

Role of insulin sensitising agents in altering PSA level in PCOS

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ABSTRACT

Background: Ovarian androgen production can be promoted by insulin resistance which leads to reproductive abnormalities in Polycystic Ovarian Syndrome (PCOS). A wide variety of female tissues can synthesize and secrete Prostate Specific Antigen (PSA). Androgens may take part a significant role in PSA secretion in PCOS. As insulin resistance stimulates androgen production, the baseline value of PSA may decline by insulin sensitising agents in PCOS. Present study is an attempt to measure the function of PSA as a marker of androgen excess in PCOS and to assess the role of insulin sensitising agent metformin in altering PSA level in PCOS.

Methods: The study was undertaken to assess the insulin resistance, testosterone and PSA level in 45 women diagnosed as PCOS and 45 healthy controls. Alteration of insulin resistance, serum testosterone and PSA levels by metformin was also analysed.

Results: A significant increase in testosterone, PSA level and insulin resistance was observed in PCOS cases when compared with control ($p < 0.001$). When metformin was given for 4 months, improvement in insulin resistance and testosterone level was found in cases, but PSA values observed no change. Correlation was not found linking insulin resistance with PSA level prior to and after therapy.

Conclusions: Serum PSA level could be detected in high significant concentration in PCOS women. Various researches explain that insulin resistance and BMI may perhaps control serum PSA level, but our result demonstrate no effect of insulin sensitising agent on serum PSA value.

Keywords: Polycystic ovarian syndrome, Insulin resistance, Metformin, Prostate specific antigen

INTRODUCTION

4-11% of women of reproductive age group in Indian population suffer from Polycystic Ovarian Syndrome (PCOS), which is the most common endocrine reproductive disorder of females.¹ PCOS manifest as irregular menstrual cycles concurrently with hirsutism and/ or acne and occasionally obesity is associated with it.² Insulin resistance with the consequent hyperinsulinemia has a pathogenic role in PCOS.³ Insulin can promote ovarian androgen production, either directly by stimulating ovarian enzyme complex P450c17 α or

indirectly by stimulating pituitary luteinizing hormone (LH) secretion.⁴ In vitro studies have also suggested amplification of ACTH (Adrenocorticotrophic hormone) stimulated adrenal androgen secretion by hyperinsulinemia.⁵

Prostate Specific Antigen (PSA), a serine protease of molecular weight 33KD is expressed by both normal and neoplastic prostate tissue. With the development of ultrasensitive immunoassay, several studies could identify the presence of PSA in a wide variety of female tissues (breast, ovary, endometrium, etc.) and body fluids

(amniotic fluid, milk, breast cyst fluid, etc.).⁶ On the other hand the cause of circulating PSA in women is not determined yet. PSA production is mostly associated with steroid hormones such as androgens, progesterin and glucocorticoids which has been found in breast tissues obtained from androgenised females and breast tumour cases.^{7,8} Some researchers have observed increase in PSA level in PCOS cases in response to androgen therapy.⁹ Other researchers have also shown that anti androgen drugs have lowered PSA levels by 50% in hirsute PCOS women regardless of the type of drugs used.¹⁰ But the important negative aspect of androgen deprivation therapy is aggravation of insulin resistance which may further exaggerate the symptoms of PCOS.¹¹

Metformin an insulin sensitizing agent is used in PCOS patients to improve their reproductive abnormalities. Numerous studies have also been done to observe the effect of metformin on PSA level in prostate carcinoma patients. Mechanisms which underlie the effects of metformin on PSA level in those patients are mostly attributable to its anti neoplastic action.^{12,13}

After metformin therapy, many researchers have demonstrated improvement in clinical and biochemical abnormalities, while some others failed to observe any in PCOS cases. Based on the above observations, it is assumed that PSA level may be elevated in response to high level of androgen present endogenously in PCOS women. As hyperinsulinemia augments androgen production in PCOS, the baseline value of PSA may decline by insulin sensitising agents such as metformin.

Present study is to assess the effect of metformin an insulin sensitizing agent in changing serum androgens and PSA value in PCOS.

