**Relationship between serum Prostate Specific Antigen (PSA) in women with polycystic ovary syndrome and some reproductive hormones in Kirkuk city**

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**Abstract**

PCOS is one of the most common endocrine disorders among women between 12 and 45 years of age, affecting 5-10% of women. The patients were included in the current study based on the criteria of Rotterdam in the diagnosis of polycystic ovarian syndrome with at least two of the following three criteria: menstrual cycle disorder, chemical criteria for high levels of androgen, detection of polycystic ovary using ultrasound (10 or more cysts of 2-10 mm in diameter). Sixty (60) patients were diagnosed with the syndrome and 30 healthy women were considered as control groups aged between 16 and 46 years. A number of criteria have been adopted to exclude patients who have had previous ovarian surgery as well as women taking contraceptives, steroids and herbal medicines that affect ovarian function for at least two months. The study was conducted at the Azadi Teaching Hospital in the city of Kirkuk for the period from October 2016 to February 2017. Blood collected for all participants on the second or third day of the menstrual cycle. Body mass index (BMI) was calculated and prostate specific antigen (PSA) level and the level of sex hormones such as Anti-mullarian hormone (AMH), Luteinizing hormone (LH), Follicular Stimulating hormone (FSH), Testosterone hormone (T) as well as Luteinizing hormone/Follicular stimulating hormone (LH/FSH) ratio were determined. The relationship between PSA and all studied variables was investigated after dividing the study sample into three age groups A (16-25), B (26-35), and C (36-45) years. Each age group included 30 patients with PCOS and 10 women as a control group. The results showed a significant increase (p <0.05) in the level of the PSA, AMH, LH, T and LH/FSH ratio, conversely the level of FSH was significantly reduced (p <0.05) when comparing women patients with the control group. Correlation results showed a positive correlation between the PSA level and the values of all the studied variables except for FSH, which was inversely correlated with serum PSA in PCOS patients and for most age groups except for category C where AMH showed a negative correlation with PSA. The results also indicated a significant correlation between PSA and T, LH, and LH/FSH ratio for all age groups. PSA can therefore be considered as a biochemical marker for androgen activity changes in patients with PCOS.

**Key words:** Polycystic ovary syndrome, Prostate specific antigen, gonadotrophichormones, Androgens

**Introduction**

Polycystic ovary syndrome (PCOS) more often becomes the condition affecting not only adult women, but also girls [1]. PCOS is one of the most frequent endocrine disorder and ovarian dysfunction affecting 5-10% of women in reproductive age (12-45 years) across the world, it is often complicated by chronic anovulatory, infertility and hyperandrogenism with the clinical manifestations of oligomenorrhea, hirsutism and acne [2,3]. Androgen excess is the main pathology in PCOS which associated with changes in ovarian morphology. Metabolic abnormalities, insulin resistance, hyperinsulinism, type II diabetes mellitus, endometrial carcinoma, dyslipidemia and psychosocial dysfunction are presented in PCOS [1,4]. The absolute level of circulating LH and its relation to FSH levels are significantly higher in women with PCOS, compared to healthy women. According to Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2003 [5], PCOS is diagnosed by the presence of two of the three following diagnostic criteria: oligo - amenorrhoea, polycystic ovaries morphology and hyperandrogenemia [6,7,8]. Another reliable parameter in PCOS diagnosis seems to be the Anti-Mullerian Hormone (AMH) [9].

Prostate specific antigen (PSA), a 33 kDa glycoprotein containing 237 amino acids, 4 carbohydrate side chains and multiple disulphide bonds is homologous with the proteases of the kallikrein family and hence called human glandular kallikrein-3 (KLK3), which is now known as (hk-3). It is a serine protease which splits the seminal vesicle proteins semenogelin I and II resulting in liquefaction of the seminal coagulum [10,11]. As well, PSA is the best cancer marker currently available and widely used for screening, diagnosis and management of prostate cancer [12,13,14,15]. PSA, in male is produced by prostate gland. In female, PSA has been detected in some tissues such as breast, ovarian and endometrial tissues, amniotic fluid and milk. PSA production seems to be up-regulated by steroid hormones such as androgens, progesterin and gonadocorticoids [16,17,18]. Although the serum concentration of PSA differs between men and women by about 1000-fold [19]. Therefore, Several reports have been indicated that androgens stimulate PSA production, it is expected that hyperandrogenemic condition, such as PCOS and hirsutism can be associated with higher level of PSA in women supposed to have these diseases [17,20]. The purpose of this study was to evaluate serum levels of PSA and establish if a relationship exists...
between PSA and some reproductive hormones in women with PCOS in Kirkuk city.

