot in time rather than long-term insights [12]. While genetic predisposition is recognized as a factor in insulin resistance in PCOS, there is limited research on specific genetic and epigenetic mechanisms. There is a lack of comprehensive data on how insulin resistance in PCOS varies among different ethnic and racial groups. Most studies are conducted on Caucasian populations, with insufficient data on other ethnicities, which may have different genetic, lifestyle, and environmental influences on insulin

resistance [13].There is a need for more robust clinical trials comparing the efficacy and safety of different pharmacological treatments for insulin resistance in PCOS, including newer medications like GLP-1 receptor agonists and inositol.

The primary objective of this study is to evaluate effectiveness of a multimodal treatment strategy for managing insulin resistance in patients with Polycystic Ovarian Syndrome (PCOS). It uses a comprehensive approach that includes metformin, a healthy diet, and regular exercise. By assessing this approach, the study seeks to determine the improvements in insulin sensitivity and overall metabolic health in PCOS patients after treatment.

METHODOLOGY

It is a multicenter randomized control study conducted at Sandeman Provincial Hospital Quetta from 1st May 2023 to 30th April 2024. Female patients aged 18 years or above with confirmed diagnosis of PCOS based on the Rotterdam criteria, clinical evidence of insulin resistance defined by elevated fasting insulin levels and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score >2.5 were included in this study. Participants known endocrine disorders such as thyroid dysfunction, adrenal hyperplasia, Cushing's syndrome were excluded from this study. In addition, participants with type 1 or type 2 diabetes mellitus, pregnant or lactating mothers, history of taking hormonal therapy (e.g., oral contraceptives, anti-androgens) within the last three months and patients with known allergies or intolerance to any medications or interventions used in the study were also excluded. After screening, 107 women were selected for inclusion in this study with 7 cases lost in follow up. The participants received tablet Metformin 500mg thrice a day along with a diet plan by the dietician & exercise plan made by the physiotherapist. A low calorie diet plan was designed for both groups with < 450 calories than the regular meal taken by the participant. Similarly, an individualized exercise plan was designed for participants with mix of endurance, aerobic and weight training according individual capacity and preferences.

The demographic data including age, BMI, history of diabetes in family was collected. Each participant was kept under observation for 3 months and their BMI, caloric intake, serum FSH, LH, testosterone, fasting blood glucose and fasting insulin levels were measured at the time of enrollment and after 3 months of treatment. The results were compared to determine the effects of treatment. The data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 24.00. For quantitative variables, the calculations were mean and standard deviation; for qualitative variables like age, the calculations were frequencies and percentages. The p value of ≤ 0.5 was considered significant.

RESULT

The study compared the effectiveness of different interventions on metabolic parameters in women with polycystic ovarian syndrome (PCOS). The average age of participants was 26.78 years (±6.54), indicative of a younger adult population under study. Body Mass Index (BMI) averaged at 30.13 (±5.41), suggesting a cohort where weight management could be a significant factor in health outcomes. Daily caloric intake, was recorded at 2210 kcal (±399), reflecting dietary habits within the studied group. Fasting insulin levels was measured to be 15.4 ±3.2µU/mL. Fasting blood glucose levels averaged 117.6 mg/dL (±8.2). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score was noted at 4.2 (±0.8), further corroborating the presence of insulin resistance in the studied population. Hormonal markers included Follicle-Stimulating Hormone (FSH) at 5.1 U/L (±1.7) and Luteinizing Hormone (LH) at 9.2 U/L (±5.5). Total testosterone levels measured 76.3 ng/dl (±12.4), indicating potential hyperandrogenism. (Table 1, Figure 1).

