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Study of serum PSA levels in type 2 diabetic men

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Abstract

Objective: The aims of this study was to assess and compare the serum prostate-specific antigen(PSA) levels in men with type 2 diabetic subjects and non-diabetics control, to determine the effect of type2 diabetes mellitus (DM) on the serum level of prostatic specific antigen (PSA) in Hadoti region of Rajasthan (India).

Research Design And Methods: The study include 50 diabetic men aged 35-81 (55±12)years and 50 non-diabetic men aged 45-79 (57±10)years. Blood was collected and serum was analyzed for various biochemical parameters, fasting blood sugar, lipid profile, renal function tests, Prostate specific antigen and Glycated hemoglobin HbA1c.

Results: There is correlation between PSA and age in the group of men free from diabetes ($r=0.741$; $p<0.0001$), however it was lower in diabetic subjects ($r=0.140$; $p=0.332$). A lower PSA concentration is observed in with type2 diabetic men (diabetic mean PSA: 1.04 ng/dl, non-diabetic mean PSA: 3.4ng/dl, $p<0.0001$). A strong negative correlation found between serum HbA1c levels and serum PSA ($p<0.0001$ and $r= -0.0493$) concentrations in men with diabetic.

Conclusions: Our results suggest that values of serum PSA are less age dependent in type2 diabetic patient than in non-diabetics and there is significant impact of type2 diabetis mellitus on serum PSA.

Keywords: PSA, DM, Metabolic

Introduction

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period [1]. The etiopathology includes defect in insulin secretion, insulin action, or both, and disturbance of carbohydrate, fat and protein metabolism [2]. Current classification of diabetes mellitus, proposed by the American Diabetic Association in 1997 and accepted in a slightly revised form by World Health Organization (WHO) divide it into four main types ; type 1 diabetes is less common (less than 10% of total number of diabetics have this type of disease) and its basic characteristic is the lack of insulin caused by predominantly autoimmune destruction of pancreatic β cells; type2 diabetes which is more common, has two different defects i.e. insulin

resistance and failure of β cell to secrete insulin adequately, This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. Other specific types of diabetes and gestational diabetes are the remaining two classes [3].

Increased oxidative stress triggers the development and progression of diabetes mellitus and its complications such as nephropathy, retinopathy, cardiovascular complications and peripheral neuropathy associated with damaged blood vessels and nerves [4]. With the changing lifestyle of modern world, the prevalence of type2 diabetic mellitus becomes higher than before. India currently represents 49 percent of world diabetes burden with an estimated 72 million cases in 2017, a figure expected to almost double to 134 million by 2025.[5]

Prostate Specific Antigen (PSA) is a glycoprotein produced primarily by the epithelial cells of the prostate gland, and its regulation under the control of androgens and progestrins. It is a serine protease with chymotrypsin-like enzyme activity and has a molecular weight of about 30kDa. The PSA gene is member of the human kallikrein gene family, which consists of at least 14 genes. All of them which encoded for serine protease have significant homologies and structural similarities. Three major PSA fractions, the complex of PSA and α2-macroglobulin, the complex of PSA and α1-antichymotripsin (PSA-ACT) and free un complexed PSA, have been identified in serum.[6]

Physiological function of PSA is not entirely understood; the well-known and accepted physiological function is that PSA proteolytically cleaves seminogelins and fibronectin are present in seminal plasma and thus cause liquefaction of seminal clot after ejaculation. This process does promote the release and motility of sperm cells.[7]

High PSA levels may be a sign of prostate cancer, a noncancerous condition such as prostatitis, or an enlarged prostate gland. PSA is most valuable prostatic cancer marker that is used for population screening, diagnosis, and monitoring of patient with prostate cancer.[8]

Patients with diabetes have been reported to be at increased risk of numerous cancers, including cancers of the pancreas, liver, colon and breast cancer. There are several pathways by which alterations in glucose metabolism may lead to cancer progression.[9] Hyperglycemia leads to elevated insulin levels, and the activation of the insulin/insulin-like growth factor (IGF) pathway has been implicated in Prostate Carcinoma growth though positive effects on cellular proliferation and anti-apoptosis.[10]Hyperglycemia also leads to the production of advanced glycosylated end products with resultant oxidative stress which can lead to DNA damage.[11] Finally, chronic inflammation is seen with DM and the metabolic syndrome and results in release of several cytokines that can promote tumor growth.[12]

However, the connection between serum PSA and diabetes is currently less understood. recent studies have suggested that men with diabetes are at a decreased risk of prostate cancer, So the aim of this study was to determine the association between type 2 diabetes mellitus and serum PSA level and to investigate the factors that may affect such association.[13]

Material and Methods

Design: The study group will be comprised of total 100 subjects, 50 men with type2 diabetic mellitus aged 35-80 years and 50 non-diabetic men aged 45-79 years as

controls, recruited from outpatient department and collection center of S.R.G. Hospital.

