

The Association between Diabetes Mellitus and Serum Prostate-Specific Antigen Levels

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Abstract

Background: Diabetic patients were indicated to have an improved risk for cancers of the liver, pancreas, and colon; nevertheless, recently many studies have suggested that diabetes mellitus (DM) decreased possibility for developing the cancer of prostate in men.

Objective: To analyze if the levels of prostate-specific antigen (PSA) in serum of men with type two DM were low in comparison with healthy group, and to investigate the factors that could influence the PSA level in diabetic patients.

Method: 120 diabetic men patients were analyzed for PSA levels in the serum compared with equal number age-matched control group. The relationships between the serum PSA levels and **body mass index** (BMI), age, hypertension, smoking and glycosylated hemoglobin (HbA1c) were considered.

Results: Serum PSA levels were statistically significantly ($p < 0.05$) lower in diabetic patients compared to healthy men. The present study demonstrated that age, BMI and high HbA1c showed independent determining factors of the PSA level in men.

Conclusions: Our study strongly support that DM has inverse relationship with the levels of PSA marker and more severe cases of diabetes mellitus, older age and high body mass index in diabetic patients are associated with lower levels of the serum PSA. This result confirms that diabetes mellitus is a protective factor for prostate cancer among populations.

Keywords: *Diabetes mellitus, PSA, prostate cancer.*

Introduction

Diabetes mellitus (DM) and various cancers are commonly diagnosed in the same persons⁽¹⁾, which suggest that the two diseases may have common risk factors and pathogenesis. The possible links include insulin resistance, hyperinsulinemia, hyperglycemia, oxidative stress, and chronic inflammation; which are factors that have potential promoting effect on the progression of cancer in many ways^(2,3).

Many studies have stated that patients with diabetes mellitus are at high risk of many types of cancers, including liver and pancreatic cancers, and the two

organs have a major role in the pathogenesis of diabetes mellitus⁽⁴⁾.

Different studies consistently report type two diabetes mellitus is inversely related the cancer of the prostate^(5,6), but not all studies have reached to this conclusion⁽⁷⁾.

The mechanisms for these paradoxical associations are not clear. Several studies reported that increased duration since diagnosis of type two DM decreases the risk of prostate cancer⁽⁸⁾ and there is some suggestion that prostate cancer risk is increased in the years immediately after the diagnosis of DM^(6,9).

Measuring the PSA is the most useful available tumor marker for the diagnosis of the cancer of the prostate⁽¹⁰⁾. It is commonly used for screening of the cancer of the prostate cancer⁽¹¹⁾.

Although there are variable recommendations, the age of 50 years is suggested by several organizations for PSA screening⁽¹²⁾.

Method

The study was conducted on 120 previously diagnosed type 2 diabetic men with age ranging from 38-70 years old and 120 age matched normal healthy control men. Patients with type 2 DM were selected from the diabetic clinic and outpatient clinics of urosurgery with no urological disease that may affect the PSA level at Al-Ramadi teaching hospital and Al-Yarmook teaching hospital, and the controls were healthy volunteers, between October 2016 and April 2018. Type two DM was diagnosed according to the American Diabetes Association (ADA) criteria for the diagnosis of diabetes 2010⁽¹³⁾.

The controls should be never diagnosed with type 2 diabetes. A written consent was taken and ethical approval was obtained from Al-Anbar Medical college ethics committee.

The collection of data were based on structured questionnaires.

Men with evident prostatic disease (like prostate cancer, benign prostatic hypertrophy and prostatitis) and men with history of type 1 DM were excluded from this study.

The hemoglobin A1c (HbA1c) was used as a marker of glycemic control. Its level is used as indicator of glycemic control within the past 3 months⁽¹⁴⁾. The HbA1c levels less or equal 6% was considered normal and 6.1% to 7% as high, and we used 6.1% as cutoff value, which was adopted by Bennett et al.⁽¹⁵⁾ to diagnose patients with diabetes mellitus. The height and weight were measured to calculate the patient's BMI, BMI of < 25 was considered as normal weight, BMI of >25 and <30 as overweight, and BMI of >30 as obese⁽¹⁶⁾. Waist circumference was also measured.