METHODS

The present study was a cross-sectional, follow up study conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynecology and Department of Microbiology, IMS & SUM Hospital Bhubaneswar. The study was undertaken in 45 PCOS patients within the age group of 15-35 years and 45 ages matched healthy control. PCOS was diagnosed from the history of chronic oligomenorrhoea (less than 9 cycles per year or cycle length >35 days), amenorrhoea (cycle length >12wks), infertility along with hirsutism or acne and ultrasound finding of multiple cysts in ovaries.¹⁴ Females having glucose intolerance or NIDDM, other endocrine disorders and pregnancy were excluded from the study.

Fasting plasma glucose (FPG), lipid profile, serum insulin, total testosterone and PSA levels were estimated in the study group. Out of 45 cases, 23 women were administered with metformin at a dose of 750 mg BD for 4 months. Post treatment assessments were done for all the above parameters. FPG and lipid profile were

estimated using COBAS 400 plus autoanalyser using commercially available kits. Specific tests for insulin, total testosterone and PSA were performed using electro chemiluminescence method by COBAS e411 immuno chemistry analyser.

The results obtained were analysed by student's t test, Pearson's correlation coefficient with SPSS-19. Institutional ethical committee has approved this study protocol.

RESULTS

Our study groups consist of 45 PCOS cases out of which 45% of patients were within 21- 25years of age. 42.6% of these cases were overweight having BMI $\geq 25\text{kg/m}^2$.

Table 1: Biochemical, hormonal and PSA levels in study group.

Parameter (Mean \pm SD) (mg /dl)	Control (n = 45)	PCOS cases (n 45)
FPG	77.82 \pm 6.80	78.30 \pm 7.88
Total cholesterol	139.21 \pm 14.20	163.14 \pm 26.43**
TG	106.01 \pm 23.25	147 \pm 44.4*
LDL	63.24 \pm 11.34	91.09 \pm 20.79**
HDL	48.9 \pm 4.76	42.64 \pm 6.13**
VLDL	21.69 \pm 5.19	29.56 \pm 9.79*
Serum insulin (μ IU /ml)	9.14 \pm 2.34	15.37 \pm 6.92**
Serum Testosterone (total) (ng/ml)	0.4 \pm 0.23	1.30 \pm 0.60**
Serum PSA (pg/ml)	3.7 \pm 0.8	14.4 \pm 1.9**

**p<0.001, *p<0.05

Table 1 revealed marked dyslipidemia in these groups of patients in comparison to control which may be caused due to insulin resistance.¹⁵ The hormones show a rise of serum insulin and testosterone in PCOS cases when compared to control (p<0.001), indicating the role of hyperinsulinemia in the pathogenesis of PCOS.^{16,17} A significantly higher (p<0.001) mean PSA levels of cases were observed than the control group which was in similar with the observations of Melegos et al and Gullu et al, confirming that PCOS, a hyperandrogenic disease is likely to be present with high levels of PSA.^{18,19} Taking the fasting glucose to insulin ratio of ≤ 4.5 as insulin resistance, 62% of cases and 8.3% of controls were considered as insulin resistant.²⁰

The PCOS patients who were administered with metformin at a dose of 750 mg BD for 4 months, 50% of them revealed a reduction of insulin resistance. Though there was a significant change of serum HDL and LDL (p<0.05) subsequent to treatment, rest all lipid parameters shown no obvious difference. Analogous interpretation was also documented by researchers who showed that metformin decreases insulin resistance which in turn modifies dyslipidemia (Table 2).²¹

Table 2: Metabolic, hormonal and PSA changes before and after therapy in 23 pcos cases (n = 23).

Parameters (Mean±SD)	Before therapy	After therapy
FPG (mg/dl)	74.82±8.49	76.7±9.25
Total cholesterol (mg/dl)	165.82±29.82	161.27±29.55
TG (mg/dl)	155.46±45.37	155.86±39.47
LDL (mg/dl)	93.29±28.44	89.45±23.57*
HDL (mg/dl)	44.82±4.41	48.64±3.89*
VLDL (mg/dl)	31.19±9.87	31.07±7.32
Serum Insulin (IIU/ml)	19.76±5.73	15.34±6.21**
Serum total testosterone (ng/ml)	1.40±0.85	1.39±0.82
Serum PSA (pg/ml)	13.3±5.03	13.4±4.69

**p<0.001, *p<0.05

Percentage of patients having overweight with BMI $\geq 25\text{kg/m}^2$ was reduced from 33.2% to 25.4%. However, change in BMI in these patients was statistically insignificant after therapy.

