Original Article

Impact of poor glycemic control of type 2 diabetes mellitus on serum prostate-specific antigen concentrations in men

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ABSTRACT

Background: To evaluate the impact of poor glycemic control of type 2 diabetes mellitus (T2DM) on serum prostate-specific antigen (PSA) concentrations in men.
Methods: We performed a prospective analysis of 215 consecutive patients affected by erectile dysfunction (ED). ED was evaluated using the IIEF-5 questionnaire and the poor glycemic control (PGC) of T2DM was assessed according to the HbA1c criteria (International Diabetes Federation). Patients were divided into PGC group (HbA1c $\geq$ 7%) and control group (CG) (HbA1c < 6%). Correlations between serum HbA1c levels and various variables were evaluated and multivariate logistic regression analyses were carried out to identify variables for PGC.
Results: We compared 110 cases to 105 controls men ranging from 44 to 81 years of age, lower PSA concentrations were observed in men with PGC (PGC mean PSA: 0.9 ng/dl, CG mean PSA: 2.1 ng/dl, p < 0.001). Also mean prostate volume was 60% was smaller among men with PGC compared with men with CG (PGC mean prostate volume: 26 ml, CG prostate volume: 43 ml, p < 0.001). A strong negative correlation was found between serum HbA1c levels and serum PSA (p < 0.001 and r = −0.665) concentrations in men with PGC. We also found at the multivariate logistic regression model that PSA, prostate volume and peak systolic velocity were independent predictors of PGC.
Conclusion: Our results suggest that there is significant impact of PGC on serum PSA levels in T2DM. Poor glycemic control of type 2 diabetes was associated with lower serum PSA levels and smaller prostate volumes.

1. Introduction

Measurement of prostate-specific antigen (PSA) is widely applied for early detection of prostate cancer. However, several factors influencing serum PSA levels in men include age, benign prostatic hyperplasia, prostatitis, and body mass index (BMI).[1,2] Type 2 diabetes (T2DM) is a complex metabolic disease characterized initially by insulin resistance and hyperinsulinemia. It is estimated that 11% of American men have type 2 diabetes.[3,4] Many studies have investigated the association between T2DM and PSA with most evidence supporting a modest inverse association; the reported reduction in risk ranges from 10% to 20% in diabetics.[5,6] There are several possible explanations as to why PSA may be lower in men with T2DM than in those without, including lower testosterone and higher estrogen concentrations, greater obesity, and more frequent use of medications for dyslipidemia.[7–9] These reports have focused on the relationship between serum fasting glucose values and PSA in men with T2DM but the effect of poor glycemic control [PGC; as assessed by hemoglobin A1c (HbA1c)] on serum PSA concentration was not discussed in those publications. Also, the role of severity of T2DM is yet to be explored as more detailed data are still lacking.

In this study, we examined effect of PGC (HbA1c $\geq$ 7%) on serum PSA levels in men with T2DM. We also investigate the relationships

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between HbA1c levels and prostate volumes and investigated what factors may be associated with serum PSA levels in men with PGC.

2. Materials and methods

2.1. Design

Between January 2013 and March 2014, 350 consecutive patients with erectile dysfunction (ED) were prospectively enrolled in this study at a single academic outpatient andrology clinic. Patients who were taking α-blockers, phosphodiesterase type 5 inhibitors, and 5α-reductase inhibitors and those with neurogenic bladder, postvoid residue >150 mL, prostate cancer, bladder cancer, bladder stone, urethral stricture, men with diabetes who suffered from end organ damage (creatinine levels > 250 μm), or absence of hepatic dysfunction (high transaminase plasma levels) were excluded from the study. Okmeydanı Training and Research Hospital Ethics Committe approval and informed consent from all the participants were obtained. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All patients' detailed medical and sexual history were evaluated. Patients underwent physical examination including digital rectal examination, genitourinary, endocrine systems, and prostate volume estimated by transrectal ultrasonography. Participants completed a baseline questionnaire that ascertained information on urinary symptoms, medical histories, physical examination (weight, height, BMI, waist circumference, and blood pressure), and various demographic and behavioral characteristics.

Lower urinary tract symptoms were evaluated by culturally and linguistically validated versions of International Prostate Symptom Score (IPSS). ED was evaluated using the International Index of Erectile Function short form (IIEF-5) questionnaire, with normal erectile function as 22−25 points, mild dysfunction 17−21, mild-to-moderate ED 12−16, moderate ED 8−11, and severe ED 5−7 points.[10]

Blood samples were drawn from overnight-fasted patients and serum levels PSA, free PSA, fasting blood glucose, HbA1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglyceride were recorded. A venipuncture was performed between 8:00 AM and 10:00 AM for total testosterone measurement.