Patients who were taking α-blockers, phosphodiesterase type 5 inhibitors, and 5α- reductase inhibitors and those with neurogenic bladder, post-void residual volume>150mL, prostatitis, prostate cancer, bladder cancer, bladder stone, urethral stricture, men with diabetes who suffered from end organ damage (creatinine levels > 2.5mg/dl) will excluded from the study by taking Medical history, General physical examination, digital rectal examination, urine test and renal function test.

A written informed consent from the patients was obtained after complete explanation of the study.

Detailed history regarding the presenting complaints, nature, duration, compliance of treatment, inpatient stays, pharmacy records, laboratory values, pathology reports, imaging tests, and vital measures were recorded.

Collection of blood sample: Blood samples were drawn from overnight-fasted patients and levels of serum PSA, HbA1c, fasting blood glucose, high density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglyceride were done.

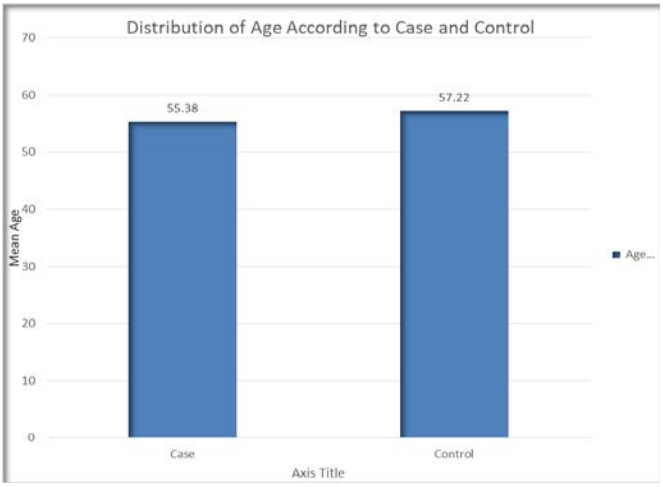
Hormonal measurement: PSA analyses on chemiluminescence immunoassay (SnibeMaglumi 1000).

Metabolic parameters measurements: Plasma fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, Urea and Creatinine were determined on fully automated analyzer Back men Coulter AU 680.

HbA1c measurements: HbA1c measured by high pressure liquid chromatography (HPLC).

Results

The mean age is 55 years in diabetic group and 57 years in non-diabetic group (Fig.1).



(Fig1)

In the group of non diabetics, a correlation between psa and age was observed (psa=3.4 +1.3*age with correlation r=0.741; p=0.0001) (Table1 & Fig.2).

In diabetic group this correlation is lower (psa=1.04+1.53*age with correlation r=0.140; p=0.332) (Table2 & Fig3)

Descriptive statistics

	Mean	Std. Deviation	N	r value	p value
Age	57.22	9.97	50		
PSA	3.44	.31	50	0.741	<0.0001*

Table1: Correlation between Age and PSA in control

Descriptive statistics

	Mean	Std. Deviation	N	r value	p value
Age	55.38	12.22	50		
PSA	1.04	1.53	50	0.140	0.332

Table 2: Correlation between Age and PSA in cases

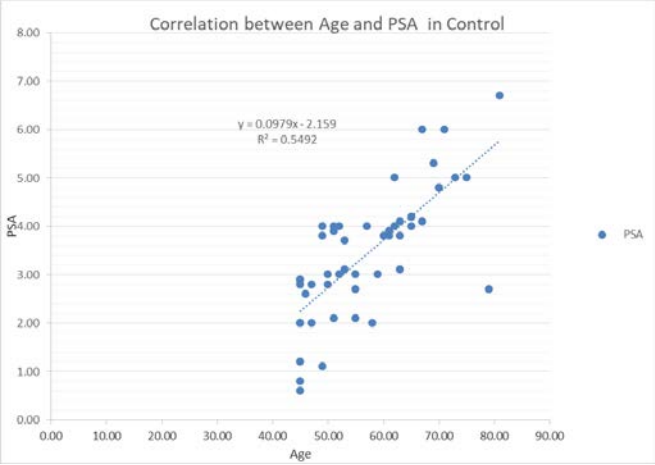


Fig. 2

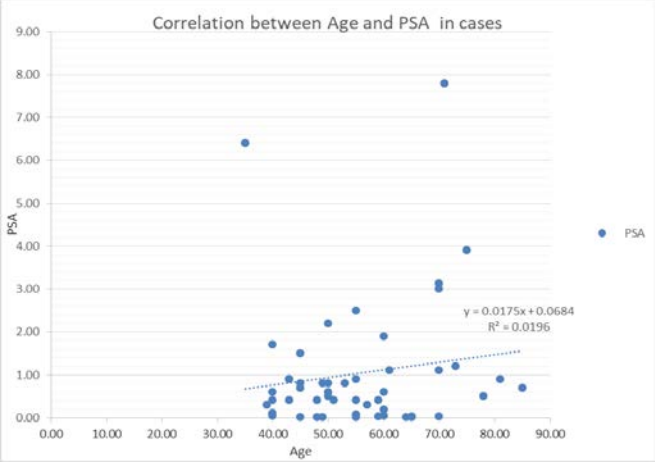


Fig. 3

Mean HbA1c levels are (6.1+6.6%) and in diabetic group HbA1c level are very high (9.2+2.1 p=0.002). (Table 3)

