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Original Research Article

Serum Prostate-Specific Antigen Levels in Men Diagnosed with Type 2 Diabetes Mellitus: A Hospital Based Case-Control Study

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Conflict of interest: Nil

Abstract:

Background and Objectives: Serum PSA (prostate-specific antigen) measurement plays a vital role in prostate cancer screening and management. Studies suggest that men with type 2 diabetes mellitus tend to have lower PSA levels compared to non-diabetic men. This study aimed to explore the differences in PSA levels between type 2 diabetics and healthy men.

Methods: The study was conducted over a period of one year in our institution. 45 diabetic men aged (40-79) years as cases and age-matched non-diabetic controls were included (fulfilling the inclusion and exclusion criterias). PSA, glucose, and glycated haemoglobin (HbA1C) levels were estimated by immunometric immunoassay, glucose oxidase peroxidase and turbidimetric methods respectively in Vitros 5600 autoanalyzer.

Results: The mean PSA was significantly lower in diabetic men than non-diabetic (0.560 ng/ml vs 1.052 ng/ml; p=0.003). PSA showed a negative correlation with HbA1C in cases (r = -0.303;p = 0.043). Diabetics with HbA1C more 7% had significantly lower PSA than those with HbA1C less than or equal to 7%. Additionally, PSA levels were lower in diabetic men with a disease duration exceeding 5 years compared to those with a shorter duration.

Interpretation and Conclusion: These findings suggest that glycemic status and diabetes duration may influence PSA levels in diabetic men, highlighting the importance of considering these factors when interpreting PSA test results to ensure optimal clinical outcomes.

Keywords: diabetes duration, glycated haemoglobin, glycemic control, prostate cancer screening, prostate-specific antigen, type 2 diabetes mellitus.

Introduction

Global diabetes prevalence has surged from 30 million cases in 1985 to 415 million in 2017, projected to reach 642 million by 2040 according to International Diabetes Federation. While both type 1 and type 2 diabetes rates are increasing, type 2 is escalating more rapidly. [1]

While epidemiological studies often associate type 2 diabetes mellitus with elevated risks of pancreatic, liver and colon cancers, the relationship with prostate cancer remains unclear, with proposed mechanisms including hyperinsulinemia, hyperglycemia and chronic inflammation.[2-6] Globally, the burden of prostate cancer is rising, [7] making it the most prevalent malignancy among males and ranking second only to lung cancer. [8]

Based on PBCRs (population based cancer registries) of India, prostate is the second commonest site of cancer among Indian males in cities like Delhi, Kolkata, Pune and Thiruvananthapuran and third leading site of cancer in Bangalore and Mumbai. [9] Prostate cancer constitutes 4.6% of all cancers in men of Kamrup Urban district. [10]

Early detection of prostate cancer is crucial for successful treatment. Use of screening procedures like DRE (digital rectal examination) and tumor marker PSA estimation is pivotal for effective treatment, revolutionizing prostate cancer management. PSA, a glycoprotein produced by the prostate gland, typically exhibits higher total levels in men with malignancy, inflammation or enlargement, contrasting with lower levels in those with milder pathology.

Recent studies indicate that factors like age, [11,12] BMI(body mass index),[12] diabetes mellitus, [13] prostatitis, [14] BPH(benign prostatic hyperplasia)

[14] and certain medications (such as metformin and statins) [15,16] affect serum PSA levels in men. Specifically, it has been noted that PSA levels are lower in men with type 2 diabetes compared to non-diabetics. [13,17] This study aims to investigate the influence of type 2 diabetes mellitus on serum PSA levels in men and observe any changes in PSA levels based on diabetes status and duration.

Materials and Method

Study Design, Setting, and Participants: A one-year case-control study was conducted from October 2019 to September 2020 at our institute. 45 diabetic males were randomly selected from the Department of Medicine as cases, while equal number age-matched non-diabetic men from same institute formed the control group through simple random sampling. Informed written consent was obtained from all participants.

Inclusion criteria included men in age group (40-79) years with diagnosis of type 2 diabetes mellitus.

Exclusion criteria for the study included men who did not provide consent, those with type 1 diabetes or other specific types, serum PSA levels exceeding 10 ng/ml, known or suspected prostate issues (cancer, BPH) or recent prostate procedures (biopsies), men taking medications such as finasteride, flutamide, buserelin, or testosterone, known cases of hemoglobinopathy or chronic liver disease and men with a history of other cancers like lung, breast, colon or glandular cancers.

