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A predictive role of Obesity and Insulin resistance in patients with PCOS: A case – control study

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Abstract

Polycystic ovary syndrome is a one of the most common endocrinological disorder which affects about 9-18% of females in the reproductive age group. Obesity plays an important role in the pathogenesis of PCOS, and the majority of subjects with PCOS are overweight or obese. Hyperandrogenism leads to Hyperinsulinemia and vice-versa in PCOS. Due to the unknown and contradictory pathophysiology of PCOS, we aimed to evaluate the hyperandrogenism and its relationship with biochemical markers of Insulin resistance and obesity in women with PCOS. An observational case- control study with 100 subjects (50 Cases and 50 Controls) between the age group of 18- 40 years were recruited after imposing certain inclusion and exclusion criteria. Subject's detailed clinical, menstrual history was noted down. The biochemical parameters such as Serum Testosterone, LH, FSH, Insulin, and FBS was estimated by using commercially available kit methods. BMI and HOMA-IR were calculated using adequate formula. Mean serum level of FBS, LH, Testosterone, Insulin, HOMA-IR, BMI were found to be significantly increased in cases compared to control, however no significant differences could be seen with respect to FSH level in both the groups. Age-wise comparison of biochemical parameters showed elevated levels of LH, Testosterone, Insulin, HOMA-IR in Group I (18-26) as compare to Group II (27-40). The correlation of serum testosterone with BMI, HOMA-IR showed significant positive correlation. The linear regression model indicated that BMI and HOMA-IR may act as significant predictive marker. The present study reported significant increase in BMI and markers of insulin resistances in accordance to excess androgen production in PCOS. Although the complex metabolic interrelationship between obesity and insulin resistance in PCOS have not yet been completely understood, the co-occurrence of these metabolic condition in PCOS leads to increase the severity of the disease and causes several health consequences.

Keywords: Polycystic ovary syndrome, Obesity, Insulin Resistance, Hyperandrogenemia.

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1. Introduction

One of the most common endocrine ailments in women is Polycystic Ovary Syndrome (PCOS). It's believed to be a heterogeneous disorder resulting in ovarian hyper androgen production and Insulin Resistance. The clinical manifestation includes both reproductive and metabolic symptoms ranging from irregular menstruation, infertility, hyper androgenic features like acne and hirsutism male pattern hair fall to metabolic symptoms such as obesity, type II Diabetes Mellitus, Dyslipidemia, hypertension [1]. According to Rotterdam criterion (2003) PCOS affects between 4%- 21% of women worldwide [2]. In India the prevalence of PCOS varies from 3.7% to 22.5% depending on the population studied and the criteria used for diagnosis.

The PCOS Society reports, that one in every 10 women in India has PCOS [3-4]. The PCOS symptoms are challenging endeavor since, it is a complex disorder with major symptoms that may varies with age, thereof treatment should be tailored to meet the specific condition of each patient [5]. The Rotterdam criteria for identifying adult women with PCOS have been accepted globally [6]. Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60% - 100% with the condition both clinical (hirsutism, alopecia and acne) and biochemical hyperandrogenism (Increase Total testosterone, free testosterone, decrease SHGB).

Both features of hyperandrogenism are challenging to assess and vary by methods of assessment, ethnicity and confounding factors including excess weight and life stage [7]. It has been estimated that by 2030, 38% of the young population would be overweight with 20% of the population being obese [8]. Androgen excess may predispose to abdominal fat deposition and have a stimulatory effect on

lipolysis, and impaired adipocyte differentiation, insulin – signaling and generation of adipokines [9]. Obesity causes menstrual dysfunction, anovulation, tubal infections, dysregulation of ovarian function, subfertility, increased risk of complications before and after pregnancy, lower implantation, and higher rates of miscarriage in adult women. It also induces insulin resistance and hyperinsulinemia, which may lead to hyperandrogenemia [10]. The majority of women with PCOS (50% -90%) have insulin resistance. There is poor understanding regarding the origin of IR in PCOS and the mechanism implicated [11-13]. However, Insulin can increase androstenedione production on its own and, more importantly, it can synergize with LH to increase androgen biosynthesis. It's a well-known fact that hyperinsulinemia begets hyperandrogenism [14]. Furthermore, life-style modification with alteration in diet and increase in physical activity can resolve multiple biochemical abnormalities and as well as improve fertility among women with PCOS. In view of above, the present study was planned to evaluate the hyperandrogenism and its correlation with Insulin resistance and obesity in Polycystic ovary syndrome.