A strong negative correlation found between serum HbA1c levels and serum PSA (p<0.0001 and r= -0.0493) concentrations in men with diabetic.

	Mean	Std. Deviation	N	r value	p value
PSA HbA1c (%)	3.444 6.136	1.318 6.667	50 50	- 0.106	0.0464

Table 3: Correlation between PSA and HbA1c in control

	Mean	Std. Deviation	N	r value	p value
PSA HbA1c (%)	1.0400 9.2370	1.531 2.195	50 50	- 0.493	<0.0001 *

Table 4: Correlation between PSA and HbA1c in cases

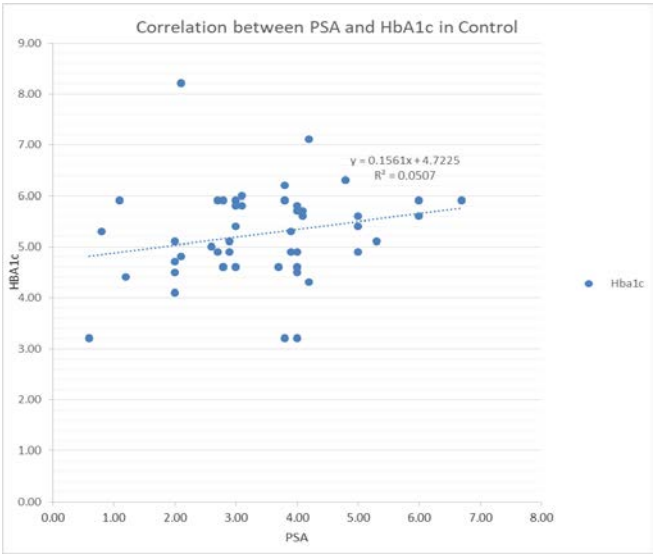


Fig.4

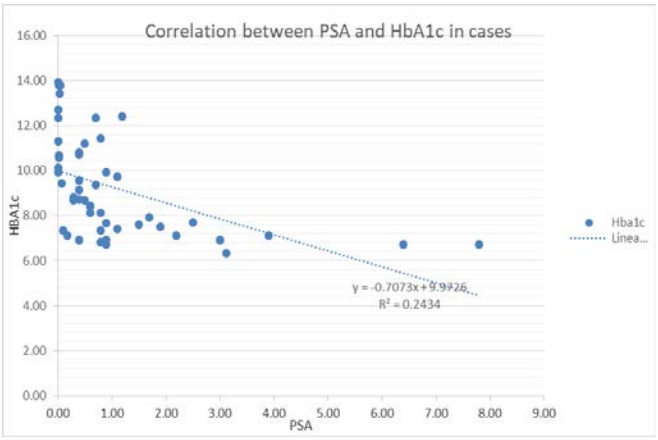


Fig.5

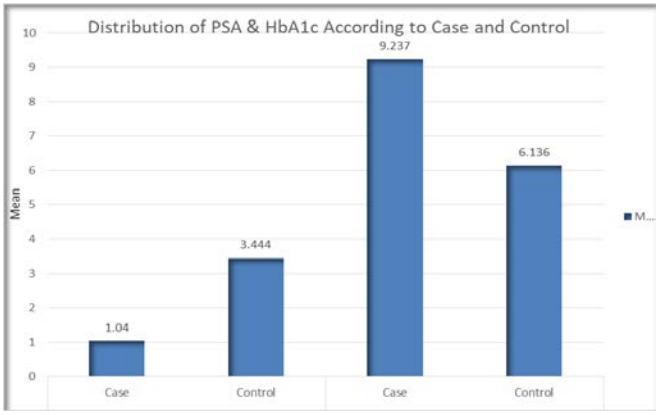


Fig.6

Serum PSA levels did not differ between patients treated with and without insulin or based on the severity of diabetic nephropathy or retinopathy.

Discussion

PSA is most useful biomarker for the detection and monitoring of prostate cancer. Elevated serum PSA concentrations are known to be connected with the three most common prostatic diseases, i.e. prostate cancer, benign hyperplasia and prostatitis [10]. A variety of factors can affect PSA and should be taken in consideration on interpretation of results. Physical activity, infection, prostate biopsy and cystoscopy can cause secondary elevation of PSA and some medicines can suppress PSA causing false negative results [11].

