Article

Effect of 3-Beta Hydroxysteroid Dehydrogenase on Serum Testosterone Level in Obese Women With Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome(PCOS) is the most prevalent endocrinological condition affecting women in their reproductive years, which is typified by elevated (LH:FSH) ratios, hyperandrogenism, and persistent ovulatory failure. Insulin resistance and obesity have been connected to PCOS. That being said, a significant number of thin women are now receiving PCOS diagnosis. 3-Beta hydroxysteroid dehydrogenase (3βHSD2) deficiency is a rare kind of congenital adrenal hyperplasia (CAH) that causes the gonads and adrenals to produce less steroid hormones. A large number of follicles larger than 8 mm make up PCOS. When the follicles' sacs are still developing, the eggs develop. Ovulation does not occur in PCOS due to these sacs' incapacity to release an egg. The aim of the Study to study the relationship between 3Beta hydroxysteroid dehydrogenase and serum testosterone level in women with Polycystic ovary syndrome.

Material and methods: The study included approximately ninety women, ages (18 – 40) years old, who were split into four groups**:** 30 obese women with PCOS , 30 non-obese women with PCOS and the control group comprises of 30 women (15 obese and 15 non obese) who look to be in good health. All participants been evaluated by detail history, physical exam and investigation performed LH, FSH, testosterone,TSH ,prolactin and 3beta hydroxysteroid dehydrogenase.

Results: A considerable increase in serum level of Testosterone, LH, LH:FSH and Prolactin levels, while the decline of 3β HSD($p < 0.05$) and FSH($p < 0.001$). in serum level patients value in PCO women than the control group .The the receiver operating characteristic curve (ROC) analysis of 3βHSD for distinguishing patient from controls demonstrated an AUC of 0.866, indicating poor diagnostic potential.

Conclusion: the present study focusing on less frequently identified enzyme and hormones that might be interrelate with the pathogenesis of PCOS. For 3βHSD, the results stated that poor diagnostic value in the diagnosis of PCOS in non obese and obese PCOS patients.

Key words: 3βHSD, PCOS,Obese , Hyperandrogenism, LH, FSH.

Introduction

Polycystic Ovary Syndrome (PCOS) is defined by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnose [1].

One of the most important factors in PCOS diagnosis is hyperandrogenism. Hyperandrogenism can be between 60% and 80% common in women with PCOS. High testosterone level can cause hormonal issues, hirsutism, alopecia, acne vulgaris, and irregular menstruation [2].

Increased pulsatility in the hypothalamus in response to gonadotrophin-releasing hormone (GnRH) triggers the pituitary gland to secrete more luteinizing hormone (LH). This leads to the eventual development of polycystic ovarian (PCO) morphology, ovarian hyperandrogenism, and irregular menstrual cycles, which affect women in their early reproductive years [3].

Three distinct methods were utilized to diagnose it, the criteria of the 2003 ESRHE/ASRM Rotterdam consensus meeting, which expanded upon the 1990 NIH classification, are presently used to diagnose PCOS. It is predicated on at least two of the following characteristics: polycystic ovaries by ultrasonography, hyperandrogenism, and oligo-anovulation. In an effort to streamline diagnosis, the Androgen Excess Society (AES) assembled a committee of specialists in 2006 to examine all of the PCOS data that had been released. In order to meet the AES requirements, oligo/anovulation, clinical and/or biochemical hyperandrogenism, and ultrasonographic evidence of polycystic ovaries must all occur concurrently [4].

According to Iraqi research, more Iraqi women in Al-Hilla city than anywhere else in the world have PCOS, with an estimated 33% of them having both signs and symptoms [5] and high frequency of obesity in patients (73%), with an Android form of obesity characterized by a greater waist to hip ratio and front wall fat [6].

According to the Society for Androgen Excess and PCOS, there are more than 12 small follicles in a polycystic ovary, which indicates ovarian dysfunction. oligo or amenorrhea with fewer than six to nine monthly periods, as well as infertility and symptoms of clinical and/or biochemical hyperandrogenism, such as androgenic alopecia, acne, and hirsutism [7].

Ovulatory dysfunction: Clinically overt irregular menstrual cycles, which are defined as recorded vaginal bleeding episodes lasting more than 35 days or fewer than 21 days, are commonly observed when PCOS is diagnosed [8]. Enlarged ovaries, higher than normal theca cell and androgen production are the most common clinical signs of PCOS. Greater androgenic secretion is caused by increased enzyme activity in the steroid production pathway [9].

Ovarian folliculogenesis is regulated by a precise equilibrium between extraovarian and intraovarian factors. Any perturbation to this equilibrium may have an effect on follicular growth and oocyte maturation, which might eventually lead to infertility [4].