2. Materials and Methods

The present study was an observation case-control study. A total of 100 Subjects (50 PCOS diagnosed Cases and 50 apparently healthy Controls) in the age group of 18-40 years were enrolled for the study with their written informed consent. The sampling method used was randomized. The cases were enrolled on the basis of Rotterdam criteria. Subjects with a history of liver diseases, cardiovascular diseases, infectious diseases, thyroid diseases and other endocrine disorder were excluded from the study. Subject with normal menstrual cycle, normal serum testosterone level in the age group of 18 – 40 years were considered apparently healthy controls. Further, Cases were categorized on the basis of age; Group-I (18-26) and Group-II (27-40). Body Mass Index (BMI) was calculated as body weight (kg)/ height (m^2). The detailed clinical, demographic and menstrual history was noted down with the help of data collection proforma. The study was approved by Institutional Ethics Committee.

2.1. Sample Collection

Under aseptic condition, 4 ml of venous blood was drawn from the subjects. 2 ml of whole blood was stored in plain vial which was further subjected to centrifugation at 3000 rpm, serum was separated which was further used for the estimation of hormonal assay (Serum Insulin, Testosterone, LH, FSH), whereas the remaining 2 ml of whole blood was transferred into fluoride vial and was used for the estimation of Fasting Blood Sugar.

2.2. Laboratory Investigations

Fasting Blood Sugar level was measured, using commercially available colorimetric enzymatic Kit by (Glucose- Oxidase – Peroxidase Method). Serum Insulin, Testosterone, LH, FSH were estimated by ECLIA (Electrochemiluminescence Immunoassay) using Cobas e 411 auto-analyzer. HOMA-IR was calculated using adequate formula.

2.3. Statistical analysis

Statistical analysis was done by using IBM (SPSS Statistics software, version 20.0.) All data were expressed as mean ± SD. An unpaired t – test was performed to compare the study parameters between cases and controls. Pearson's correlation coefficient was employed to determine the relationship between variables. Linear regression was carried out for the predictive signifance of independent variable for PCOS. A p value of < 0.05 was considered statistically significant.

3. Results and Discussion

A total of 100 subjects were enrolled in this case-control study. The results of the statistical analysis have been summarized in the tables. Table 1 represents the comparison of anthropometric and biochemical parameters between the two groups. (Cases and Control group). BMI, Serum FBS, LH, Testosterone, Fasting Insulin, and HOMA-IR were significantly elevated in cases compared to controls. However, no significant differences could be observed with reference to FSH level in both groups. Table 2 represents the comparison of parameters between the two age-groups. Elevated levels of testosterone, LH, fasting insulin and HOMA-IR were observed in Group-I as compared to Group-II. Table 3 and Figures 1 & 2 represent person's correlation coefficient among the variables in Cases. In cases, when serum testosterone was correlated with BMI, FBS, Serum Fasting insulin, HOMA-IR it showed significant positive correlation. Table 4 represents linear regression model which indicated that BMI and HOMA-IR may act as significant predict markers. The etiophathophysiology of PCOS remain largely unknown, but it is thought to be multifactorial [15-16].

From last few decades there are extensive studies are being carried out to find out the exact cause. The clinical representation of PCOS has been lately recognized as a disorder of metabolic origin that impairs reproductive function [17]. The interrelationship between obesity, PCOS and Insulin resistance is complex. The present study included 100 participants which was categorized into two groups (50 PCOS Cases and 50 healthy controls). The cases were enrolled on the bases of Rotterdam criteria, (which defines by any of the two of the following characteristics oligo and/ or anovulation; clinical and/or biochemical sign of Hyperandrogenism and PCOM polycystic ovary morphology i.e., follicle number per ovary of ≥ 12 with a diameter of 2-9 mm and/or ovarian volume $10cm^3$ or greater). The comparison of anthropometric and biochemical parameters between the Cases and Controls were carried out. BMI, Testosterone, LH, FBS, fasting insulin, HOMA-IR showed significant elevation in Cases, when compared to controls. However, no significant difference could be observed with reference to FSH in both the groups (Table 1).