Data collection: All participants detailed medical history was evaluated. Cases were asked about duration of disease, duration of treatment and dosage of medications. Relevant data was collected from control group also. Demographic information, family history was reported via a standardized structural questionnaire.

Ethical clearance

Clearance from the Institutional Ethics Committee (Human) was obtained (Vide NO. AMC/EC/PG/2110 dated 14 thOctober, 2020) prior to the commencement of the study.

Determination of biochemical parameters

5ml of blood was aseptically drawn from the ante-cubital vein for cases and controls. Blood for FPG (fasting plasma glucose) and 2-h PG (2-hour plasma glucose) was collected in fluoride vials, while for HbA1C and serum PSA, blood was respectively collected in K2EDTA(ethylenediamine tetraacetic acid) and clot activator vials regardless of fasting status. After collection, blood in fluoride and clot activator vials was centrifuged at 3500 rpm for 15 minutes to separate plasma and serum. Processing for required parameters occurred the same day, unless unavoidable delays necessitated storing serum for PSA at -20°C after aliquoting. Reagents were brought to room temperature before testing.

Glucose, HbA1C and PSA were estimated by glucose oxidase peroxidase, [18] turbidimetric [19] and immunometric immunoassay [20] in Vitros 5600 integrated system (Ortho clinical Diagnostics, United Kingdom: Johnson & Johnson).

Variable definition:

- Diabetes mellitus was diagnosed as per criteria of American Diabetes Association, 2020.
- Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Based on the WHO criteria reported as mean kg/m^2. The weight was measured using body weight and the height were measured using a portable stadiometer.

Diabetes Diagnostic standards

The participants were diagnosed with diabetes according to ADA (American Diabetes Association, 2020) [21] if they had either of the following

- FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hour.*

OR

- 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT (Oral glucose tolerance test). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

- HbA1C ≥ 6.5 % (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP (National Glycohemoglobin Standardization Program) certified and standardized to the DCCT (Diabetes Control and Complications Trial) assay.*

OR

- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).*

In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Age adjusted reference intervals used for serum PSA were (0-2.5), (0-3.5), (0-4.5) and (0-6.5) ng/ml in (40-49), (50-59), (60-69) and (70-79) years respectively.[22]

Statistical analysis: Statistical analyses were

conducted using Microsoft Excel 2007 and Stats Tester 3.5.6. To compare two average numbers, Student's t-test was employed, while ANOVA was utilized for comparing three average numbers.

The relationship between PSA and parameters such as age, FPG, 2-h PG, and HbA1C was determined using the coefficient of correlation (r). For all statistical comparisons, significance was considered as p-value < 0.05.

Results

Serum PSA levels and age group:

The mean age in cases and controls were 57.867 ± 10.945 years and 57.711 ± 11.799 years respectively. Comparison of mean PSA levels showed that (Table 1) PSA was significantly lower in diabetic group than non-diabetic. On analyzing the mean PSA in four different age groups it was observed that (Table 2) PSA was lower in cases than controls but the difference was statistically significant only in age group (60-69) years and (70-79) years.

Table 1: Comparison of different parameters in the study subjects

Serial No.	Parameter (Mean ± SD)	Cases	Controls	p value
1.	FPG(mg/dl)	162.31 ± 63.79	84.378 ± 8.357	0.000
2.	2-h PG(mg/dl)	278.400 ± 98.792	120.044 ± 23.916	0.000
3.	HbA1C(%)	9.562 ± 2.745	5.491 ± 0.587	0.000
4.	PSA(ng/ml)	0.560 ± 0.528	1.052 ± 0.941	0.003
5.	BMI(kg/m^2)	26.082 ± 3.119	24.611 ± 2.430	0.016

Table 2: Age wise distribution of mean PSA in study subjects

Serial No.	Age Group (Years)	Cases		Control		p value
		Number (N)	PSA (ng/ml) (MEAN ± SD)	Number (n)	PSA (ng/ml) (MEAN ± SD)	
1.	40-49	14	0.302 ± 0.236	14	0.439 ± 0.378	0.261
2.	50-59	10	0.837 ± 0.646	10	0.859 ± 0.578	0.936
3.	60-69	13	0.436 ± 0.384	13	1.104 ± 0.755	0.009
4.	70-79	8	0.854 ± 0.703	8	2.270 ± 1.174	0.011
Total		45		45		

Serum PSA levels and Glycaemic status correlation analysis: Pearson correlation analysis showed that there was no statistically significant correlation between PSA and age, FPG and 2-h PG in cases and PSA and FPG and 2-h PG in controls. A significant positive correlation was observed between PSA and age in controls.