After the results of the patients' laboratory testing were finalized, patients were consulted with internal medicine department for the diagnosis of T2DM. Poor glycemic control of T2DM was defined as HbA1c ≥ 7% according to the standards defined by the American Diabetes Association,[11] and 170 patients were diagnosed with T2DM by the Internal Medicine Department (Okmeydanı Training and Research Hospital) and 110 of those patients were diagnosed with PGC. There were 105 patients with ED who had no diabetes recruited as a control group (CG; HbA1c < 6%).

2.2. PSA, HbA1c, and hormone measurements

PSA and HbA1c were measured in blood samples. PSA analyses were done using the total and free prostate-specific antigen test (Cobas 6000; Roche Diagnostics, Indianapolis, IN, USA) on a Modular E-Module of Roche Diagnostics. HbA1c analysis was done using high-performance liquid chromatography on the Premier Hb9210 system (Trinity Biotech, Bray, Wicklow, Ireland). Total testosterone was evaluated by commercial electrochemiluminescence immunoassay methods (Roche Diagnostics). All measurements were done in a central laboratory in blinded fashion and according to the manufacturer's instructions.

2.3. Transrectal and penile duplex Doppler ultrasonography measurements

To calculate prostate volume, a prostate transrectal ultrasound analysis was performed with a high-resolution echo-color Doppler (iU22; Philips, Eindhoven, The Netherlands) equipped with a 9−5 MHz Broadband Curved Array Transducer. Prostate volume was calculated using the standard ellipsoid formula (width × height × length × π/6).[12]

For penile duplex Doppler ultrasonography measurements, patients received a single intracavernous injection of Bimix (15 mg papaverine and 1 mg phentolamine). The erectile response was evaluated for tumescence and rigidity by palpation of the penis. The penis was scanned by a ventral approach at the base with the probe held transversally or in an oblique-longitudinal position.[13] Peak systolic velocity (PSV) and end diastolic velocity (EDV) within the cavernosal arteries were measured. Patients with PSV > 35 cm/s were considered with a normal arterial response, while < 25 cm/s signified arterial insufficiency. Corporal veno-occlusive dysfunction was defined as EDV > 5 cm/s.[14,15]

2.4. Metabolic parameters measurements

Plasma fasting glucose was determined by enzymatic test (COBAS C720; Roche Diagnostics), total cholesterol was determined by enzymatic colorimetric test (CHOD-PAP, COBAS C720; Roche Diagnostics), and high-density lipoprotein cholesterol and triglycerides were measured by enzymatic colorimetric test (COBAS C720; Roche Diagnostics). Creatinine was determinate by the Jaffe method. For all parameters, the intra- and interassay coefficients of variation were < 8% and 10%, respectively.

2.5. Statistical analyses

All statistical analyses were completed using SPSS version 22.0 packages (SPSS Inc, IBM Corp, Somers, NY, USA). Mean standard deviation, median minimum, maximum, frequency, and ratio values were used for descriptive statistics of the data. The distribution of the variables was measured by Kolmogorov−Smirnov test. The continuous variables, presented as median, were tested by Mann−Whitney U test. Correlations between serum HbA1c levels and various variables were examined by Spearman's rank correlation analyses. Univariate and multivariate logistic regression analyses were carried out to identify variables for PGC (HbA1c ≥ 7). For all statistical comparisons, significance was considered as $p < 0.05$.

3. Results

3.1. Descriptive analyses

Table 1 lists the clinical characteristics of participants included in the analysis. Median age was 60.0 years (range, 44−71 years), median IPSS was 14 (range, 6−22), median IIEF-5 score was 11 (range, 3−25), and median PSA was 2 ng/dL (range, 0.3−12.2 ng/dL). Of all participants, 69 (32%) had mild ED, 60 (28%) had mild to moderate ED, 41 (19%) had moderate, and 45 (21%) had severe ED. IPSS was ≤19 in 86 (40%) of participants, PSV was ≤ 25 cm/s in 144 (67%), EDV was 5 cm/s ≥ in 116 (54%) participants. In the PGC group (HbA1c ≥ 7%) patients' total testosterone was ≤ 326 ng/dL in 30 (27%) participants, while in the CG (HbA1c ≤ 6%), total testosterone level was ≤ 326 ng/dL in 21 (20%).

