Original Article

Serum Level of Prostate-specific Antigen in Diabetic Patients in Basrah, Iraq

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Abstract

Objectives: The aim of this study was to determine the effect of type 2 diabetes mellitus (DM) on the serum level of prostate-specific antigen (PSA) in men in Basrah, Iraq. **Patients and Methods:** A case–control study was done including 70 confirmed type 2 diabetic patients and 70 non-diabetic persons. Data about age and family history of diabetes were collected. For diabetic patients, data related to disease history were also enquired about. Weight and height were measured and body mass index (BMI) was calculated. Blood examination was done to estimate fasting plasma glucose and PSA. **Results:** The mean ages of diabetic and non-diabetic patients were 55.2 ± 10.5 and 55.9 ± 10.9 years, respectively. The mean total serum PSA was significantly lower among diabetic than non-diabetic men (1.97 ± 1.05 ng/ml vs. 2.60 ± 1.22 ng/ml, respectively, $P = 0.001$). The multivariate linear regression analysis showed that age, DM and BMI were independent predictors of serum PSA variation. Age was significantly related to PSA in non-diabetics, but not in diabetic patients. **Conclusion:** Serum PSA level is significantly lower and less age dependent in type 2 diabetic patients than in non-diabetics. Therefore, DM should be considered in setting of PSA threshold when screening for prostate cancer.

Keywords: Basrah, body mass index, diabetes mellitus, glycosylated haemoglobin, insulin-like growth factor 1, Iraq, prostate-specific antigen, prostate

Introduction

Many studies reported that diabetic patients are at higher risk of developing specific malignancies such as cancers of the pancreas, colon and liver compared to non-diabetics.[1] One possible reason for such increased risk is hyperglycaemia.[2] However, recent studies showed that diabetic men showed a decreased risk of prostate cancer.[3,4]

Prostate-specific antigen (PSA), which is a glycoprotein secreted by the prostate gland, is commonly used as a biomarker in screening, diagnosis and prognosis of prostate cancer.[5]

In Iraq,[6] as in other Middle East countries,[7,8] the incidence of prostate cancer is low, but the disease is being increasingly reported.[9] The crude incidence rate of prostate cancer in Iraq was reported to be 2.78/100,000 in 2011.[6]

Previous studies have demonstrated an inverse association between serum PSA level and type 2 diabetes mellitus (DM).[10-12] It was suggested that men with long-term diabetes have a lower risk of prostate cancer than non-diabetic men, and recently diagnosed men have a higher risk.[13] Higher concentrations of insulin and insulin-like growth factor 1 (IGF-1) in early diabetes and the lower testosterone and IGF-1 levels and higher oestrogen concentrations in long-term diabetes may explain such association.[14,15] Understanding the effect of diabetes on PSA serum concentration may help clinical detection of prostate tumours, and positive results may lead to considering diabetes when setting the PSA cut-off value at screening. Further, the lack of studies targeting Iraqi men signifies a research specific to Basrah, Iraq.

The aim of this study was to determine the association between type 2 DM and serum PSA level and to investigate the factors that may affect such association.

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Patients and Methods

This case–control study was conducted in Basrah for the period from January 2016 to August 2016. To remove the potential confounding effects of high PSA values, individuals with evident prostate disease (e.g., prostate cancer, benign prostate hypertrophy and prostatitis), lower urinary tract symptoms, recent prostate manipulation (i.e., rectal examination within 1 week and prostate biopsy, surgery or cystoscopy within 1 month) or those whose serum PSA levels >4 ng/ml were excluded from the study.

One hundred sixty-five individuals (80 cases and 85 controls) were targeted. Of those, 12 individuals (5 cases and 7 controls) refused to participate giving a response rate of 92.7%. According to the exclusion criteria, 13 participants (5 cases and 8 controls) were excluded. The remaining 140 men (70 cases and 70 controls) representing the final sample size were included in the study. The diabetic patients (cases), attending Al-Sadr Teaching Hospital during the study period, were chosen randomly. The control group included healthy non-diabetic men who attended a primary healthcare centre for screening tests, were chosen by a simple random sampling.

DM was defined as the presence of both fasting plasma glucose (FPG) of ≥126 mg/dL and HbA1c of ≥6.5% or a positive medical history.[16]

Sociodemographic information and family history of diabetes were enquired about by interviewing using a special questionnaire designed for the purpose of the study. Only the diabetic patients completed the data related to DM such as duration of the disease and the type of antidiabetic treatment. Body weight and height were measured and body mass index (BMI) was calculated (weight in Kg/height in m^2), and it was categorised as underweight (<18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) or obese (BMI ≥30).[17] Serum was obtained for analysis of FPG and PSA.

