

Prostate specific antigen is raised in polycystic ovary syndrome

Abstract

Background: Prostate specific antigen (PSA) has been observed to increase in polycystic ovary syndrome (PCOS). Expression of prostate specific antigen (PSA) gene is thought to be under androgenic regulation. Therefore, PCOS, a hyperandrogenic state is expected to be associated with higher level of PSA.

Aims: To assess serum PSA level in PCOS women in Bangladesh.

Methods: This cross-sectional study enrolled 40 PCOS patients diagnosed on the basis of revised Rotterdam 2003 criteria and 25 controls. Serum PSA (ng/ml) and testosterone (ng/dl) were measured along with ultrasonogram (USG) for pelvic organs. PSA and testosterone was measured by direct chemiluminometric technology.

Results: Serum PSA and testosterone level were significantly higher in PCOS subjects than control (0.05 ± 0.01 vs. 0.04 ± 0.01 ng/ml; $p < 0.02$; 40.18 ± 21.12 vs. 28.92 ± 13.65 ng/dl; $p < 0.01$ respectively). PSA positively correlated with observed polycystic ovaries by USG in the PCOS group ($r = 0.397$, $p = 0.011$) but not with either testosterone ($r = -0.075$, $p = 0.644$) or hirsutism score ($r = 0.012$, $p = 0.940$).

Conclusions: Present study observed that serum PSA is higher in PCOS patients than control and correlate with polycystic ovary detected by USG but does not show any association with hyperandrogenism.

Keywords: PCOS, PSA, testosterone

Volume 6 Issue 4 - 2018

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Received: May 06, 2018 | Published: July 26, 2018

Abbreviations: PSA, prostate specific antigen; PCOS, polycystic ovary syndrome; BSMMU, Bangabandhu sheikh Mujib medical university

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disorder that has both adverse reproductive and metabolic implications, which has been considered as the most common cause of hyperandrogenaemia in women of reproductive age.¹ These patients are at higher risk of developing infertility, endometrial carcinoma, and a number of metabolic disorders, including insulin resistance, diabetes mellitus, hypertension and cardiovascular diseases.² Different studies have observed a prevalence rate of PCOS 5% to 20% among women of reproductive age.^{3,4} About 75% of all anovulatory women may have polycystic ovaries.⁵ Therefore, a surrogate serum marker has long been being tried which could precisely be suggestive of PCOS.

Prostate specific antigen (PSA) is determined to be a 33-kDa serine protease that is primarily a product of prostatic tissue and secreted into the seminal fluid.⁶ PSA is used as a highly specific and valuable marker of prostatic carcinoma regarding the screening, diagnosis and monitoring of disease.⁷ Recent development of ultrasensitive assays demonstrated presence of PSA in wide variety of female tissues and fluids particularly breast, ovary, milk, endometrium and amniotic fluid.⁸ However, the main source of serum PSA in women is still unknown, although some authors suggest that it is produced by periurethral glands which are highly homologous to male prostate. The gene expression and protein production of PSA in non prostatic tissues are under the regulation of steroid hormones via their receptors. Androgens, glucocorticoids and progestins regulate the

PSA gene expression. Estrogen by itself seems to have no effect on PSA regulation but it can impair its production.⁹

As a diagnostic marker of PCOS, PSA level has been found to have relatively high specificity (80%) and sensitivity (70%).¹⁰ Serum PSA level remain stable throughout the menstrual cycle with less intracyclic variations.¹¹ PSA is not operator dependent, like ultrasound ovarian morphology and also widely available. Hence, PSA value could be a diagnostic marker of PCOS. To assess whether serum PSA assay may fulfill this role, the present study was designed to see the serum PSA level in PCOS women and control subjects in a tertiary level hospital.

Methods

This cross-sectional observational study was conducted in the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka encompassing 40 PCOS patients of age 16-35 years and 25 control women of similar age. Control women were eumenorrheic, non-hirsute, without any family history of hirsutism and had no endocrine disorders. Women who did not agree to participate in the study or detected pregnant were excluded. This study was approved by the Institutional Review Board of the hospital. Informed written consent was obtained from PCOS patients as well as from controls.