The blood samples were used for the measurement of the PSA and HbA1c. The PSA levels were measured using Minividias Machine using its costume kit. HbA1c analyses were done (Nycocard™ HbA1c). All measurements were done at Al-Ramadi Teaching Hospital Laboratory according to the instructions of the manufacturer.

Statistical Analysis: ANOVA test was used to analyze the statistical differences between group means and McNemar's test for comparison of proportions, also chi square was used for comparing categorical variables. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 24) software.

Results

The age of subjects enrolled in this study ranged from 38 to 70 years with mean of 61.59 and 60.20 year in cases and in control group respectively, there was no significant statistical difference between the age, the prevalence of smoking and family history of prostatic cancer among the two groups. Table (1).

Table (1) Characteristic of study groups.

Variable	Groups		P value
	Cases	Controls	
Mean age/years ± SD	61.59±8.97	60.20±9.68	0.249
Age distribution N/%			
< 50	15/12.5	17/14.2	0.847
50 – 59	40/33.4	38/31.7	0.847
>60	65/54.16	65/54.16	1.000
Body Mass Index/(kg/m ²) ± SD	25.34±2.48	24.19±2.62	0.001
Body mass index distribution N/%			
< 25	16/13.4	75/62.5	0.000
25 – 30	59/49.2	34/28.4	0.002
>30	45/37.5	11/9.2	0.000

Variable	Groups		P value
	Cases	Controls	
Smokers N/%	44/36.7	52/43.4	0.333
Hypertensive N/%	71/59.2	37/30.8	0.000
Family history of prostate cancer N/%	9/7.5	8/6.6	0.949
Hb A1C(%)± SD	7±1.50	4.9±0.99	0.000
Mean PSA(ng/ml) ± SD	1.122±0.118	1.400±0.142	0.000

There was a highly significant statistical difference in the mean PSA level among the three studied age groups of cases, while no statistical difference among

the controls. Independent to other factors the BMI was inversely related to the mean PSA level in both groups with statistically significant difference. Table (2).

Table-(2) The association of BMI and age with mean PSA in both groups

Variables	Csaes (N)	Mean PSA (ng/ml)±SD	P value	Controls	Mean PSA (ng/ml) ± SD	P value
Body mass index (kg/m²)						
< 25	16	1.260±0.089		75	1.437±0.133	
25 – 30	59	1.126±0.105	0.000	34	1.367±0.127	0.039
>30	45	1.067±0.102	0.000	11	1.245±0.121	0.000
25 – 30	59	1.126±0.105		34	1.367±0.127	
>30	45	1.067±0.102	0.018	11	1.245±0.121	0.029
Age distribution/years						
< 50	15	1.230±0.106		17	1.376±0.152	
50 – 59	40	1.138±0.123	0.025	38	1.392±0.136	0.932
>60	65	1.080±0.101	0.000	65	1.411±0.143	0.678
50 – 59	40	1.138±0.123		38	1.392±0.136	
>60	65	1.080±0.101	0.034	65	1.411±0.143	0.815

The mean PSA was not statistically different in smokers compared to nonsmokers in the cases but was lower in smokers compared to nonsmokers in the controls with statistically significant difference. Table (3)

Table (3) The association of Hypertension and smoking history with mean PSA in both groups.

Variables	Cases (N)	Mean PSA (ng/ml) ± SD	P value	Controls(N)	Mean PSA (ng/ml) ± SD	P value
Smoking state						
Smoker	44	1.118±0.117		52	1.342±0.136	
Non smoker	76	1.124±0.119	0.778	68	1.475±0.111	0.000
Hypertensive state						
Hypertensive(N)	71	1.119±0.120		37	1.410±0.137	
Non hyprtensive(N)	49	1.125±0.118	0.801	83	1.395±0.145	0.580

Regarding duration of DM, no significant difference. Table (4).

Table (4) The association of duration of diabetes mellitus and HbA1c with the mean PSA level in cases group.

