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Prostate-Specific Antigen Levels Among Diabetic Men: Exploring Patients Attending Outpatient Clinic in Yemen

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Abstract: **Introduction:** It has been reported that patients with diabetes have a decreased risk for developing prostate cancer. The study aimed to measure Prostate-specific antigen (PSA) levels among diabetic men who had not previously been diagnosed with prostate cancer. **Methods:** A cross-sectional study was carried out in public hospitals among diabetic men in Aden, Yemen. A predesigned structured questionnaire, including the personal data as well as physical and clinical characteristics of the study population, such as height, weight, smoking status, the duration of diabetes, and the type of treatment, was included. Blood samples were collected from the respondents, and the levels of fasting blood glucose (FBG) and PSA were measured. The data were analyzed using descriptive and inferential statistics. **Results:** A total of 145 diabetic male patients were included in this study. The mean PSA level of the respondents was 2.56 ng/ml. There were significant differences in PSA levels according to patient age (p=0.000). The elderly patients exhibited significantly higher PSA levels than the younger groups. The PSA levels of smokers (2.60±0.48 ng/ml) were significantly higher (p=0.035) than those of nonsmokers (2.45±0.65 ng/ml). However, no significant difference was found in PSA levels according to body mass index (BMI) category, the type of treatment, or the duration of diabetes. Additionally, our results showed that PSA levels were not significantly correlated with FBG levels. **Conclusion:** PSA levels were associated with age and smoking status, but not with BMI, the type of diabetic treatment, the duration of diabetes, or with FBG levels.

Keywords: Prostate-specific antigen; Diabetes mellitus; Blood glucose; Prostate cancer; Body Mass Index

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1. Introduction

Prostate-specific antigen (PSA) is a glycoprotein produced primarily by the prostate gland, and its regulation is under the control of androgens and progestins (1, 2). It is a serine protease with chymotrypsin-like enzymatic activity, and it has a molecular mass of approximately 30 kilodaltons (kDa) (1, 2). PSA is a member of the human kallikrein family and is also known as human kallikrein 3 (hk3). The function of PSA is in the liquefaction of the seminal coagulum to allow for the release of spermatozoa (3).

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PSA was established as a main biomarker of prostate cancer (PCa) with its discovery in 1979. It became rapidly available and was also a widely used diagnostic test in the early 1990s (3). Currently, PSA is widely used for the detection or screening of PCa and for monitoring patients after treatment (4). PCa is the second most common malignancy (after lung cancer) in men worldwide. Approximately 1,276,106 new cases caused 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018 (5). It has been reported that the incidence of PCa was 191,054, and approximately 81,229 deaths were recorded in Asian countries in 2012. In Yemen, as in other countries in the Middle East, the incidence of PCa is low, but the disease is being increasingly reported. The crude incidence rate of PCa in Yemen was reported to be 0.9/100,000 in 2012 (6).

Diabetes has been linked to an increased risk of developing cancer, including pancreas, liver, and breast cancer. How-

ever, the connection between PCa and diabetes is currently less understood (7). There are some epidemiological studies on the relationship among diabetes, PCa risk and PSA. However, the results have often been discrepant. Several meta-analyses have indicated that diabetes mellitus (DM) is associated with a 9–16% decreased risk of PCa (8, 9). Diabetes is a chronic health problem and is characterized by high blood glucose levels, which result from defects in insulin production, insulin action, or both (10). DM is an important public health problem and the top four noncommunicable diseases (NCDs), including cardiovascular disease, cancer, and chronic respiratory disease. The prevalence of diabetes has been gradually growing over the past few decades (9). Worldwide, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The international prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. This reflects a rise in related risk factors such as being overweight or obese. In the past, diabetes prevalence has risen faster in countries with low- and middle-income than in high-income nations (7). Diabetes caused 1.6 million deaths in 2016. Almost half of all deaths attributable to high blood glucose occur before the age of 70 (11). Several studies have reported that hyperglycemia and insulin resistance are linked with physical inactivity, obesity, and poor diet, and may be associated with hyperinsulinemia. The independent presence and/or combination of these metabolic perturbations may increase PCa risk (11).