PCOS patients were diagnosed on the basis of Revised Rotterdam Consensus 2003 criteria.¹² Patients with following diseases were not included: hyperprolactinemia diagnosed by the presence of serum prolactin values greater than 25 ng/ml, hypothyroidism, considered by serum TSH greater than 5 μ IU/ml and non-classical congenital

adrenal hyperplasia, which was diagnosed in case of basal or ACTH-stimulated 17-OH progesterone greater than 10ng/ml.¹³ Anthropometric measurements were taken in all PCOS patients and control women. BMI lower than 25kg/m² were considered as non-obese, and those with a BMI equal or higher than 25kg/m² as obese.¹⁴ Detailed menstrual history was taken. Oligomenorrhoea was defined as menstrual cycle>35days in length and amenorrhoea was defined as absence of menstrual period for more than 3months.¹⁵

Samples for hormonal assay were taken on the early follicular phase (days 3-5 of menstrual cycle) in women with regular menstrual cycle or oligomenorrhoea and on any other day in patients with amenorrhea. Clinical hyperandrogenemia was considered if the participant had at least one of the following-hirsutism, evaluated by using a modified Ferriman-Gallwey score, acne and androgenic alopecia. Normal level of serum testosterone was taken as <53ng/ml.¹⁶ Serum PSA has not been in routine use for female patients, levels considered to be normal are not well clarified. Age specific ranges are also not available and moreover, there is possible ethnic variability, in black and white women-0.0-0.36 μ g/L, in Hispanics-0.0-2.2 μ g/L.¹⁷ Therefore, no cut off for PSA was used to define normal in study subjects. Polycystic ovary was considered by presence of 12 or more follicles in each ovary measuring 2-9mm in diameter, and/or increased ovarian volume (>10ml).¹²

Serum PSA level and testosterone was analyzed by chemiluminescent immunometric assay, which was carried on the ADVIA Centaur PSA assay. USG was done by the same sonologist for each subject. All data were expressed as frequencies and mean (\pm SD) as applicable. Student's t-test and one way ANOVA for continuous variables (PSA, hormone levels etc.) and Chi-square test for discrete variables (PSA under various cut-offs) were used. Correlation among variables was assessed by using Pearson's correlation tests. Pvalues \leq 0.05 were considered as significant.

Results

Anthropometric characters of study subjects are shown in Table 1. Age range of 40 PCOS subjects were 16-35years (mean \pm SD, 22.35 \pm 4.30years) and their BMI ranged from 21.60 to 37.10kg/m² (mean \pm SD, 28.85 \pm 4.38kg/m²). Control subjects ranged in age from 23-34years (mean \pm SD, 27.08 \pm 3.11years) with BMI ranging from 16.90-26.20kg/m² (mean \pm SD, 22.05 \pm 2.13kg/m²). The differences of PCOS and controls in terms of age and BMI were significant (p=<0.001 for both). Waist circumference as well as both systolic and diastolic blood pressure were significantly higher in PCOS group than those of control group (p=<0.001 for all). None of the control subjects exhibited any acne, acanthosis nigricans, hirsutism or menstrual irregularities, frequency of which were 27.5%, 67.5%, 80.0% and 90% respectively in PCOS.

Table 2 depicts serum PSA and testosterone level which were significantly higher in PCOS subjects than control (0.05 \pm 0.01 vs. 0.04 \pm 0.01ng/ml; p<0.02; 40.18 \pm 21.12 vs. 28.92 \pm 13.65ng/dl; p=<0.01 respectively). Holding cut-off for serum testosterone at 53ng/dl, all control subjects fell in the group having testosterone <53ng/dl whereas in the PCOS, 8(20%) subjects had testosterone level \geq 53ng/dl (p=<0.02, Table 3). As shown in Table 4, PSA level was similar in the groups of PCOS patients divided by testosterone level at cut off of 53 ng/dl (0.0525 \pm 0.007 vs. 0.0528 \pm 0.011ng/ml, p=0.940). Similar to that as grouped under testosterone cut off, PSA level in subjects

with or without hirsutism in PCOS group did not differ statistically (0.0528 \pm 0.010 vs. 0.0525 \pm 0.012ng/ml, p=0.940, Table 5). As displayed in Table 6, PSA level seemed a bit lower trend with increased age group, but difference was statistically non significant (p=0.835). Table 7 shows that PSA positively correlated with observed PCO by USG in the PCOS group (r=0.397, p=0.011) but not with testosterone (r=-0.075, p=0.644) or hirsutism score (r=0.012, p=0.940).