Table 1
Clinical characteristics of participants ($n = 215$).

	Range	Median	Mean ± SD
Age (y)	44–71	60.0	59.8 ± 9.6
BMI (kg/m^2)	15.8–36.1	27.8	27.8 ± 4.3
HbA1c (%)	4.4–13.8	9.0	8.4 ± 2.5
Glucose (mg/dL)	87–720	180.3	199.1 ±130.4
PSA (ng/dL)	0.3–12.2	2.0	3.5 ± 435
free PSA (ng/dL)	0.1–5.0	0.4	0.7 ± 0.8
Creatinine (mg/dL)	0.6–1.5	0.9	0.9 ± 0.2
Triglyceride (mg/dL)	89–522	198.7	220.1 ± 86.9
HDL-C (mg/dL)	20–65	35.0	35.7 ± 7.5
LDL-C (mg/dL)	57–1,125	123.0	146.2 ± 126.8
Total cholesterol (mg/dL)	140–304	195.0	205.8 ± 40.7
Total testosterone (ng/dL)	111–644	366	392 ± 70
Prostate volume (mL)	18–112	30.3	36.6 ± 18.1
IPSS	6–22	14.0	12.3 ± 3.1
IIEF-5 Score	3–25	11.0	10.9 ± 4.7
PSV (cm/s)	7–40	14.0	16.4 ± 7.2
EDV (cm/s)	4–11	5.2	5.4 ± 1.1

BMI, body mass index; EDV, end diastolic velocity; HDL-C, high-density lipoprotein cholesterol; IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LDL-C, low-density lipoprotein cholesterol; PSA, prostate-specific antigen; PSV, peak systolic velocity; SD, standard deviation.

3.2. Comparison of the groups

The mean age was 61 years in the PGC group (mean ± standard deviation, 59.5 ± 9.6 years), and 59 in CG (60.1 ± 9.5 years, $p = 0.46$). BMI of PGC group patients was lower than CG but it was not statistically relevant ($p = 0.81$). No differences were observed in lower urinary symptoms, which were assessed with IPSS ($p = 0.63$). Lower free and total PSA concentrations were observed in men with PGC patients compared to Cg (PGC mean total PSA: 0.9 ng/dL, CG mean total PSA: 2.1 ng/dL, $p < 0.001$; PGC mean free PSA: 0.3 ng/dL, CG mean free PSA: 0.8 ng/dL, $p < 0.001$). Also, mean prostate volume was 60% was smaller among men with severe PGC compared to control participants (PGC mean prostate volume: 26 mL, CG prostate volume: 43 mL, $p < 0.001$), total testosterone levels were not significantly different between the groups ($p = 0.27$). Mean PSV was lower in PGC patients compared to control group (T2DM mean PSV: 12.1 cm/s, CG mean PSV: 19 cm/s, $p < 0.001$), but there were no

differences in terms of mean EDV values and IIEF-5 scores. There were no differences between the groups in terms of serum creatinine and lipid profiles (Table 2).

3.3. HbA1c and correlation analysis

Mean HbA1c levels was approximately 185% higher (PGC = 10.6 ± 1.4% and CG = 5.7 ± 0.8%) and mean fasting plasma glucose levels was 240% higher (PGC = 260 ± 81 mg/dL and CG = 104 ± 14 mg/dL) among with PGC patients compared with the CG. A strong negative correlation was found between serum HbA1c levels and serum total in the PSA ($p < 0.001$ and $r = -0.665$) and free PSA ($p < 0.001$ and $r = -0.558$) concentrations in men with PGC. Also, a strong negative correlation was found between serum HbA1c levels and prostate volume ($p < 0.001$, $r = -0.538$) and PSV ($p < 0.001$, $r = -0.337$) in PGC patients.

We found no correlation between serum HbA1c levels and plasma total testosterone concentrations ($p = 0.095$, $r = 0.114$; Fig. 1).