However, several studies have determined that obese men have lower serum PSA concentrations than nonobese men (12, 13). Additionally, some reports found no relationship between body mass index (BMI) and PSA level or percent free PSA (14, 15). Nevertheless, few publications suggest that recent-onset diabetes increases PCa risk (in line with a positive association of diabetes and colorectal cancer) but that long-standing diabetes lowers PCa risk (16, 17). A study was carried out in Egypt and included 501 men; 207 of them had type 2 DM, and they were 55 and above years old. The results showed that the mean PSA level in diabetic patients was 2.3 ng/ml, while the corresponding value for nondiabetic individuals was 3.5 ng/ml. Generally, a significant negative correlation was found between the duration of DM treatment and PSA values (18). A multiethnic prospective cohort study, including 215,251 men aged 45-75 years at recruitment living in Hawaii and Los Angeles county, reported a highly significant association between type 2 diabetes status and PCa incidence, with men with diabetes having an ~20% lower risk of developing PCa than nondiabetic men (19). Moreover, a meta-analysis reported that diabetic patients have a statistically significant 9% decrease in the risk of developing carcinoma of the prostate (20).

Although several studies (21-23) have been conducted to estimate PSA levels in diabetic patients, the relationship between PSA levels and DM is unclear and less understood. Some studies have reported that patients with long-standing diabetes mellitus showed decreased PSA levels compared to individuals without diabetes. On the other hand, some studies reported that patients who had diabetic mellitus for five years or more had a higher incidence of PCa than men without diabetes (21-24). To the best of our knowledge, there is a lack of information about PSA levels in diabetes mellitus and between PSA levels and other variables, such as age, smoking, and BMI; thus, this study investigated the relationships between these variables and PSA levels in men from Aden, Yemen. Therefore, this study was undertaken to measure PSA levels in diabetic men in Aden, Yemen.

2. Methods

2.1. Study design and population

This cross-sectional study was carried out in four main outpatient clinics in public hospitals in Aden Governorate, Yemen (Al-Gamhourea, 22 May, Al-Sadaqah and Basuhaib), among diabetic patients older than 30 years of age. The study was conducted between July 2019 and October 2019. Two-tailed α was used with a p value = 0.05 at a 95% confidence interval (CI); therefore, $Z\alpha$ = 1.96 for all variables. To calculate sample size, the prevalence of diabetes in Yemen, which was approximately 10% with a degree of precision = 5 %) was used.

$n=z^2pq/d^2$

Where, n is the sample size and z is the z statistic for a level of confidence (e.g., for a level of confidence of 95%, the z-value= 1.96). p is the prevalence of DM, which was calculated based on the prevalence reported in a previous study conducted in Yemen (24, 25), which was 10.4%. Hence, the minimum sample size was calculated:

$n=1.96^2(10.4)(89.6)/5^2$ =143

The study excluded nondiabetic men; men younger than 30 years of age; patients with prostate cancer; and patients who had undergone rectal biopsy, prostate massage rectal operation or transurethral resection of the prostate. Such conditions were ascertained from the patients' medical history.

2.2. Ethical consideration

The protocol of the study was approved by the Research and Ethics Committee of the Faculty of Medicine, University of Aden, Yemen (Research Code: REC- 57-2019). Before participation in the study and before we obtained participant data, all respondents were fully informed that participation was voluntary and that it was possible to withdraw from the research without notice. Those who wished to participate were asked to sign a consent form.

2.3. Data collection method

Diabetic patients who consented to participate in the study were administered a structured questionnaire that was designed to gather information regarding sociodemographic information. The questionnaire was first developed in English and then was translated into the Arabic language. Sociodemographic information included the patient's age, marital status, education level, height and weight, family history of diabetes, duration of the disease and type of antidiabetic treatment. Body weight and height were measured, and BMI was calculated (weight in kg/height in m2), which was categorized as underweight (<18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25–29.9), or obese (BMI ≥30) (26). The team explained the entire process to the patients and then invited them to participate in the study. Then, written and signed consent was collected. Blood was withdrawn after an overnight fast (8-12 hours with no food or drink except for water). A 5 ml venous blood sample was collected from respondents by venipuncture, and 2 ml was transferred into an ethylenediaminetetraacetic acid (EDTA) tube for the measurement of glucose and spun at 3000 rpm for 5 min to obtain plasma. The remaining blood (3 ml) was transferred into a sterile gel tube and allowed to clot for the measurement of PSA. The clotted blood sample was spun at 3000 rpm for 5 min, and the serum (the supernatant) was aliquoted, transferred into a labeled Eppendorf tube, and stored at -20°C until PSA determination.

FBG was analyzed using enzymatic methods (glucose oxidase method) according to a commercial kit (Glucose Mono Reagent From Atlas Medical) and assessed using spectrophotometric methods. The collected serum was tested for PSA by using a commercial ELISA kit according to the manufacturer's protocol (DRG International, Inc., United States of America, Lot # RN-59574).