Table 1 Characteristics of study subjects

| Variables | PCOS(n=40) | Control(n=25) | p |
|--|--------------------|-------------------|---------|
| Age(mean \pm SD, year) | 22.35 \pm 4.3 | 27.08 \pm 3.11 | <0.0001 |
| BMI(mean \pm SD, kg/m ²) | 28.85 \pm 4.38 | 22.05 \pm 2.13 | <0.0001 |
| Waist circumference(cm) | 85.70 \pm 9.74 | 74.56 \pm 5.58 | <0.0001 |
| Blood Pressure(mm Hg) | | | |
| Systolic Pressure | 119.88 \pm 13.13 | 101.60 \pm 7.46 | <0.0001 |
| Diastolic Pressure | 76.75 \pm 9.2 | 68.00 \pm 6.46 | <0.0001 |
| Acne | 11(27.5) | 0 | |
| Acanthosis nigricans | 27(67.5) | 0 | |
| Hirsutism | 32(80.0) | 0 | |
| Menstrual irregularity | 36(90.0) | 0 | |
| PCO in USG | 35(87.5) | 0 | |

(Data were expressed as frequency, percentage, mean \pm SD)

Comparison between PCOS and Control done by Student's t-test and Chi-square test

BMI, body mass index; PCOS, polycystic ovary syndrome

Table 2 Testosterone and PSA levels of PCOS and control subjects

| Variables | PCOS(n=40) | Control(n=25) | p |
|---------------------------------------|-------------------|-------------------|-------|
| S. PSA(mean \pm SD, ng/dl) | 0.05 \pm 0.01 | 0.04 \pm 0.01 | <0.02 |
| S. Testosterone(mean \pm SD, ng/dl) | 40.18 \pm 21.12 | 28.92 \pm 13.65 | <0.01 |

(Data were expressed as mean \pm SD)

Comparison between PCOS and Control done by Student's t-test

PCOS, polycystic ovary syndrome; PSA, prostate specific antigen

Table 3 Frequency of PCOS and controls by testosterone cut-off at 53ng/dl

| Group | PCOS(n=40) | Control(n=25) | p |
|-----------|------------|---------------|-------|
| >53ng/dl | 8(20) | 0 | |
| < 53ng/dl | 32(80) | 25(100) | 0.019 |
| Total | 40 | 25 | |

(Data were expressed as frequency, percentage)

Comparison between PCOS and Control done by Chi-square test

PCOS, Polycystic ovary syndrome

Table 4 PSA level(ng/ml) in PCOS and control divided by testosterone cut off at 53ng/dl

| Testosterone | PCOS(n=40) | Control(n=25) |
|--------------|--------------|---------------|
| >53ng/dl | 0.0525±0.007 | - |
| < 53ng/dl | 0.0528±0.011 | 0.0476±0.007 |
| P | 0.94 | |

(Data were expressed as mean±SD)

Comparison between PCOS and Control done by Student's t-test

PCOS, polycystic ovary syndrome; PSA, prostate specific antigen

Table 5 PSA level(ng/ml) in PCOS and control with/without hirsutism

| Hirsutism | PCOS(n=40) | Control(n=25) |
|-----------|--------------|---------------|
| Yes | 0.0528±0.010 | - |
| No | 0.0525±0.012 | 0.0476±0.007 |
| P | 0.94 | |

(Data were expressed as mean±SD)

Comparison between PCOS and Control done by Student's t-test

PCOS, polycystic ovary syndrome; PSA, prostate specific antigen

Table 6 PSA level(ng/ml) in women with PCOS according to various age groups

| Group of subjects | Total | PCOS(n = 40) | p-value |
|-------------------|-------|--------------|---------|
| Whole group | 40 | 0.0528±0.010 | |
| Age group(years) | | | |
| 16–20 | 18 | 0.0533±0.008 | 0.835 |
| 21–25 | 12 | 0.0533±0.011 | |
| 26–30 | 10 | 0.0510±0.014 | |