Further the study group (N=50) was classified into two groups on the bases of age. Group I (Age 18-26, N= 34) i.e., 68% and Group II (Age 27-40, N=16) i.e., 32%. LH, Testosterone, Insulin, HOMA-IR were significantly elevated in Group I (18-26), when compared to Group II (27-40). However, no significant difference was found in FSH, FBS, BMI levels between the both groups (Table 2). BMI is an important indicator of Body weight. In the present study we found that PCOS subjects has significantly elevated BMI in comparison to controls (26.29±3.36 vs 23.28±2.23). A study

carried out in United Kingdom population by Michel more et al., reported that mean value of BMI was raised in PCOS patients compared to controls [18]. Another prospective study with 164 participants found that the percentage of overweight or obese PCOS population was higher (75.61%). The results of the previous study were in consistent with the finding of a study which included 71 cases and 53 controls and reported that women with PCOS have higher BMI then the healthy controls [19]. Roshan Dadachanji et al., performed a study in which BMI was elevated in PCOS female then in non- PCOS female [20]. In PCOS, due to altered HPA (Hypothalamus Pituitary Adrenal) axis leading to increased LH secretion in theca cell, results into defect signaling in adipocytes and myocytes which leads to dysregulation in adipocyte production and signaling from adipose tissue. Obesity causes increase in (5-alpha reductase enzyme) which in turn can exaggerate hyperandrogenism (Figure 3) [21].

Age-wise comparison of BMI showed no significant difference between the two groups, but there was slightly increased in BMI in age-group of (27-40), with increase in age the BMR drops down drastically, muscle mass loss and reduction in brown tissue leading to easily weight gain in females. Luteinizing Hormone stimulates the production of testosterone. It plays an important role in various gonadal function. LH in synergy with FSH stimulates steroid synthesis, follicular growth and ovulation. Thus, normal follicular growth is the result of complementary action of LH and FSH. In the present study serum testosterone and serum LH were significantly higher in cases compared to controls (84.01±7.90 vs 40.02±4.15, 13.60±4.62 vs 6.18±1.64). FSH level were decreased in PCOS subjects then in control, however the differences were not-significant (5.19±0.96 vs 5.58± 1.31). This was in consistent with the study by Alev Ozer et al., who found that mean serum level of testosterone and LH was significantly elevated in subjects with PCOS then, subjects without PCOS [19]. Numerous studies have found that the PCOS subjects has increase serum level of testosterone, LH and decrease level of FSH [20,22-23]. Hyper androgen synthesis and secretion by ovarian theca cells is one of the main complications of PCOS [24-25]. The increase in LH, decrease SHBG and increase in androgen synthesis enzymes cumilitate and leads to hyperandrogenism that further results in arrest in antral follicles, no corpus luteum formation, anovulation, formation of multiple cysts, subfertility and poor reproductive health. Further, when these hormones were compared within the two age-groups, The LH, Testosterone levels were significantly elevated in Group I (18-26) as compare to Group-II (27-40). The probable reasoning may be that with increase in age female hormones fluctuate in a varied way.