Serum PSA was measured using a sandwich-type enzyme-linked immunosorbent assay technique using immunoassay kit supplied by Human Diagnostics Worldwide (HUMAN.de Germany) with an analytical sensitivity of 0.05 ng/mL. The principle of the method is as mentioned by Nilsson *et al*.[18]

This study was conducted in accordance with the ethical principles stated in the declaration of Helsinki and approved by the Ethical Committee of the College of Medicine, University of Basrah (2016-02). Informed consent was obtained from all participants.

Statistical analysis

Statistical analyses were done using Statistical Package for the Social Sciences (SPSS), Version 20 (IBM Corp., Chicago, Illinois, USA). The results were presented in Tables. Frequencies and percentages were calculated for the categorical variables, while continuous variables were expressed as means and standard deviations. Differences were assessed using Chi-square, *t*-test or ANOVA where applicable. Correlations between serum PSA level and various variables were examined by Pearson's correlation analyses. $P < 0.05$ was considered statistically significant.

Results

The mean age of the studied population was 55.6 ± 10.6 years (55.2 ± 10.5 for cases and 55.9 ± 10.9 for controls without a significant difference). No significant difference was noticed between cases and controls regarding smoking status and presence of co-morbid conditions. BMI was significantly higher among diabetic than non-diabetic men.

The PSA level was significantly lower among diabetic than non-diabetic men (1.97 ± 1.05 ng/ml vs. 2.60 ± 1.22 ng/ml, respectively, $P = 0.001$) [Table 1].

To examine the independent effect of certain variables on serum PSA level, a multiple linear regression analysis was done. It demonstrated that age ($\beta = 0.279$, $P = 0.001$), DM ($\beta = -0.181$, $P = 0.026$) and BMI ($\beta = -0.175$, $P = 0.034$) were significant independent determinants of serum PSA level [Table 2].

In non-diabetic men, PSA level increased significantly with age (correlation $r = 0.463$; $P < 0.001$), while in diabetic patients, it increased with age until the age of 60 years and then it decreased. No significant association was found between serum PSA level and age in diabetic patients (correlation $r = 0.141$; $P = 0.242$) [Figure 1].

In diabetic patients, age and family history of diabetes showed no significant association with serum PSA level. However, BMI, HbA1c, insulin treatment and duration of diabetes showed significant association with serum PSA level ($P < 0.05$) [Table 3].

Table 1: Descriptive characteristics of the study population (*n*=140)

Parameter	Diabetics (*n*=70)	Non-diabetics (*n*=70)	*P*
Age (years), mean±SD	55.2±10.5	55.9±10.9	0.676
BMI (kg/m^2), mean±SD	27.5±3.3	25.6±3.5	0.001
FPG (mg/dl), mean±SD	173.2±41.2	104.8±11.6	<0.001
HbA1c (%), mean±SD	7.3±1.9	5.2±0.6	<0.001
Positive family history of DM, *n* (%)	34 (48.6)	29 (41.4)	0.396
Smoking, *n* (%)			
Current	58 (82.9)	47 (67.1)	0.078
Ex-smoker	4 (5.7)	5 (7.1)	
Non-smoker	8 (11.4)	18 (25.7)	
Co-morbid conditions, *n* (%)			
Hypertension	23 (32.9)	20 (28.6)	0.649
Coronary heart disease	5 (7.4)	5 (7.4)	
PSA (ng/ml), mean±SD	1.97±1.05	2.60±1.22	0.001

BMI: Body mass index, FPG: Fasting plasma glucose, HbA1c: Glycosylated haemoglobin, DM: Diabetes mellitus, PSA: Prostate-specific antigen, SD: Standard deviation

Table 2: Multiple regression analysis to examine the predictors of serum level of prostate-specific antigen

Parameter	β	r^2	*P*
Age	0.279	0.314	0.001
Diabetes mellitus	−0.181	0.384	0.026
BMI	−0.175	0.422	0.034

BMI: Body mass index

Table 3: Serum prostate-specific antigen level (ng/ml) in diabetic patients according to age and clinical characteristics (*n*=70)

Variable	*n* (%)	Mean±SD	*P*
Age (years)			
<40	5 (7.1)	1.54±1.40	0.482
40-49	13 (18.6)	1.75±0.78	
50-59	21 (30.0)	2.02±0.96	
60-69	26 (37.2)	2.21±1.18	
≥70	5 (7.1)	1.73±0.74	
BMI (kg/m^2)			
<25	16 (22.9)	2.48±0.90	0.037
25-29.9	36 (51.4)	1.95±1.07	
≥30	18 (25.7)	1.57±0.99	
Family history of DM			
Positive	34 (48.6)	1.99±1.00	0.858
Negative	36 (51.4)	1.94±1.10	
HbA1c (%)			
<7	39 (55.7)	2.51±0.99	<0.001
≥7	31 (44.3)	1.30±0.65	
Duration of DM (years)			
<5	25 (35.7)	2.42±0.86	0.011
5-10	29 (41.4)	1.86±0.97	
>10	16 (22.9)	1.46±1.12	
Anti-diabetic treatment			
Oral	47 (76.1)	2.29±1.01	<0.001
Insulin + oral	23 (32.9)	1.32±0.81	