These abnormalities include low Follicle-stimulating hormone (FSH), high Luteinizing hormone (LH) production, hyperandrogenemia from the adrenal glands or ovaries, and hyperinsulinemia with insulin resistance. Additionally, folliculogenesis and oogenesis rely on intraovarian factors, specifically follicular fluid factors (FFFs) [10].

An elevated LH/FSH ratio is present in a considerable number of women (55–75%) with PCOS, most likely due to elevated LH levels rather than reduced FSH production. In reality, because of the activation of GnRH, these women create an excessive quantity of LH. In this case, the frequency or amplitude of GnRH can be higher [4].

The attraction and stimulation of ovarian follicle development is the function of FSH. Larger follicles, measuring 7-8 mm, have aromatase activity and may increase oestradiol (E2) and inhibin B, which decreases FSH levels in the late follicular stage. Smaller follicles, measuring 2-4 mm, respond to FSH [4].

Since many PCOS affected women appear to be insulin resistant, compensatory hyperinsulinemia is hypothesized to contribute to hyperandrogenism by directly stimulating ovarian androgen production and reducing hepatic synthesis of sex hormone binding globulin (SHGB), which increases testosterone availability. Moreover, insulin promotes LH stimulated ovarian steroidogenesis and ACTH mediated adrenal androgen synthesis [11].

There is a correlation between obesity and insulin resistance, and 60–70% of PCOS affected women are overweight or obese. Nonetheless, a number of studies have shown that insulin resistance is a common condition in slender women with PCOS [4].

The enzyme 3βHSD is in charge of the intermediate steroidogenic process, which produces progesterone, mineralocorticoids. glucocorticoids and estrogens in the placenta, adrenal cortex, gonads, and other peripheral target tissues [12]. Because 3βHSD has two functions and depends on where it is located in Leydig cells or hepatocytes, it is necessary for both steroidogenesis and steroid breakdown [13].

Normal production of testosteron and estrogen is prevented in gonads with reduced 3βHSD2 activity [14]. Because steroidogenic tissues do not store steroids, synthesis takes place in the mitochondria only when necessary. The steroidogenic pathway's enzymes are found in all steroidogenic tissues as well as certain nonsteroidogenic tissues, such as the skin and kidney [15].

A uncommon form of congenital adrenal hyperplasia (CAH) that results in decreased steroid hormone synthesis in the gonads and adrenals is 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2) deficiency[16].

The aim of the Study to study the relationship between 3Beta hydroxysteroid dehydrogenase and serum testosterone level in women with Polycystic ovary syndrome.

Materials and Methods

The study involved 90 females divided into four groups (30) obese women with polycystic ovarian syndrome, (30)non-obese women with polycystic ovarian syndrome and the control group contains 30 women who appear to be in good health women(15obese and 15 non obese). ages around between (18-40) years old in the four groups. The PCOS women were interviewed using a structured questionnaire to determine the smoking women and take other information like their medical history, family history, surgical history and body mass index. A study was carried out in the Al-Hindia General Hospital in Karbala city and private clinics between November to March. An ELISA was used to estimate the serum concentrations of 3β HSD (enzyme-linked immunosorbent assay). and Total Testosterone, FSH, LH,TSH, Prolactin by Cobas e411.

Ethical approval

Before collecting samples, all study participants were informed and allowed to verbally consent. A local college and hospital ethics committee examined and approved the study protocol, subject information, and permission form by the document number [IRB: 10004 /21 /12 /2023].

Statistical Analysis

The data was analyzed using Software Package for Social Science (SPSS-26.0 version). The data was presented as a mean and Standard deviation (SD). Continuous variables were tested for normality according to the ANOVA test and linear regression analysis that have been used to determine the significant difference between the groups. The *P* values less than (0.05) was considered significant and less than (0.001) considered highly significant.

Results

The Study Subject Demographic Characteristics

Table 1 depicts the distribution of ages.

Table1: Comparison between patient & control according age

Parameter	Group	N	Mean ± sd	P. Value
Age	Obese with PCOS	30	28.6 ±5.4	0.86 NS
	Control obese	15	26.53±6.07	
	non obese with PCOS	30	26.66±3.78	0.93 NS
	Control non obese	15	28.33 ± 4.6	
NS: Non-Significant. *p* value >0.5				

Age

Age is the single most important determining factor affecting female fertility, because fertility declines rapidly after 35 years of age. In the current study, the mean age of obese patients was (28.6 ± 5.4) years old and non-obese Patients (26.6 ± 3.78) years old of PCOS with a range of (18-40) years old, Table 1.

This age matching helps to eliminate differences in parameters result that may originate due to the big variation in acording to the results of this study distribution of age patients were found aproximal to distribution of PCOS of other studymore cases of PCOS in 18-40 years age that agree with previous study of Muhammad Salman Butt *et al*. The most susceptible age group was between the ages of 18 and 40 [17]

BMI

The mean ± SD of BMI for obese pcos patients' group was (32.1 ± 2.7) kg/m2 and non obese patients with pcos (23.69 ± 1.42) that of obese control group was (31.7 ± 1.55)kg/m2 and non obese control group(22.76± 2.23) kg/m2 there was no significant difference between patients and control groups ($p > 0.05$) as shown in Table 2.