During early 20's to mid-20's the hormones tend to increase rapidly which leads to stimulate the production of sex hormones and results in maturation of ovaries, uterus, vagina and increases the ability to conceive or reproduce. In late 30's and closer to 40's it starts plateauing that leads to decrease in egg count, ovarian reserve and poor fertility rate. Furthermore, In the present study we found that the fasting blood sugar and fasting insulin levels were significantly increased in the PCOS subjects compared to controls (86.78±9.08 vs55.21±8.02, 15.52±5.87 vs 6.81±2.56). The result of the present study was in consistent with the findings of the previous studies which reported a similar result in PCOS [19-20,26-27]. Moreover, the study also included Homeostasis Model Assessment of Insulin- Resistance (HOMA-IR) which act as a surrogate marker of Insulin Resistance [28]. HOMA-IR in the present study was significantly higher in PCOS cases then in controls (3.35±1.47vs0.91±0.37). These findings were in consistent with the previous study which reported similar results [19,26-27]. Hyperandrogenism favored hyperinsulinemia in PCOS patients and leads to Insulin Resistance [29]. Accumulation of excess abdominal fat increases Insulin resistance [30]. IR is considered a consequence of defects in insulin-mediated glucose transport and signaling in adipocytes. Compensatory hyperinsulinemia suppresses the hepatic SHBG in circulation more androgens are left unbound and therefore produce a greater clinical response in terms of hirsutism, acne, and other manifestations of androgen excess (Figure 3) [21]. When these insulin resistance makers were compared within the two age-groups, fasting Insulin and HOMA-IR were increased in Group I (18-26) when compare to Group II (27-40), that may be because with age insulin becomes less sensitive that tends to increase glucose and fat in blood leads to poor sugar control. Furthermore, the above findings were supported by other statistical tools such as Pearson correlation and linear regression model. The Pearson correlation showed significant positive correlation among the variables in PCOS Cases (Table 3 and Figures 1 & 2). BMI showed strong significant positive correlation with testosterone and HOMA-IR. BMI is associated with an increased risk of wide range of clinical complications. Of particular interest are those related to the degree of Insulin Resistance, as Insulin resistance seems instrumental in the co-development of PCOS, together elevated BMI (Obesity) and IR results in increase androgen synthesis by theca cells of ovarian follicles leading to consequences such as formation of multiple cysts, irregular menses poor fertility rate in women with PCOS [21]. Further, the linear regression analysis was carried out between the dependent and independent variable (Table 4). The dependent variable was Testosterone and the independent variables were BMI and HOMA-IR respectively. The regression model indicated that BMI and HOMA-IR may act as significant marker in PCOS as the R square value is (0.559) and (0.261) which explains that (55.9%) of variation in PCOS is due to BMI and (26.1%) of variation is due to HOMA-IR. The regression model represents that BMI may be consider as predict marker in PCOS as obesity plays a pathogenic role in development of PCOS, increase in body mass index led to a concomitant increase in insulin resistance, thus HOMA-IR should also mark as one of the important variables in progression of PCOS.

Overall, in the present study women with PCOS have increased Insulin resistance, high BMI leading to increase weight gain and poor glycemic control that drive clinical severity and may lead to infertility in women, if remain untreated for prolonged [31]. In today's scenario due to sedentary lifestyles, stress and rapid increase in desk jobs, Lifestyle modification such as regular exercise, eating healthy and nutritious food with good amount of sleep is recommended primarily to avert the clinical consequence, rather than rushing towards the pharmacotherapy. Limitation of the study includes small sample size and not accounting variation in ethnicity or diagnostic criteria.

Table 1: Comparison between anthropometric and biochemical parameters in Cases and Controls.

Parameters	Cases (PCOS)	Controls	P – value
BMI (kg/m^2)	26.29±3.36	23.83 ± 2.23	P<0.05
Testosterone (ng/dl)	84.01±7.90	40.02±4.15	P <0.05
LH (MIU/ml)	13.60±4.62	6.18±1.64	P < 0.05
FSH* (mIU/ml)	5.19±0.96	5.58±1.31	P > 0.05
FBS (mg/dl)	86.78±9.08	55.21±8.02	P <0.05
Fasting Insulin (mIU/L)	15.52±5.87	6.81±2.56	P< 0.05
HOMA-IR	3.35±1.47	0.91±0.37	P<0.05

*p>0.05 was not statistically significant.

Table 2: Age-wise comparison of parameters in PCOS Cases.

Parameters	Age (18-26) (N=34) 68%	Age (27-40) (N=16) 32%	P-value
LH (MIU/ml)	14.02 ± 4.60	12.71±4.70	P<0.05
FSH*(mIU/ml)	5.258±0.94	5.063±1.00	P>0.05
Testosterone (ng/dl)	85.114±6.25	80.1±3.85	P<0.05
FBS*(mg/dl)	85.188±6.73	84.75±8.23	P>0.05
Fasting Insulin (mIU/L)	16.788±4.30	12.82±4.48	P<0.05
HOMA-IR	3.61±1.16	2.65±1.25	P<0.05
BMI*(Kg/m^2)	26.714±3.52	27.137±3.37	P>0.05

*p>0.05 was not statistically significant.