**Material and Methods**

**Subjects**
This study was investigated 90 women (60 patients and 30 controls), their age between 16-45 years who attended to the Azadi teaching hospital in Kirkuk city from October 2016 to the February 2017. The investigated Women had polycystic ovary syndrome diagnosed by the physician and by laboratory tests. The exclusion criteria included none of women had previous ovarian surgery, no contraceptive or any herbal drugs, no receiving sex steroids or any drug known to affect ovarian function for at least two months. Body mass index was calculated as weight (kg) per height (m2). Women were considered as normal weight at BMI (18.5 -24.9 kg/m2), overweight women at BMI (25- 29.9 kg/m2) and obese women at BMI (30kg/m2) (WHO, 2000).

All individuals had been blood collecting in the second or third day of menstrual cycle for all testing. By using a sterile disposable syring, 10 ml of venous blood was collected in gel separator tube and allowed to clot at room temperature for 20 minutes, and then centrifuged at 3000 rpm for 15 minutes, sera were removed and distributed upon three eppendorf tubes for each sample, then stored at -30 °C until used for the assessment of biochemical parameters, which includes the level of PSA and AMH, LH, FSH, T. hormones.

PSA and LH, FSH. Test. hormones were measured by using immunoenzymometric assay which is performed entirely in the TOSOH AIA System Analyzer (TOSOH, Japan). AMH was estimated by using a sandwich type immunoassay and a solid phase enzyme-linked immunosorbent assay (ELISA).

Correlation of PSA level with these parameters was made after subdivided PCOS women into three age groups, A (16-25), B (26-35), C (36-45) years old. Each group included 30 individuals, 20 of them were suffered from PCOS and the remaining 10 women were healthy women.

Statistical analysis of the data was performed using significant F-test and A NOVA was used to look for association between different variables in the study groups, also Microsoft Excel spreadsheet 2010 were used to analyze the data. The multiple comparisons between the means were analyzed by Duncan post HOC test and a value of (p<0.05) was statistically considered significant.

**Results**

Figure (1) showed a significant PSA level elevation (p<0.05) in PCOS patient (0.047±0.031 ng/mL) compared to control group (<0.01). Results of the current study showed that mean BMI in women with PCOS (30.68 ± 6.02 kg/m2) increased significantly (p<0.05) compared to those of the control subjects (26.22 ± 5.14 kg/m2) as shown in figure (2).

The mean hormones levels of PCOS patient were compared to those of the control subjects showed significant differences (p<0.05). The mean levels of AMH, LH, T hormones and LH/FSH ratio showed significant elevation in PCOS group (4.04 ± 3.21 ng/mL; 6.96 ± 3.31 mIU/ml; 32.43 ± 22.16ng/dL; 1.079 ± 0.523) respectively compared to control group (2.61 ± 0.83ng/mL; 4.09 ± 0.95mIU/ml; 19.53 ± 3.8ng/dL; 0.515 ± 0.11) respectively as shown in Figs. (4.2). However, the mean level of FSH showed significant decrease in PCOS group (5.75 ± 1.53mIU/ml) compared to control group (8.15 ± 0.91mIU/ml) as shown in figure (3).

Correlation data (table1) showed a positive correlation (p<0.05) between the PSA and BMI of all age groups A, B and C of PCOS women (r=0.782, r=0.886 and r=0.645) respectively. Results also showed a positive correlation between PSA and AMH, LH, T and LH/FSH ratio (r=0.802, r=0.780, r=0.801 and r=0.230) and a negative correlation with FSH (r= - 0.148) in age group A of PCOS women (Table 1). The data in table (1) indicated that there was a positive correlation of PSA with AMH, LH, T and LH/FSH ratio (r=0.881, r=0.831,r=0.813 and r=0.581). On the other hand, a negative
correlation of PSA with FSH \((r=-0.398)\) in age group B of PCOS women. As for the age group C of PCOS women, the result showed a positive correlation of PSA with AMH, LH, T and LH/FSH ratio \((r=0.502, \ r=0.631, \ r=0.661, \ r=0.736)\), while a negative correlation of PSA with FSH \((r=-0.445)\) (Table 1).