The post-treatment outcomes following a regimen of metformin, dietary modification, and exercise reveal significant improvements across various metabolic and hormonal parameters in the studied cohort. Participants experienced a notable reduction in BMI from 30.13 (±5.41) to 26.2 (±2.9) with a corresponding P value of 0.03. Caloric intake over a 24-hour period also showed a trend towards improvement, decreasing from 2210 kcal (±399) to 1500 kcal (±210), The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), decreased significantly from 4.2 (±0.8) to 2.1 (±0.5)

with a P value of 0.02, reflecting improved insulin sensitivity in response to treatment. Similarly, fasting insulin levels dropped from 15.4 µU/mL (±3.2) to 10.2 µU/mL (±2.0) (P value = 0.01), indicating reduced insulin secretion after intervention. Fasting blood glucose levels also improved, decreasing from 117.6 mg/dL (±8.2) to 96.4 mg/dL (±5.6) (P value = 0.04), suggesting enhanced glucose control.

Hormonal markers such as FSH and LH levels showed significant changes, with FSH increasing from 5.1 U/L (±1.7) to 7.9 U/L (±2.8) (P value = 0.02) and LH decreasing from 9.2 U/L (±5.5) to 6.5 U/L (±1.7) (P value = 0.02), indicating improved ovarian function and hormonal balance. Total testosterone levels also decreased from 76.3 pg/ml (±12.4) to 63.8 pg/ml (±9.7) (P value = 0.01), indicating reduced hyperandrogenism. Furthermore, improvements in metabolic health were evident with fasting triglyceride levels decreasing from 135.7 mg/dL (±16.1) to a statistically significant level (P value = 0.02). Menstrual regularity and ovulation restoration also showed substantial improvements, with 71% and 59% of participants respectively reporting enhanced outcomes following treatment (both P values = 0.01). (Table 2, Figure 2)

Table 1: Pre-treatment assessment of different parameters

Parameter	Result
Age (years)	26.78±6.54
BMI	30.13±5.41
Caloric intake in 24 hour	2210 ± 399
Fasting Insulin (µU/mL)	15.4 ± 3.2
Fasting blood glucose level	117.6±8.2
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) Score	4.2±0.8
FSH U/L	5.1±1.7
LH U/L	9.2±5.5
Total Testosterone levels ng/dl	76.3 ± 12.4
Fasting Triglycerides (mg/dL)	162.5 ± 18.3