Table 3: Correlation between the variables in PCOS Cases.

Parameters	R value

BMI	Testosterone	.760**
	FBS	.572**
	Insulin	.652**
	HOMA-IR	.696**
Testosterone	FBS	.456**
	Insulin	.415**
	HOMA-IR	.502**
FBS	Insulin	.357*
	HOMA-IR	.508**
Insulin	HOMA-IR	.948**

HOMA-IR - homeostasis model assessment of insulin- resistance, FBS – fasting blood sugar, BMI– basal metabolic index
*. correlation is significant at the level 0.01 level (2-tailed)
**. correlation is significant at the 0.05 level (2- tailed)

Table 4: Linear regression between the dependent variable (testosterone) and independent variables (BMI and HOMA-IR).

Parameters	R	R^2	Sig. F Change
BMI (Kg/m^2)	.747	.559	.000
HOMA-IR	.511	.261	.000

The linear regression analysis indicated that BMI and Homa-IR may act as significant predictive marker as the R square value is (0.559) and (0.261) which explain 55.9% and 26.1% of variation in PCOS is due to BMI and Homa-IR respectively.

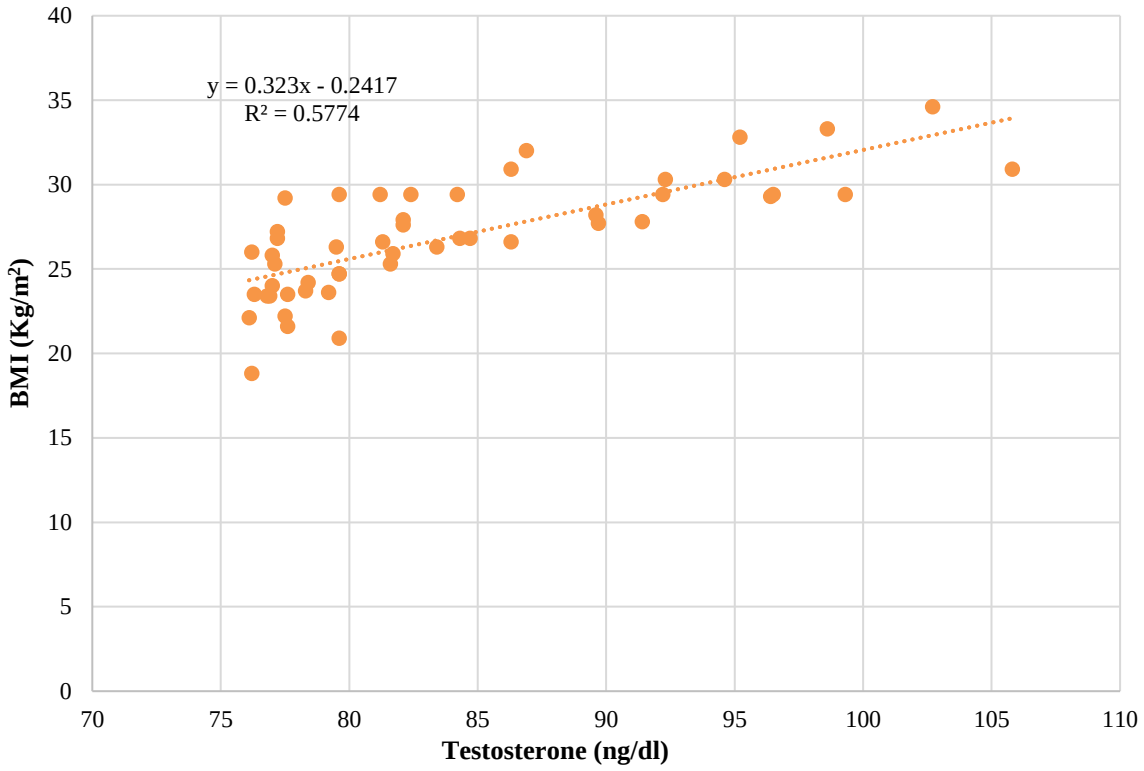

Figure 1: Correlation between serum testosterone and BMI in PCOS.