Table 2 also revealed a fall in fasting serum insulin (p<0.001) and serum testosterone level, though decrease in testosterone was non-significant. Association of serum insulin and testosterone levels in PCOS cases has been shown by Insulin infusion studies which suggest a cause and effect relationship.²² Insulin resistance also reduced from 75.62% of cases to 42.3% after therapy, which was in concurrence with the studies that metformin exert its effects by encouraging peripheral glucose utilisation.^{16,23} When we studied the effect of metformin on PSA level, no significant change was observed in our group of patients. Jonathan L, et al demonstrated a decrease in PSA level in their group of prostate cancer patients after metformin therapy.²⁴ Ahmed, et al showed both increase and decrease in PSA level in healthy male population after administration of drug.²⁵ Randazzo M, et al registered no difference in PSA level after therapy when studied on prostate cancer grade or incidence.²⁶

Table 3: Correlations of various parameters in PCOS.

Variables	r value	p value
Total testosterone/ PSA	0.94	<0.001
Insulin/ PSA	0.09	Not significant

The most pertinent finding of present study is the significant positive correlation between serum PSA and total testosterone (Table 3). This may be attributed to the hypothesis that expression of PSA gene is under androgenic regulation.⁸ Similar observations have also been registered by other workers who observed a higher PSA in hyper androgenic states and after testosterone therapy.^{9,10} But there is no correlation between serum insulin and PSA values in present study population. June Hyun, et al demonstrated negative correlation between insulin resistance and BMI with serum PSA level in healthy men, indicating that serum PSA level might be

influenced by insulin resistance and BMI through the hypogonadal-obesity-adipocytokine level.²⁶

DISCUSSION

PSA is synthesised and secreted by cells having definite hormone receptors which are under steroidal regulation.⁷ This has been confirmed from our study demonstrating a significant rise in serum PSA in PCOS patients. Many researchers also claim a strong association between antiandrogen therapy and reduced PSA level. This strongly supports the evidence that PSA synthesis is under androgenic regulation.¹⁰

Irrespective of obesity, insulin resistance is found in 60-70% of patients. Compensatory hyperinsulinemia plays a crucial role in the pathophysiology of PCOS. Androgen synthesis is augmented by insulin in thecal cells and also it lowers sex hormone binding globulin (SHBG) synthesis in the liver, thus it increases free androgen availability.³ Due to high occurrence of insulin resistance, PCOS contribute to components of metabolic syndrome such as gestational and type II diabetes, impaired glucose tolerance, abnormalities in lipid profile, abdominal obesity, hypertension, endothelial dysfunctions and most likely cardiovascular diseases.

Administration of metformin, an insulin sensitizing agent, by increasing insulin sensitivity of tissues in PCOS, has beneficial role in lowering serum testosterone level.²³ It can also improve some of the features of metabolic syndrome such as dyslipidemia, hypertension and obesity. It has been observed that metformin decreases PSA level in prostate cancer patients by activating adenosine monophosphate activated protein kinase (AMPK) pathway, thus diminishing the mammalian target of rapamycin (mTOR) signalling cascade downstream, down regulating cyclin D, by p-53 activation and also suppression of HER2 oncoprotein expression.^{12,13,24} While some other researchers have shown an increase in PSA level in their group of healthy male persons after therapy.

CONCLUSION

Present study finds a remarkable improvement in insulin resistance and hyperandrogenism in PCOS cases after metformin therapy. But no definitive change was observed in PSA level. A few studies have been done on PCOS patients to know the effect of metformin on PSA level. Though PSA may be regarded as a promising marker of androgen action in androgen sensitive tissues, further researches are needed to evaluate the role of metformin on PSA value in women with PCOS.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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