(Data were expressed as mean±SD)

P-values were calculated using one-way ANOVA

PCOS, polycystic ovarian syndrome

Table 7 Correlations of PSA with BMI, age, Testosterone, hirsutism and polycystic appearing ovaries in USG in PCOS and control

| Determinants of " r" | PCOS (n=40) | | Control (n=25) | |
|------------------------|-------------|-------|----------------|-------|
| | r | p | r | p |
| BMI vs PSA | 0.077 | 0.637 | 0.127 | 0.545 |
| Age vs PSA | -0.005 | 0.976 | -0.101 | 0.627 |
| PSA vs PCO in USG | 0.397 | 0.011 | - | - |
| Testosterone vs PSA | -0.075 | 0.644 | 0.071 | 0.737 |
| Hirsutism score vs PSA | 0.012 | 0.94 | - | - |

PCOS, polycystic ovary syndrome; BMI, body mass index; PSA, prostate specific antigen; USG, ultrasonogram.

Discussion

Impact of PSA level as marker of PCOS is still far from clear. In the context of observed higher level of PSA in patients with PCOS by some investigators,¹⁰ present study was conducted to measure and compare the serum PSA level in women suffering from PCOS with that of controls. It was observed that there was statistically significant difference of PSA level between the PCOS and control subjects. This

result is in agreement with the findings of some other studies.^{18–21}

Interestingly, though we observed a decreasing trend of PSA level with age in PCOS patients, there was no significant difference of PSA among age groups. Apropos with this, some investigators also observed no correlation between age and PSA.²¹ On the other hand, some others noted an inverse relation between these two parameters.¹⁸ Since hyperandrogenaemia is one of the typical features of PCOS, it was of interest to see whether PSA level correlate with serum androgen level, as to reflect the degree of hyperandrogenemia. About 20% of PCOS patients had raised level of serum testosterone (≥ 53 ng/dl). Both PSA and testosterone level were found significantly increased in PCOS than those of control in the present study. But, contrary to the expectation, PSA levels in PCOS women did not significantly correlate with either testosterone or hirsutism.²² It is further accompanied by the observation that the level of PSA was statistically similar in subjects with or without hirsutism as well between the subgroups of PCOS divided by testosterone at cut off of 53ng/dl. Similar results were found by Obeizu et al and they did not find any association between hirsutism score and urinary PSA which they explained as a fact that PSA reflects the level of circulating androgen but the hirsutism score is mostly attributable to either circulating or local androgens produced and acting in the skin.²³

Clinical manifestations like hirsutism, acne, acanthosis and menstrual irregularities are well known features of PCOS, which were also significantly higher in our PCOS group. Nearly similar frequencies were observed in other studies done in our population previously.^{22,23} Present study did not evaluate the androgen and PSA level at various phases of menstrual cycle. Therefore, whether any variation is present in different phases of menstrual cycle is beyond the capacity of this study to discern. This study also did not follow the PCOS patients for change of PSA on treatment.

Conclusion

We conclude that PSA level is increased in PCOS than that of control. It may be a promising marker in patients with PCOS in future. Relationship of PSA and testosterone as well as hirsutism is not yet fully clear and need wide scale study for exploration of their exact relationship in PCOS.

Acknowledgements

We thank the Institutional Review Board as well as Department of Endocrinology of BSMMU for moral support and acknowledge the grant of Aristopharma Bangladesh Ltd.

Contribution by authors

MA Hasanat and Hurjahan-Banu devised the concept. MA Hasanat, Hurjahan-Banu and Sukanti-Shah designed the study and interpreted the results. Tania-Sultana, Nazma-Akhtar, Sukanti-Shah and Hurjahan-Banu did the statistical analysis and prepared the manuscript. Naseem-Akhtar Chowdhury and MA Hasanat supervised and coordinated the study. Md Fariduddin, and Sadiqa-Tuqan contributed for collection of clinical data. All investigators contributed to writing of the paper and approved the final draft.

Financial support

Hurjahan-Banu and Nazma-Akhtar were obtained a grant from Aristopharma Bangladesh Ltd. for the study.

Conflict of interest

There is no conflict of interest in reporting the results of the study.

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