HbA1c: Glycosylated haemoglobin, BMI: Body mass index, DM: Diabetes mellitus, SD: Standard deviation

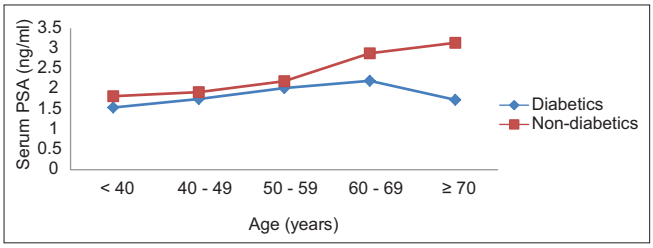

Figure 1: Mean serum prostate-specific antigen level among diabetics compared to non-diabetics according to age

Discussion

This study showed that the 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.[12,19] Since PSA is androgen regulated,[20] such association may be partly explained by lower serum testosterone concentration among diabetic patients.[21] However, other studies rebutted such association between serum testosterone concentration and serum PSA level.[12,22] It was postulated that the intraprostatic androgen status seems to be more important than the circulating levels in determining the risk of prostate cancer.[12]

IGF-1 was reported to be a prostate cell growth promoter[23] and is positively related to PSA.[24] The low level of IGF-1 in long-term diabetes[15] as insulin production drops[25] may further explain the low level of PSA in diabetic patients.

Impaired kidney functions[26] as well as antidiabetic medications particularly metformin[27] or other common medications, which are commonly used by diabetics such as statins, may also lower serum total prostate-specific antigen.[28]

Although the association between BMI and serum PSA is controversial, our study showed an inverse correlation between BMI and serum PSA in both diabetic and non-diabetic men, a result which agrees with that reported by others.[29] The exact mechanism for the inverse association between BMI and PSA is not well elucidated and several pathways had been suggested. However, some researchers attributed their findings to the hormonal hypothesis, which suggests that serum PSA is influenced by steroid hormone levels.[30] Alternatively, other researchers suggested a haemodilution hypothesis, which suggests that obesity increases plasma volume, thus leading to reduction in circulating PSA concentration.[31]

This study showed an inverse association between HbA1c and serum PSA, a result that is consistent with that reported by others.[10,32]

Similar to what was reported by Civtković *et al*.[33] and Ainahi *et al*.,[34] our study showed that serum PSA is less age dependent in diabetic patients than in non-diabetics, particularly in elderly people. In diabetic patients, PSA increased with age until age of 60 years and then decreased without significant association. While in non-diabetic patients, it increased significantly with age. This may be attributed to the diminished capability of prostate to produce PSA or its decreased leakage[33] due to prostate ischaemia resulting from local microvascular complications associated with DM.[35]

As reported previously,[19] our study showed that serum PSA was inversely associated with duration of diabetes. A plausible explanation is that with advanced duration of diabetes, the action and level of insulin decrease leading to a subsequent decrease in serum PSA level.[36]

In agreement with the results of Müller *et al*.,[10] our study showed that diabetic men on insulin combined with oral treatment had lower serum PSA level than those on oral antidiabetic medications alone. In addition, serum PSA level was significantly lower in patients on treatment (whether oral or combined oral and insulin) than that in non-diabetic men. Use of insulin may be an approximate surrogate of diabetes severity[10] and an indicator of a later stage of diabetes that is characterised by a lower level of circulating insulin and insulin resistance and consequently low serum PSA concentration.[11]

In line with what was reported by Fukui *et al*.,[12] multivariate linear regression analysis revealed that age, diabetes and BMI were independent determinants of serum PSA. It showed that only 42.2% of variation in serum PSA was related to these factors. It should be noted that serum level of PSA is affected by many other factors such as demographic, lifestyle and health characteristics.[10]

Some limitations have to be considered in this study. The first is that the prostate volume was not measured which may affect the influence of prostate growth on PSA level. The second imitation is the small sample size, which is mainly due to financial constraint. Furthermore, duration of treatment, dosage of medications 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 is affected by DM.

Conclusion

This study supports the evidence that DM 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. Therefore, DM should be considered in setting the PSA threshold when screening for prostate cancer, and special attention should be warranted in evaluation of PSA of elderly diabetic patients with further investigation are needed when prostate cancer is suspected.

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Conflicts of interest

There are no conflicts of interest.

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