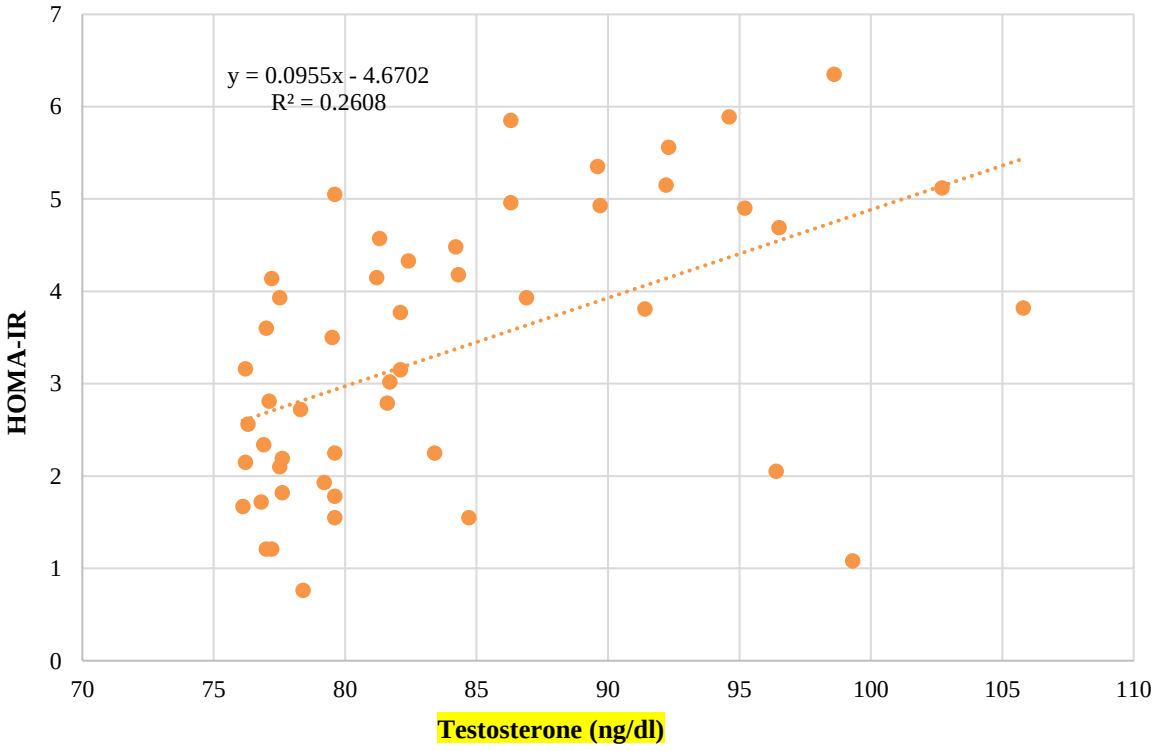

Figure 2: Correlation between serum testosterone and HOMA-IR in PCOS.