3.4. Univariate and multivariate regression analysis

Univariate logistic regression analysis demonstrated that BMI [odds ratio (OR) = 1.18 kg/m^2, 95% confidence interval (CI) 1.10–1.28 kg/m^2, $p < 0.05$], PSA (OR = 3.80, 95% CI 2.61–5.54, $p < 0.01$) and free PSA levels (OR = 4.80 ng/dL, 95% CI 2.90–3.20 ng/dL, $p < 0.01$), prostate volume (OR = 1.22 mL, 95% CI 1.15–1.30 mL, $p < 0.01$), IIEF-5 scores (OR = 1.55, 95% CI 1.38–1.73, $p < 0.01$), and PSV values (OR = 1.30 cm/s, 95% CI 1.20–1.41 cm/s, $p < 0.01$) significantly increase the risk of PGC. We also found at the multivariate logistic regression model that total PSA (OR = 1.92 ng/dL, 95% CI 1.09–3.16 ng/dL, $p < 0.01$), free PSA (OR = 2.62 ng/dL, 95% CI 1.6–4.1 ng/dL, $p < 0.01$), prostate volume (OR = 1.72 mL, 95% CI 1.31–2.31 mL, $p < 0.01$), and PSV (OR = 1.62 cm/s, 95% CI 1.09–2.42 cm/s, $p < 0.01$) were independent predictors of PGC Table 3.

4. Discussion

We observed a significant impact of severe PGC on total PSA concentrations in men with PGC. An inverse relationship between high HbA1c levels and total PSA concentrations were shown in two

Table 2
Comparison of the groups.

	HbA1c ≥ 7%		HbA1c < 6%		p[a]
	Mean ± SD	Median	Mean ± SD	Median	
No. of participants	110		105		
Age (y)	59.5 ± 9.6	59.0	60.1 ± 9.5	61.0	0.46
BMI (kg/m^2)	26.5 ± 5.1	26.9	29.2 ± 2.8	29.0	0.81
HbA1c (%)	10.6 ± 1.4	10.0	6.2 ± 0.8	5.9	< 0.001
Glucose (mg/dL)	260.5 ± 81.2	250	134.7 ± 31.1	112	< 0.001
PSA (ng/dL)	1.2 ± 0.8	0.9	5.9 ± 2.5	4.1	< 0.001
free PSA (ng/dL)	0.3 ± 0.1	0.3	1.1 ± 1.0	0.8	< 0.001
Creatinine (mg/dL)	0.9 ± 0.2	0.8	1.0 ± 0.2	1.0	0.06
Triglyceride (mg/dL)	208.5 ± 108	194	232.3 ± 54.8	220	0.07
HDL-C (mg/dL)	38.5 ± 8.0	38	32.9 ± 5.5	32	0.08
LDL-C (mg/dL)	127.7 ± 43.9	120	165.6 ± 174.2	123	0.15
Total cholesterol (mg/dL)	182.6 ± 28.5	180	230.1 ± 37.4	220	0.92
Total testosterone (ng/dL)	391.4 ± 104	371	378.7 ± 66.2	389	0.28
Prostate volume (mL)	26.3 ± 4.9	26.0	47.4 ± 10.4	43	< 0.001
IPSS	12.4 ± 3.2	12.0	12.2 ± 3.1	12	0.63
IIEF-5 Score	12.4 ± 3.3	13.2	14.1 ± 3.8	15.2	0.05
PSV (cm/s)	12.6 ± 3.3	12.1	20.5 ± 7.9	19	< 0.001
EDV (cm/s)	5.5 ± 1.1	5.3	5.4 ± 1.1	5.2	0.45