Results of our study indicated that the values of PSA were less age dependent in diabetic patients(r=0.140; p=0.332), than in Nondiabetic (r=0.741; p<0.0001).Similar to reported by Civtković et al[12] and Ainahiet al[13]. This may be because prostate enlarge with years and contains more PSA producing tissues [10]. Lower serum PSA levels may be due to the diminished capacity of the prostate to produce PSA or decreased leakage[12] due to prostate ischemia resulting from local microvascular complications associated with diabetes mellitus[]. It is widely accepted that in a patient with prostate cancer, elevation of serum PSA concentration is due to the increases cell count and destruction of prostatic architecture.[14]

This study showed that the inverse relationship between serum Hba1c levels and serum PSA (p<0.0001 and r= -0.0493) concentrations in men with diabetic. Mean level of PSA was significantly lower among diabetics in comparison with non diabetic men, a result which has been found in several previous studies [15, 16].

There are several possible explanations for PSA being lower in men with T2DM which includes obesity, more frequent use of medications to treat dyslipidemia, micro vascular complications, which contribute to prostate, is chemia, and lower serum androgen levels. The diabetic population is at high risk of developing microvascular complications including diabetic retinopathy, nephropathy, and neuropathy, which contribute to disabilities and high mortality rates in patients with DM[17].Thus, in this study, an explanation for the detected low serum PSA value in T2DM men might include local microvascular dysfunction and prostate ischemia. Therefore, it is highly possible that prostate vascular function is disrupted by T2DM.

IGF-1 was reported to be a prostate cell growth promoter [18] and is positively related to PSA[19].IGF-1 binds to the IGF-1 receptor, a tyrosine kinase receptor that transduces signals to the nucleus and mitochondria primarily via the mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways[20]. IGF-1 plays important role in normal growth and cellular proliferation of prostate which lead to increase in PSA level. In diabetics the ability of pancreas to secrete insulin is compromised resulting into decrease in insulin secretion and low portal insulin, which decreases growth hormone and ultimately IGF-1 from liver. The low level of IGF-1 in long-term diabetes [21]

as insulin production drops [22] may further explain the low level of PSA in diabetic patients.

Impaired kidney functions[23] as well as antidiabetic medications particularly metformin[24] or other common medications, which are commonly used by diabetics such as statins, may also lower serum total prostate-specific antigen[25].Men with diabetes have significantly lower serum testosterone concentration than Nondiabetic men [26],and this may partially explain their lower risk of prostate cancer. Shaney felt et al[27].Terner et al[28] and Xu etal[29] observed decreased risk of prostate cancer in diabetes.

In our study PSA levels in diabetic patients is 1.04±1.53 ng/dl as compared to non diabetic (healthy control) men is 3.44±1.31, Which was significantly ($p<0.0001$) lower than that present in diabetic patients (Table4). These findings are in correlation with the study conducted by Walner et al[30], Fukui et al[16]and Khalid et al[31] reported decreased level of PSA in diabetic patients.

Study conducted by Ou X et al, Maudi et al and Sharmaet al have found higher levels in diabetics compared to Nondiabetic[32-34]which were unlike the results found in our study. Whereas study conducted by Burke JP et al did not find any relation between PSA level with diabetes.

Conclusion

Results our study suggest that in diabetic patients the values of serum PSA is less age dependent than in non-diabetic men. This study supports the evidence that type2 diabetes mellitus is associated with lower serum level of PSA. Moreover, serum PSA level in diabetic patients was influenced by a number of factors such as BMI, glycaemic control, type of treatment and duration of the disease. Further studies should be undertaken to elucidate the exact biological mechanism that exist between diabetes and prostate.

Limitations

Limitations have to be considered in this study. Firstly small sample size due to financial compellability. Second limitation was that prostate volume is not measured which may affect the influence of prostate growth on PSA level. Duration of treatment, dosage of medications were not analyzed because of lack of information. Despite these limitations, the results of our study are still in agreement with published findings that serum PSA level is affected by type2 diabetic mellitus.

Acknowledgement

The institutional ethical committee of Jhalawar Medical College and Hospital, Jhalawar (Rajasthan)approved this study.

Ethical Standards

Ethical Committee approval for conduct of above mentioned study.

Reference no 20/120, dated-19/12/2019 by Office of the Ethics committee, Jhalawar Medical College and Hospital, Jhalawar.

Research involving human participants / Animals

This research involved human participant and research work was approved by institutional ethical committee of Jhalawar Medical College and Hospital Jhalawar.

Informed Consent

Duly signed informed and written consent from all participants was obtained.

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