PSA showed a significant negative correlation with HbA1C in cases whereas among controls a significant positive correlation was observed between these two parameters (table 3).

Table 3: Correlation of PSA with different parameters in the study subjects

Serial No.	Parameter (Mean ± SD)	Cases		Controls	
		r	p	r	p
1.	Age(years)	0.252	0.090	0.666	0.000
1.	FPG(mg/dl)	-0.287	0.064	0.256	0.089
2.	2-h PG(mg/dl)	-0.133	0.382	0.073	0.632
3.	HbA1C(%)	-0.303	0.043	0.317	0.037

Figure 1 shows that diabetic males with HbA1C greater than 7% had significantly lower mean PSA (0.441 ± 0.439 ng/ml) in comparison to those with HbA1C less than or equal to 7% (0.888 ± 0.629 ng/ml). Men with duration of diabetes more than 5 years also had significantly lower mean serum PSA (0.368 ± 0.315 ng/ml) than males with diabetes duration less than or equal to 5 years (0.761 ± 0.630 ng/ml) (Figure 2).

Serum PSA levels in non-diabetics, diabetics with or without medication

A significant difference in serum PSA was found among non-diabetics, diabetics on anti-diabetic medication and diabetics not on any anti-diabetics medication. Serum PSA was significantly lower among diabetics on medication than that in non-diabetics.

However, no significant difference had been observed in PSA levels among diabetics on medication and diabetics not on medication and also among non-diabetics and diabetics not on medication (Table 4).