### Table (1) Correlation of PSA level with BMI and AMH, LH, T, FSH hormones and LH/FSH ratio in age groups of PCOS women

<table>
<thead>
<tr>
<th>Variables</th>
<th>PSA Group A(n=20)</th>
<th>PSA Group B(n=20)</th>
<th>PSA Group C(n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI(Kg/m²)</td>
<td>0.782</td>
<td>0.886</td>
<td>0.645</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>0.802</td>
<td>0.881</td>
<td>-0.502</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>0.801</td>
<td>0.831</td>
<td>0.631</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>-0.614</td>
<td>-0.581</td>
<td>-0.661</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0.230</td>
<td>0.398</td>
<td>0.445</td>
</tr>
<tr>
<td>T (ng/dL)</td>
<td>0.780</td>
<td>0.813</td>
<td>0.736</td>
</tr>
</tbody>
</table>

### Discussion

PCOS appears to be a heterogeneous disorder in which ovarian and adrenal androgen excess is presented by variety of high gonadotropic degrees and metabolic abnormalities. Moreover, PCOS patients must present either clinical or biochemical findings subsequent to androgen excess. PSA, a 33 KD a serine protease has been used as a highly specific marker of normal and cancerous prostatic tissue [12]. Recently, growing bodies of evidence indicate the production of PSA from multiple female tissues such as breast, ovary and adrenal tumors [18]. The results of the current study show increased level of PSA in serum of PCOS patients. This results is in a good agreement with several researches [21,22], who reported the increasing of PSA level in patient with PCOS. Previous studies have shown that PSA is produced by extraprostatic tissues and fluids, as the gene expression of PSA is upregulated by the androgens and progestins in hormonally responsive tissues, hyperandrogenic syndromes such as PCOS may be associated with elevated serum PSA levels[11,18]. Several studies showing increase of testosterone is directly related to the increasing of serum PSA level [19,23].Moreover, Gullu et al., [17] noted also the positive correlation between PSA and testosterone levels which strength the possibility that androgens have the stimulatory effect on PSA production. The positive correlation of PSA with testosterone has better accuracy for total testosterone and total PSA serum levels in diagnostic of PCOS [20].

The current result detected a significant increase of BMI in PCOS groups women which reflect the difference in body weight between PCOS and control groups. Our results are in a good agreement with another study which concluded that BMI was significantly increased in PCOS women [24,25,26]. Hyperinsulinism and insulin resistance were frequently observed in PCOS patients, and these traits have cause-consequence relationships with obesity [2]. Moreover, Mendoça et al., [27] reported that hyperinsulinemia and insulin resistance reduced fat breakdown and stimulate fat storage and the overproduction of androgen. This can contribute to obesity and increased of BMI mean\([2,28]\). The metabolic and hormonal disorders associated with PCOS patient reinforce obesity state which lead to high difference in mean value of BMI between PCOS and control groups.

AMH is produced by the granulosa cells surrounding preantral and antral follicles and has an important role in the development and maturation of follicles [29][30]. The results of the current study yielded significantly increase in AMH among PCOS patients compared to control. Our result is in a good agreement with another studies that confirmed the high increasing of AMH in PCOS patients\([9,31]\). This increase is due to increased synthesis and secretion of AMH by polycystic ovaries \([32]\, as its production by granulosa cells in PCOS increases 75 times higher compared to healthy women. It was also suggested that elevated serum AMH levels in PCOS patients may be caused by disturbances in folliculogenesis, due to suppression of aromatase activity by AMH and by lower follicle sensitivity to FSH [33]. The results show that LH increased in PCOS women and this result agreed with those of Akram and Rooih[34]. This result is due to the mean number of follicles which was significantly higher in PCOS women [8,35]. FSH is very important for folliculogenesis in women. Current result show decreased in FSH hormone in PCOS women compared with healthy womenand it is in accordance with several researches \([36,37]\). These changes in the gonadotropins hormones explained by hyperestroneguria raised from disturbance in insulin related to obesity through alteration in steroid hormone metabolism. Estrogen stimulate LH production and inhibit FSH production by the pituitary gland [38]. The result of the current study indicated a significant increase in LH/FSH ratio in PCOS group, and this result was in consistent with other studies \([39,40]\, who reported that the ratio greater than 1:1 in PCOS women. Our current results regarding testosterone hormone detected an increasing in the level of testosterone hormone in PCOS women compared to control groups. PCOS women may develop insulin resistance and high insulin resistance occurs a lot of excess androgen arises from the ovaries [41].