BMI, body mass index; EDV, end diastolic velocity; HDL-C, high-density lipoprotein cholesterol; IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LDL-C, low-density lipoprotein cholesterol; PSA, prostate-specific antigen; PSV, peak systolic velocity; SD, standard deviation.
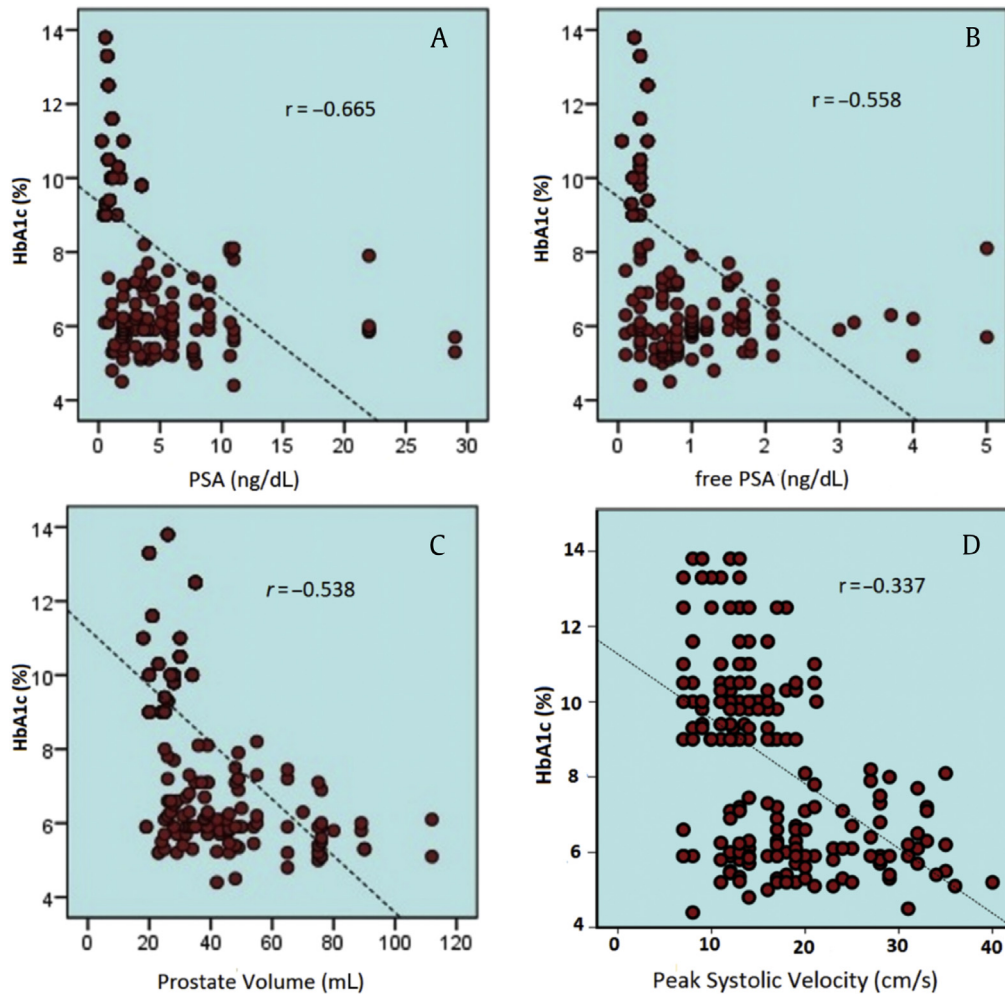[a] Mann–Whitney U test.

Fig. 1. Relationship between HbA1c and A) PSA ($r = -0.665$; $p < 0.05$), B) free PSA ($r = -0.558$; $p < 0.05$), C) Prostate Volume ($r = -0.538$; $p < 0.05$) and PSV ($r = -0.337$; $p < 0.05$) Spearman's rank correlation analysis.

Table 3
Univariate and multivariate logistic regression for significant predictors of severe poor glycemic control (HbA1c ≥ 7%).

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Age (y)	1.01	0.98–1.04	0.652			
BMI (kg/m²)	1.18	1.10–1.28	< 0.001			
PSA (ng/dL)	3.80	2.61–5.54	< 0.001	1.9	1.0–3.1	0.001
free PSA (ng/dL)	4.80	2.90–3,20	0.001	2.6	1.6–4.1	0.001
Creatinine (mg/dL)	0.52	0.68–1.69	0.067			
Triglyceride (mg/dL)	1.00	1.00–1.01	0.069			
HDL-C (mg/dL)	0.86	0.81–0.91	0.791			
LDL-C (mg/dL)	1.00	1.00–1.01	0.078			
Total cholesterol (mg/dL)	1.05	1.04–1.07	0.882			
Total testosterone (ng/dL)	0.85	0.62–1.15	0.289			
Prostate volume (mL)	1.22	1.15–1.30	0.001	1.7	1.3–2.3	0.001
IPSS	0.98	0.90–1.07	0.620			
IIEF-5 Score	1.55	1.38–1.73	0.001			
PSV (cm/s)	1.30	1.20–1.41	0.001	1.6	1.0–2.4	0.001
EDV (cm/s)	0.90	0.70–1.16	0.427			

BMI, body mass index; CI, confidence interval; EDV, end diastolic velocity; HDL-C, high-density lipoprotein cholesterol; IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PSA, prostate-specific antigen; PSV, peak systolic velocity; SD, standard deviation.

groups who enrolled in this prospective study. The association was independent of age, BMI, testosterone concentrations and serum lipid profile, suggesting that PGC itself may affect PSA.