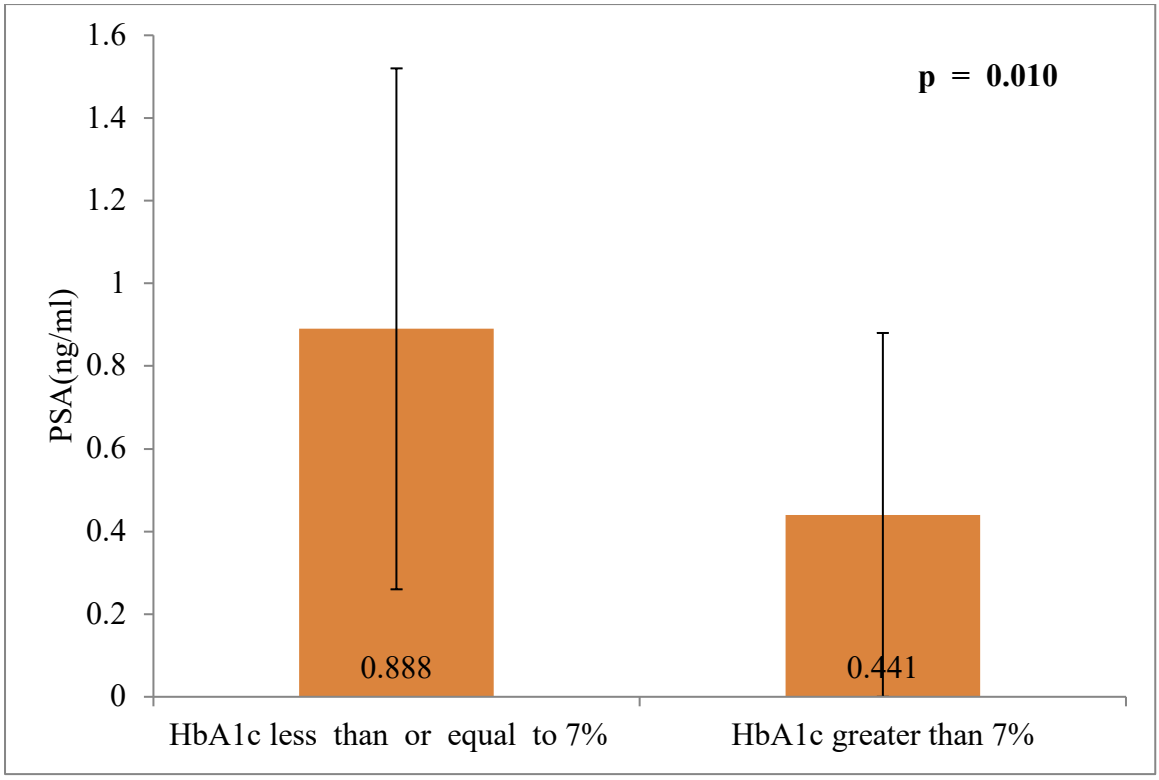

Figure 1: Mean PSA in cases according to glycemic status

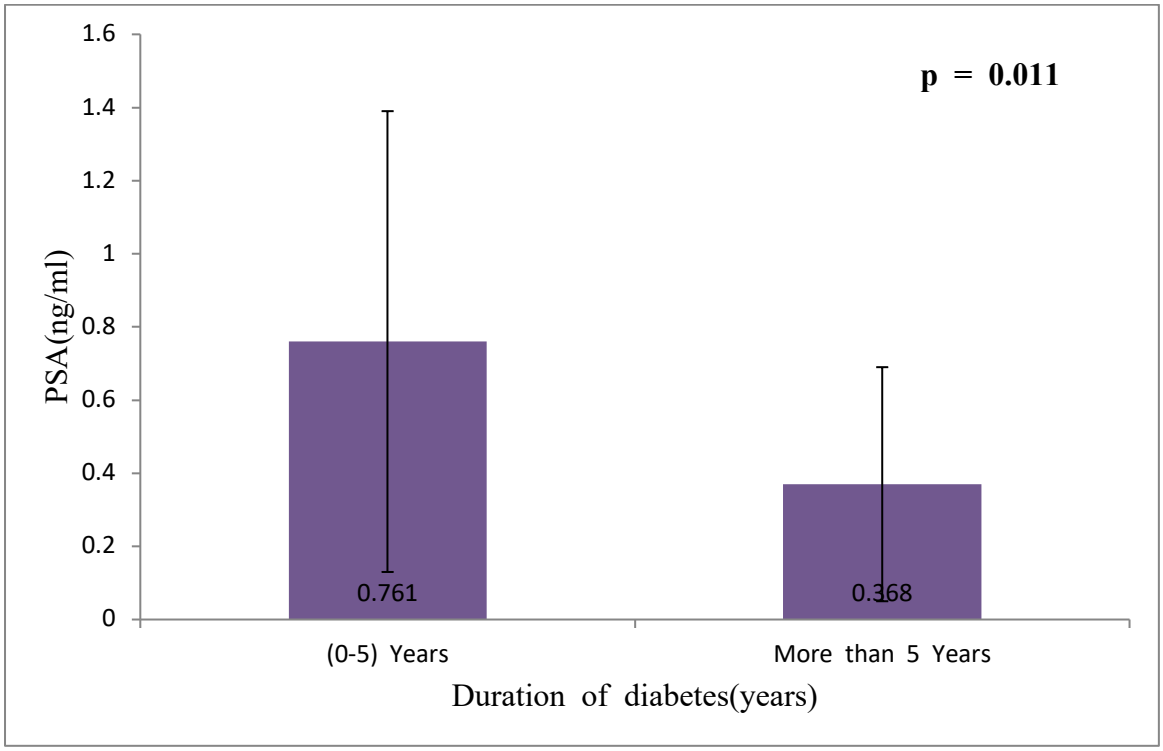

Figure 2: Mean PSA in cases based on duration of diabetes

Table 4: Mean PSA in study subjects (Non-diabetic, Diabetics on medication and not on medication)

Serial No.	Study Groups	Number (N)	PSA (ng/ml) (Mean ± SD)	p value
A	Non-diabetic	45	1.052 ± 0.941	0.012
B	Diabetic on medication	36	0.542± 0.528	
C	Diabetic not on medication	9	0.634 ± 0.552	

***A vs B; p = 0.005, A vs C; p = 0.206, B vs C; p = 0.643**

Discussion

This study revealed that serum PSA levels were significantly lower in men with type 2 diabetes mellitus compared to non-diabetic men. The lower PSA lever in diabetics in our study (0.560 ng/ml vs 1.052 ng/ml, p = 0.003), was consistent with previous findings [13,17,23,24]. The lower levels may be attributed to factors such as greater obesity, [25,26,27] lower serum testosterone, [23] microvascular complications leading to prostate ischemia [26] and more frequent use of dyslipidemia medications [26] among diabetics.