Table2: Comparison between patients and control in BMI

Parameter	Groups	N	Mean ± SD	*p* value
BMI (kg/m^2)	Patients Obese with PCOS	30	32.1 ± 2.7	0.54
	Control Obese	15	31.7 ± 1.55	
	Patients non obese with PCOS	30	23.69 ± 1.42	0.168
	Controls non obese	15	22.76± 2.23	

Table 3: Comparison between patients and control in 3BHSD

Parameter	Groups	N	Mean±SD	*p* value
3βHSD (ng/L)	Patients Obese with PCOS	30	755.14 ± 169	0.012
	Control Obese	15	891 ± 65	
	Patients non obese with PCOS	30	672.79 ± 112.5	<0.001
	Controls non obese	15	1081 ± 288	

Table 4: Comparisons of Hormones level in patients and controls group

Parameter	Groups	N	Mean±SD	*p* value
Testosterone (ng/mL)	Patients Obese with PCOS	30	1.89 ± 0.7	< 0.001
	Control Obese	15	0.6 ± 0.24	
	Patients non obese with PCOS	30	1.91 ± 0.57	< 0.001
	Controls non obese	15	0.68 ± 0.23	
LH (m.lU/mL)	Patients Obese with PCOS	30	8.97± 3.02	< 0.001
	Controls Obese	15	4.75± 1.46	
	Patients non obese with PCOS	30	9.06± 3.33	< 0.001
	Controls non obese	15	4.93± 1.52	

FSH (m.lU/mL)	Patients Obese with PCOS	30	6.2 ± 2.3	< 0.001
	Controls Obese	15	7.41 ± 1.79	
	Patients non obese with PCOS	30	6.93 ± 2.5	< 0.001
	Controls non obese	15	6.5 ± 3.06	
LH/FSH ratio	Patients Obese with PCOS	30	1.45 ± 0.6	< 0.001
	Control Obese	15	0.58 ± 0.13	
	Patients non obese with PCOS	30	1.34 ± 0.51	< 0.001
	Controls non obese	15	0.41 ± 0.16	
PRL (ng/mL)	Patients Obese with PCOS	30	20.13 ± 7.2	0.011
	Control Obese	15	11.3 ± 4.19	
	Patients non obese with PCOS	30	21.34 ± 8.51	0.054
	Controls non obese	15	14.8 ± 6.28	
TSH (µlU/mL)	Patients Obese with PCOS	30	2.17 ± 0.87	0.74
	Control Obese	15	2.27 ± 0.93	
	Patients non obese with PCOS	30	2.11 ± 0.93	0.452
	Controls non obese	15	2.33 ± 1.04	

Table 5: Area under the curve for 3BHSD between the patients and control group

AUC	COV	Sens	Spec	SE	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
0.866	807.929	0.817	0.7	0.037	0.794	0.937
AUC; Area under the curve, COV; Cut off value, Sens; Sensitivity, Spec; Specificity, SE; Std. Error						

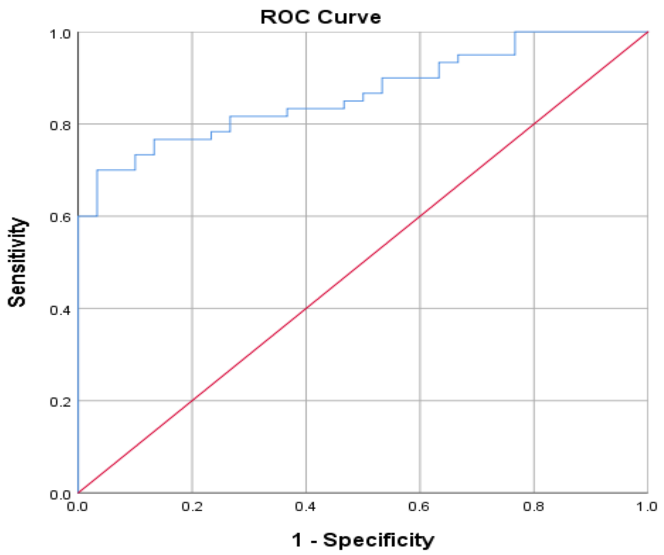

Figure 1: ROC curve for 3 βHSD between the patients and control group

Discussion

The Result of the current study reveal that there was significant decrease difference at P value < 0.05 in serum concentration of 3-Beta hydroxysteroid dehydrogenase among obese PCOS patients when compared with obese control group. also, Serum 3-Beta hydroxysteroid dehydrogenase level reveled significant decrease among non obese pcos patients in comparison with non obese control group at P value < 0.001.