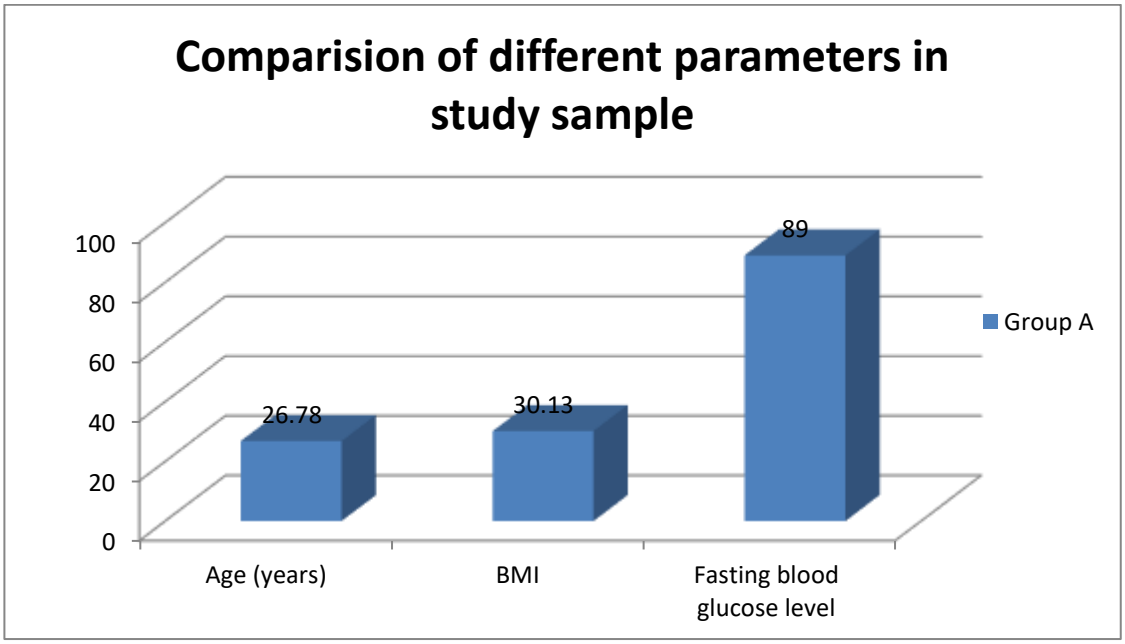

Figure 1: Comparison of different parameters in study population

Table 2: Post-treatment assessment of different parameters

Parameter	Post treatment outcome (metformin+ dietary modification+ exercise)	P value
BMI	26.2±2.9	0.03
Caloric intake in 24 hour	1500 ±210	0.07
HOMA-IR (Insulin Resistance Index	2.1± 0.5	0.02
Fasting Insulin (µU/mL)	10.2±2.0	0.01
Fasting blood glucose level	96.4 ± 5.6	0.04
FSH U/L	7.9± 2.8	0.02
LH U/L	6.5±1.7	0.02
Total Testosterone levels ng/dl	63.8 ± 9.7	0.01
Fasting Triglycerides (mg/dL)	135.7 ± 16.1	0.02
Menstrual Regularity (Improved %)	71%	0.01
Ovulation Restoration (Improved %)	59%	0.01

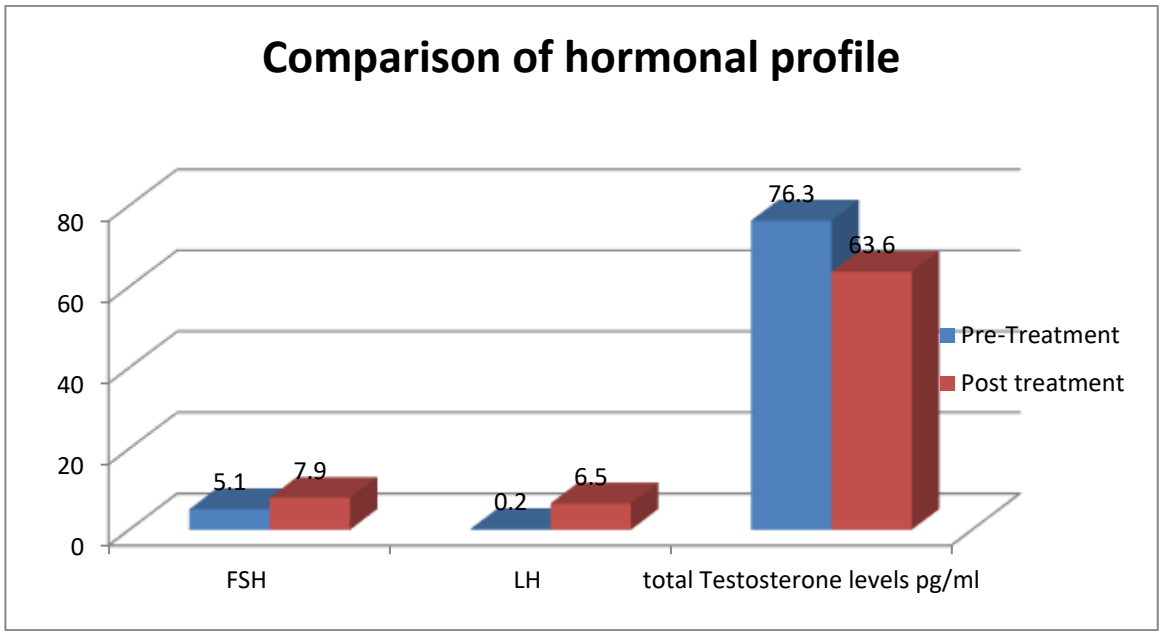

Figure 2: Comparison of post treatment hormonal profile in study population

DISCUSSION

Insulin resistance is a common metabolic feature of Polycystic Ovarian Syndrome (PCOS). Therefore, understanding and addressing insulin resistance are crucial in the comprehensive management of PCOS. It will help not only in alleviating alleviate symptoms but also in reducing long-term health risks associated with metabolic disturbances and hormonal imbalances [14]. Ongoing research continues to explore novel therapeutic approaches to better manage insulin resistance and improve outcomes for women living with PCOS.