In this study, from the obtained data it appears that PSA represents an interesting positive predictor for numerous studied parameters. The finding revealed a strong positive correlation between the PSA and BMI. Our BMI correlation with PSA results are in a good accordance with the result of Mardanian and Heidari [18] who reported a positive correlation between PSA, BMI and LH/FSH ratio. Together with the presences of higher testosterone in obese patients comparing to healthy women suggested that the influence of obesity on serum PSA could be due to the strong correlations among PSA and the
androgen. The current study noted that PSA is positively correlated with AMH in age from 15-35 but negatively correlates with AMH in women with PCOS aged from 36-45 years. This result attributed to the decreasing level of AMH with the increasing of age and BMI of PCOS patient as proposed by Quinn et al. [24]. Also the result denoted a strong positive correlation between the serum PSA and testosterone hormone. These findings correspond with the result of many researches [18,20,23]. that reported a direct association between PSA and testosterone in women with PCOS. The production of PSA in non-prostatic tissue due to the gene expression which is upregulated by the androgens and progestins in hormonally responsive tissues [11,18,19,23]. The significant correlation among testosterone and PSA levels indicates the fact that PSA can be considered as a good marker of endogenous androgen excess in females suffering from PCOS.

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مستضد البروستات النوعي في مصل النساء المصابات بمتلازمة المبيض متعدد الاكياس وعلاقته ببعض هرمونات التكاثر في مدينة كركوك

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المختصر

تعت متلازمة المبيض متعدد الاكياس (PCOS) واحدة من اضطرابات الغدد الصماء الأكثر انتشاراً بين النساء في الاعمار بين 12-45 سنة، مما يؤثر على 5-10% من النساء. تم تضمين المريضات في الدراسة الحالية استنادًا لمعايير Rotterdam لتشخيص متلازمة المبيض متعدد الاكياس. تكشف عن تكيس المبيض باستخدام جهاز السونار (عشرة اكياس أو أكثر يتجاوز قطرها بين 2-10 ملليمتر). تم تضمين (60) مريضة من اللواتين يعيشين من الاصابة بهذه المتلازمة (30) امرأة سليمة عبارة عن مجموعة مoker تحتفظ بالاضطرابات الجزيئية الاسترئوية وال�ات السريطة التي تؤثر في وظائف المبيض لفترة شهرين على الاقل. أجريت الدراسة في مستشفى أرازي التعليمي في مدينة كركوك لفترة من (61) مريضًا يعانون من الاصابة بهذه المتلازمة و(31) مريضة استعملت كمجموعة سيطرة.

تم تشريح الدم لجميع نساء عينة الدراسة في اليوم الثاني أو الثالث من الدورة الشهرية. تم اجراء الدراسة في مستشفى ازادي التعميمي في مدينة كركوك لفترة من تشرين الأول 2116 إلى شباط 2116. تم في البداية تعيين مؤشر كتلة الجسم (BMI) ثم قياس مستويات المستضد النوعي للبروستات (PSA) والهرمون الولائي (AMH) بالإضافة إلى قياس مستوى عدد من الهرمونات الجنسية مثل هرمون مضاد المولارين (AMH) والهرمون الغدي (FSH).

كما تقدمت الدراسة في النتائج الارتباطية بين مستضد البروستات النوعي (PSA) وقايا عدد من الهرمونات مثل هرمون الاندروجين (T) والهرمون الولائي (AMH) والهرمون المحفز لمجريبات (LH) والهرمون الدهني (Testosterone). كاها بات في النتائج ارتباط موجب مع المستضد النوعي للبروستات (PSA) مع مستويات الهرمون الولائي (AMH) والهرمون المحفز لمجريبات (LH) والهرمون الدهني (Testosterone)

الكلمات المفتاحية: متلازمة المبيض متعدد الاكياس، مستضد البروستات النوعي، هرمونات التكاثر، هرمون الاندروجين.