When comparing age groups, significant differences of lower PSA in diabetics than non-diabetics were observed only in the 60-69 and 70-79 age brackets, aligning with similar findings in study by Ainahi A et al. [28] Serum PSA also showed a positive correlation with age in both diabetic and non-diabetic males but it was found to be statistically significant only among non-diabetics. (r = 0.252, p = 0.090 vs r = 0.666 p = 0.000).

In the present study it was observed that serum PSA negatively correlated with FPG among diabetics whereas among non-diabetics it positively correlated with FPG but statistical analysis did not reveal any significance in both these groups (r = -0.287, p = 0.064 vs r = 0.256, p = 0.089). Similarly, serum PSA negatively correlated with 2-h PG among diabetic males and positively among non-diabetics and it was also statistically not significant in either of the study groups (r = -0.133, p = 0.382 vs r = 0.073, p = 0.632).

The study by Kobayashi M et al. [25] showed that PSA levels were significantly lower in men with higher FPG. Similarly in another study by Irer B [29] it had been observed that PSA value in the high fasting plasma glucose group (>126 mg/dl) was lower than in the low fasting glucose group (1.08 ng/dl vs 1.32 ng/dl, p < 0.0001).

This study showed a significant negative correlation between serum PSA and HbA1C among diabetics (r = -0.303, p = 0.043) whereas a significant positive correlation was observed between these two parameters among non-diabetics (r = 0.317, p = 0.037). Similar relation had also been observed among diabetic males by Atalay HA et al. (r = -0.655, p < 0.001). [26]

On studying the impact of glycemic control on serum PSA, it was observed that PSA was significantly reduced among diabetic males with HbA1C more than 7%, a result that was consistent with that reported by Atalay HA et al. [26]

As reported previously [13,26] our study also showed that serum PSA got significantly reduced with duration of diabetes. This may be due to decrease action and level of insulin with advanced duration of diabetes leading to subsequent decrease in serum PSA levels. [30]

In agreement with the results of Al-Asadi JN et al. [13] this study showed that serum PSA was significantly lower among diabetic males on treatment (oral hypoglycemic agents or combined oral hypoglycemic agents and insulin) than that in non-diabetics (0.542 ng/ml vs 1.052 ng/ml , p = 0.005). However, no significant difference had been observed in PSA levels among diabetic males on medication and those not on any medication for diabetes (0.542 vs 0.634, p = 0.643). In addition Park JE et al. also observed that diabetic males who used metformin had significantly lower PSA levels compared with nonmetformin users but no significant difference had been found in PSA levels among males over duration of metformin use. [15]

Some limitations are to be considered in this study. Firstly, the study was constrained by the limitation of time and relatively small sample size. Secondly, serum insulin and testosterone and prostate volume were not measured and their effects on serum PSA were also not studied. Moreover, dosage of medications for hyperglycemia and dyslipidemia and level of adherence to treatment were not analysed because of lack of information. Despite these limitations, the results of our study are still in agreement with published findings that serum PSA level in male is affected by type 2 Diabetes Mellitus.

To conclude the burden of diabetes and prostate cancer are increasing both globally and nationally and they individually have their health and economic consequences. If these two diseases coexist, it will exacerbate their impact and have poor outcomes. Therefore, careful screening of prostate cancer in type 2 diabetic males is necessary. Since age and diabetes related parameter like glycemic status and diabetes duration and therapy may influence serum PSA levels in type 2 diabetic males, these factors deserve careful attention in interpreting serum PSA test results to avoid under diagnosis of prostate cancer in them. Moreover, serum PSA measurement may be aided by other diagnostic tests like Doppler ultrasonography, PHI (prostate health index), select MDx etc. to ensure best clinical outcome. Further studies with larger sample size and longer duration with follow up of the study subjects are required to shed greater light in this aspect.

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