In this study, participants experienced a notable reduction in BMI from 30.13 (±5.41) to 26.2 (±2.9) (P=0.03) after 3 months of treatment. These findings correlate with randomized control trial conducted by Deshmukh et al which noticed a 10.9% weight reduction in the group taking very low caloric diet ($p < 0.0001$) with a reduction of 32.3% in free androgen index (FAI) [15]. Similarly, another study with a 6-month diet and exercise program has revealed an improvement in menstrual cycle irregularities, BMI, waist circumference, total cholesterol, and low-density lipoprotein cholesterol levels in women with polycystic ovary syndrome [16]. It significantly resonates with this study which noticed a significant decrease in fasting triglyceride levels decreasing from 162.5 ± 18.3 to 135.7±16.1 mg/dL after 3 months of dietary and lifestyle modification. The significant reduction

in HOMA-IR score further sheds light on the role of multifaceted approach in improving insulin sensitivity.

Moreover, metformin combined with dietary and lifestyle modification plays a vital role in managing insulin resistance by improving hormonal profile. The study conducted by Jungari et al has found a significant decrease in follicle-stimulating hormone, luteinizing hormone, and fasting insulin levels with 91% improvement in menstrual cycle regularity and 86% reduction in volume, theca, and appearance of polycystic ovaries on ultrasound of women [17]. Meanwhile, in this study Menstrual regularity and ovulation restoration showed substantial improvements in 71% and 59% of participants respectively with FSH increasing from 5.1 U/L (±1.7) to 7.9 U/L (±2.8) (P value = 0.02) and LH decreasing from 9.2 U/L (±5.5) to 6.5 U/L (±1.7) (P value = 0.02), indicating improved ovarian function and hormonal balance. These findings suggest that incorporating exercise into the treatment regimen may provide additional benefits in managing metabolic and hormonal dysregulation associated with PCOS [18]. The research indicates that a holistic approach to treatment involving the intake of metformin, diet adjustments, and exercising had a significant effect on various metabolic parameters, hormonal equilibrium, reproductive health outcomes among others. This shows that multifaceted interventions are crucial in managing PCOS condition in order to lower the risk of other illnesses while enhancing.

In clinical practice and public health initiatives, this study gives important insights and strategies that can be applied effectively. This research paper is trying to show that it is very important for the medicine care providers and public health authorities to always keep track of insulin sensitivity markers such as fasting glucose, and insulin levels, then make changes on how they manage them depending on different issues [19]. Themes for further inquiry that may be pursued include studying innovative treatments (e.g., nutraceuticals, anti-inflammatory agents) and determining the ultimate outcomes associated with particular present therapy methods. Hence, there are campaigns focusing on the significance of early detection, regular testing, as well as lifestyle changes designed to reduce long-term health harm caused by PCOS.

Some shortcomings of this study include its small sample size and brief time frame that may restrict the applicability of its findings. Additionally, the research depends on people reporting what they did using lifestyle changes or taking drugs as prescribed; these ways might not represent exact adherence behaviors. This study was conducted in resource-limited settings and face challenges in accessing advanced diagnostic tools impacting the implementation and generalizability of findings.

CONCLUSION

It is critical to adopt dietary modifications, regular exercise, and drug management as an important part of managing high insulin resistance in women suffering from polycystic ovarian syndrome (PCOS) since these can help increase sensibility of insulin as well as reduce the risks related to this condition such as menopause disturbances or too much male hormones (hyper-androgens. Overall, a multifaceted approach tailored to individual patient needs is critical in optimizing outcomes and reducing long-term metabolic and cardiovascular complications associated with PCOS.

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