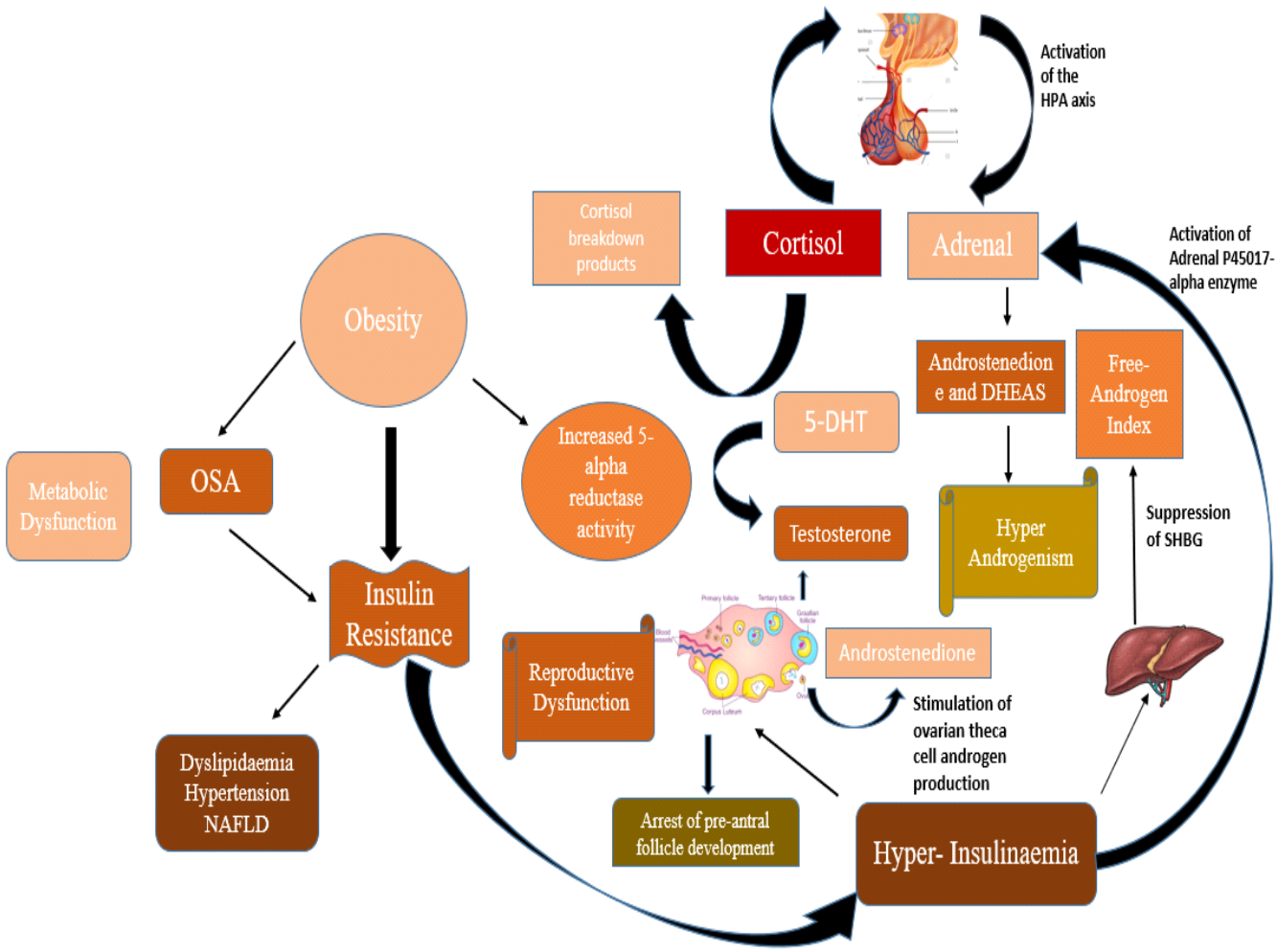

Figure 3: Overview of the possible mechanism of insulin resistance, obesity in pathogenesis of PCOS.

5-DHT: Dihydroxy Testosterone; DHEAS: Dihydroepiandrostenedione Sulphate; HPA: Hypothalamo-Pituitary Adrenal; NAFLD: Non – Alcoholic Fatty Liver Diseases; OSA: Obstructive Sleep Apnoea; SHBG: Sex Hormone Binding Globulin [21].

4. Conclusions

PCOS is a silent epidemic, health catastrophe and its etiology are undefined. The pathogenesis of PCOS is complex, multifactorial and entangled web, where insulin resistance and obesity play an important role. A major challenge in research is to untangle the complex interlink between obesity and insulin resistance in the progression of PCOS. The present study reports significant increase in BMI and biochemical markers (FBS, Fasting Insulin and HOMA-IR) of IR in accordance with increasing androgen production. The study's finding contributes to conceptual approval of the occurrence of IR and obesity in PCOS. As a result, in young girls, BMI and biochemical indicators of IR may act as a significant early predictor of PCOS. A holistic approach to PCOS treatment is required, one that addresses not just life style changes but also potential mental and emotional hurdles that might ameliorate the health burden caused due to this prevalent disorder.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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