Variables	Number	Mean PSA(ng/ml) ± SD	P value
Hb A1C(%)			
≤ 6 (Normal)	30	1.232±0.108	0.000
6.1 – 7 (High)	47	1.109±0.120	
> 7 (Very high)	43	1.023±0.0869	
6.1 -7	47	1.109±0.120	0.001
> 7	43	1.023±0.0869	
Duration of DM (Years)			
0 - 5	33	1.127±0.120	0.978
6 -10	47	1.122±0.119	
> 10	40	1.114±0.118	
6 -10	47	1.122±0.119	0.963
> 10	40	1.114±0.118	

Discussion

The cancer of the prostate is the second most frequently diagnosed cancer of men and the sixth most common cause of cancer mortality among men worldwide⁽¹⁷⁾. In most Asian Countries, the incidence of cancer of the prostate has increased during the last two decades⁽¹⁸⁾.

Saad et al. have suggested a mechanism for the occurrence and progression of type two DM consisting of two-parts⁽¹⁹⁾.

Testosterone is varied by the status of DM and its duration and prostate cancer is the only cancer that is believed to be fueled by testosterone.

Another hypothesis adopted recently is related to microvascularization, of the prostate, where the damage to the blood vessels of the prostate, as a part of DM complications, prevents the development of prostate cancer⁽²⁰⁾.

Shi et al., demonstrated that the blood level of insulin-like growth factor-I was more in patients with prostate cancer than in controls⁽²¹⁾.

So, in the early stage of abnormal metabolism of glucose and development of type two DM (the step of insulin resistance), the risk of the cancer of the prostate may be increased due to elevated levels of insulin and this is consistent with many studies that have examined the risk of the cancer of the prostate and duration of

diabetes mellitus since the diagnosis⁽²²⁾ which have found an increased risk in the early stage followed by inverse association in the later stage.

Our results are largely consistent with other study⁽²³⁾ that found there was no significant difference by duration of DM.

However, the duration of diabetes mellitus is a parameter which is difficult to be determined because 50% of patients with type two diabetes mellitus may be undiagnosed⁽²⁴⁾, and the estimated duration of diabetes mellitus may be related to the degree of medical follow up.

It is well known that as increasing ages, the PSA level will naturally increases by about 3.2% per year⁽²⁵⁾. Richardson and Oesterling suggested age-specific reference ranges for the serum PSA level in men of different races after reviewing multiple studies⁽²⁵⁾.

In controls, our results shows that the serum PSA level was found to be significantly increased with age and it is consistent with various Asian populations based studies conducted among China, south India, Korea, Singapore, and Japan⁽²⁶⁾, while in diabetics as the age increased, the mean PSA level was decreased especially among men aged 60 and over, which similar to that reported by Ainahi *et al.*⁽²⁷⁾.

Despite of statistically non-significant relationship between BMI and the PSA level seen in a smaller-scale study⁽²⁸⁾, Our findings in both cases and controls are

consistent with the findings of an inverse association between BMI and the PSA levels, where there is 5% to 21% decrease in the PSA value in men with BMI more than 30 in comparison with men with normal BMI as seen in several large-scale studies⁽²⁹⁾. The relevant reduction in the PSA level might be attributable to increased volume of the plasma found in the larger men⁽²⁹⁾ or due to less androgen levels seen in the obese and insulin resistant adult males⁽³⁰⁾.

Our findings are also consistent with the results of studies that examine the association with glycemic control in patients with T2DM. Müller et al reported that the serum PSA level is 15% and 29% lower in patients with HbA1c of 6.1–6.9% and $\geq 7\%$ respectively, in comparison with those with normal HbA1c ($< 6.1\%$)⁽³¹⁾.

Ohwaki et al suggest a positive association between HbA1c and the PSA (5.7% increase in the PSA for each unit HbA1c change), which is in contrast to many studies and our current study⁽³²⁾.

Similar to previous studies that reported the PSA level were significantly lower in smokers in comparison to non-smokers men who are over the age of 55⁽³³⁾. We found the PSA level was significantly lower as compared with never smokers in the controls. In patients with diabetes mellitus, the PSA levels were mildly lower in smokers in comparison to non-smokers, but it was statistically nonsignificant.

Among the possible explanations for lower PSA levels in patients with type 2 diabetes mellitus is hypertension⁽³⁴⁾, and this is inconsistent with our results.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq.

Conflict of Interest: Non

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