Several recent studies reported lower PSA levels with T2DM. For example, Werny et al[5] found that men with self-reported diabetes had a 21.6% lower geometric mean PSA level than men without diabetes after accounting for age. Fukui et al[6] observed that except for age group 40–49 years, serum PSA levels were lower 10–16% in diabetic men than in healthy Japanese men. These studies focused on men with T2DM, but did not examine the effects of severe PGC independent medication use. In our study, no participants reported use of any medical treatment for diabetes prior to and at the time of study recruitment.

Our findings are also consistent with those of studies in men with T2DM specifically examining the correlation between HbA1c and PSA. Sarma et al[16] found that each 10% increase in hemoglobin A1C had accompanied by an 11% reduction in prostate specific antigen ($p < 0.0001$) and PSA decreased with time-weighted ($p < 0.001$) mean HbA1c. Also, Muller et al,[17] revealed in his study that men with an HbA1c of 7% or more had 15% ($p < 0.004$) and 29% ($p < 0.003$) lower serum PSA concentrations, respectively, than men with a normal HbA1c (< 6.1%). In our study, we did not have any data about the duration of diabetes so we could not observe the time-weighted effect of HbA1c on serum PSA levels. In

addition, in our study we found that prostate volumes of diabetic patients were significantly smaller than the control group. Our study demonstrated a greater impact of current HbA1c on serum PSA concentrations or prostate volume.

There are several possible explanations for PSA being lower in men with T2DM than in those without, including greater obesity, more frequent use of medications to treat dyslipidemia, microvascular complications, which contribute to prostate ischemia, and lower serum androgen levels.

BMI and PSA levels have been investigated by Fowke et al[18]; they found that mean PSA was approximately 22% higher among men with a BMI < 25 kg/m^2 compared with men with BMI > 35 kg/m^2. BMI may reflect increasing systemic estrogen levels via CYP19 (aromatase) conversion of androgens in adipocytes and hemodilution among obese men may cause negative correlation between BMI and PSA levels.[18] Also, patients with T2DM have a frequent occurrence of hypogonadotropic hypogonadism as reflected in low plasma concentrations of total testosterone.[19] We did not find any differences between the two groups in the terms of mean BMI and plasma total testosterone concentrations. Reduction in PSA with increased HbA1c was independent of BMI and total testosterone.

The influence of statin medications on prostate-specific antigen levels were investigated by Hamilton et al[20]; after starting a statin, the median PSA decline was 4.1% ($p < 0.001$) that changes in PSA concentration were strongly associated with statin dose. Patients using medical treatments for diabetes or dyslipidemia mostly were included in studies that investigate the relationship between diabetes and serum PSA.[21,22] In our study, no patients were included in any group who use medication for diabetes or dyslipidemia and there were no differences between two groups in the terms of lipid profile.

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.[23] Thus, in this study, an explanation for the detected low total PSA value and small prostate volumes in T2DM men with PGC might include local microvascular dysfunction and prostate ischemia. There is solid evidence suggesting that the prevalence of ED is much higher in diabetic men.[24] One of the most important mechanisms of diabetes-induced ED is penile vascular dysfunction. Numerous studies in diabetic humans found loss of endothelial cells, more stenosis in pudendal and iliac arteries, and high prevalence of penile arterial insufficiency.[25] The prostate and penis are located anatomically close together and they share the same artery and venous supply.[26] Thus, it is highly possible that prostate vascular function is disrupted by T2DM. As seen in this study, PSV values were lower in patients with severe PGC than nondiabetic patients. These results support the role of microvascular injury to determine the possible prostate vascular function disturbance and penile vascular dysfunction.

In this study, we found a very significant inverse correlation between HbA1c levels and plasma PSA levels. We also found an inverse correlation between HbA1c levels and prostate volumes. However, there were several limitations. Our study demonstrated a significant effect of current HbA1c on PSA, but long-term glycemic control as assessed by time-weighted HbA1c was not measured in this study. Finally, because there were few participants who had a PSA in the range sufficient for referral to biopsy (PSA 4.0 ng/mL), we were unable to evaluate the clinical significance of PSA suppression in prostate cancer detection.

5. Conclusions

Our results suggest that there is significant impact of severe PGC on serum PSA levels in type 2 diabetic men. Poor glycemic control of type 2 diabetes was associated with lower serum PSA level and smaller prostate volume. This relationship is independent of body mass index, age, or total testosterone concentration, which suggests that factors directly related to glycaemia may affect serum PSA levels. Further studies should be undertaken to elucidate the exact biological mechanism that exist between diabetes and prostate.

Conflicts of interest

All authors have no conflicts of interest to declare.

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