The adrenal reticular cells synthesize DHEA from Pregnenolone, which is derived from adrenocorticotrophic hormone (ACTH)stimulation, due to the poor expression of type II 3-hydroxysteroid dehydrogenase (HSD2) [18].

One study found a reduction of 3bHSD-II activity in hyperandrogenic PCOS women compared to normoandrogenic PCOS ones [19].

The present study results were agreement with a previous study done Mohsin Shah, *et al*. show Serum 3βHSD concentrations were significantly decrease ($P<0.05$) in patients with Polycystic Ovary Syndrome [19].

Table 4 of the current investigation revealed that PCOS females with and without obesity had higher testosterone values than controls ($p<0.05$) [20].

In women, the total quantity of testosterone produced by the placenta, the adrenal glands, and the ovaries' thecal cells is significantly lower during pregnancy [21].

Excessive hair growth, irregular menstrual periods, acne, and hirsutism are signs of PCOS in women due to high testosterone levels [22].

On the other side, excessive androgen production can lead to polycystic ovaries, irregular periods, and oligo-ovulation by weakening ovarian function and unbalancing follicle development.These outcomes support what we discovered, which is that infertile women with higher testosterone levels these results coincide with Maha et al.'s findings [23][24].

The positive correlations between 3βHSD and testosterone in obese women with PCOS suggests that 3βHSD may play a role in the hyperandrogenism observed in PCOS, 3βHSD is an enzyme that catalyzes the conversion of dehydroepiandrosterone (DHEA) to androstenedione, which is a precursor to testosterone. Increased 3βHSD activity can lead to increased production of testosterone [25].

The Result of the current study found decreased 3βHSD and increased testosterone production because increase in the availability of DHEA, the substrate for 3βHSD, it could compensate for the decreased 3βHSD. It is possible that some individuals with PCOS have genetic variations that result in decreased 3βHSD activity but increased affinity for DHEA. This could lead to increased testosterone production despite the lower 3βHSD activity. so, a decrease in 3βHSD can lead to either a decrease or an increase in testosterone, depending on factors such as substrate availability, medication use, and genetic variations.

Table 4 of the current investigation showed that LH levels were greater in PCOS female patients with obesity and non-obesity than in controls. In addition to the fact that PCOS patients secrete less follicle-stimulating hormone (FSH) than the control group, high LH levels also raise levels of androgens, or male hormones like DHEA According to Zozan et al. (2021) [26]. suggested that endocrine hormone concentrations were significantly higher in PCOS Rebecca H. K. Emanuel, *et al*. [27]

The obesity group's much higher LH:FSH ratios compared to the control group might be the consequence of abnormal activity in the adrenal or hypothalamic-pituitary-ovarian axis, which has been associated with PCO [28]. These findings agreement with the results of Maha *et al*. [29].

GnRH pulses occur more often when testosterone levels are higher because they block the hypothalamic-pituitary axis from getting any negative feedback. Elevated hypothalamic GnRH favors LH production more than FSH production[30].In this study we found Blood testosterone levels are directly correlated with higher serum LH levels [31]. As a result, an excess of androgen is thought to be the primary component responsible for the development of this disorder's symptoms and signs [32].

The elevated levels of luteinizing hormone in the patient group compared to the control group may be related to an increase in insulin levels and obesity, as the blood was drawn on the second or third day of the menstrual cycle this agree with study Iliase K., Artemis K., et al [33].

In present study the Table 4 showed that the prolactin values of PCOS females, both obese and non-obese, were greater than controls. Among women, the most prevalent causes of infertility are hyperprolactinemia and polycystic ovarian syndrome (PCOS) [34]. Haiyan Yang found that PRL is significantly decreased in PCOS patients compared with controls [35]. Table 4 of the current study showed that the TSH levels of PCOS affected women and controls no significantly vary from one another [36].

With an Area under the curve (AUC) of 0.866, the receiver operating characteristic curve (ROC) analysis was used to compare the PCOS patient group's 3βHSD specificity and sensitivity to that of the control group at the cut-off point of 807.929. For, 3βHSD the corresponding values were 0.7% and 0.817% for specificity and sensitivity. Figure 1 of Table 5. For PCOS patients, the 3βHSD AUC value is thought to be not reliable indicator that may be poor diagnosis.

The present study results Conclusions the 3β-hydroxysteroid dehydrogenase deficiency is a risk factor of PCOS, where 3βHSD deficiency leads to increased DHEA levels and decreased cortisol levels, which in turn leads to increased testosterone production.

In addition, women with 3βHSD deficiency often have elevated levels of LH, testosterone, and prolactin, and decreased levels of FSH.

The diagnosis can be confirmed with a genetic test or a functional adrenal androgen suppression test.

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