2.4. Statistical analysis

The data in an Excel file were imported into Statistical Package for Social Sciences (SPSS) (ver. 20.0 for Windows; SPSS Chicago, IL, USA). The data were cleaned and checked thoroughly by another person to ensure correctness of the entries before embarking upon analysis. The demographic characteristics of the respondents were presented in percentages and frequencies. BMI was calculated as the weight divided by the height squared. Differences in means were assessed using a t-test or ANOVA where applicable. Correlations between the serum PSA levels and FBG levels were examined by Pearson's correlation analysis. A p-value of less than 0.05 was considered to be significant.

3. Results

3.1. General characteristics of subjects

A total of 167 diabetic patients participated voluntarily in this study and were interviewed face to face to complete the questionnaire about some demographic factors, and blood was withdrawn from them to measure FBG and PSA levels. After the removal of incomplete questionnaires and hemolyzed blood samples, the respondent rate was 81.8%. Data from 145 patients were analyzed.

The age distribution of the respondents showed that the most represented age group was the 50- to 59-year-old group (n=49, 33.8%), while the least represented age group was the 70- to 79-year-old group (n=7, 4.8%). Approximately one-third (n=50; 34.5%) of the respondents had a primary education, 46 (31.7 %) had higher education, 45 (31.0%) had a secondary education and 4 (2.8%) were uneducated. Regarding marital status, the results indicated that an overwhelming number of the respondents (n=136, 93.7%), were married and 4 (2.8%) were single, whereas 3 (2.1%) of the respondents were divorced and 2 (1.4%) were widowers.

3.2. Physical and clinical characteristics of the study population

The mean height of respondents was 169.70 ± 7.90 cm, while the mean weight was 75.99± 16.09 kg. Of these patients, 11 (7.6%) were in the normal BMI range (BMI 18.5–24.9), 71 (49.0%) were classified as overweight (BMI 25.0–29.9), 21 (14.5%) (BMI ≥30) were obese, and 42 (28.9%) were classified as underweight (BMI <18.5) (Figure 4.4). With respect to smoking status, the majority of respondents did not smoke (n=111, 76.6%), whereas 34 (23.4%) smoked.

Nearly half of the respondents (70, 48.3%) reported a family history of diabetes, and 21 (14.5%) respondents had a family history of prostate disease. Current pharmacological therapy consisted of oral hypoglycemic agents in more than half of respondents (88, 60.7%). Ninety-six (66.2%) respondents had been living with diabetes for less than 10 years, and only 10 (6.9%) respondents had been living with diabetes for less than 30 years (Table 1).

3.3. Serum prostate-specific antigen levels in diabetic patients according to age and clinical characteristics

The mean fasting blood glucose (FBG) level of the respondents ± the standard deviation (SD) was 209.8 ± 76.9 mg/dl (range 70 – 459 mg/dl). However, the PSA concentration for the respondents ranged from 1.50 to 4.45 ng/ml, and the mean ± the SD was 2.56 ± 0.62 ng/ml.

Table 2 shows the PSA level (ng/ml) in diabetic patients according to age, BMI and smoking. The PSA level was significantly associated with age ($p < 0.05$). Regarding BMI,

there was no significant difference in mean PSA levels among the various BMI category groups ($p > 0.05$). With respect to smoking status, the PSA level of men was significantly higher in smoking patients (2.60±0.48 ng/ml) than in nonsmoking patients (2.45±0.65 ng/ml) ($p < 0.05$).

PSA level (ng/ml) in diabetic patients according to type and duration of diabetes is showed in Table 3. PSA levels were not significantly different based on the duration of DM or the type of diabetic treatment ($p > 0.05$).

3.4. The correlation between PSA levels and FBG levels

The correlation between PSA levels and FBG levels among the study population was determined using Pearson correlation tests. PSA levels were not significantly correlated with fasting blood glucose level ($r= -0.07$, $p = 0.379$).

4. Discussion

The study aimed to measure PSA levels among diabetic men who had not previously been diagnosed with prostate cancer. The findings suggested that PSA levels were significantly associated with age and smoking status, but not with BMI, the type of diabetic treatment, the duration of diabetes, or with FBG levels.

PSA has become the most useful serum tumor marker in addition to digital rectal examination (DRE) for the management of PCa (27). However, an examination of the characteristics of serum PSA levels in several populations could be of great support for clinicians, as it would help guide PCa screening practices and assess the response to therapy and tumor progression (28, 29). To our knowledge, this is the first study to estimate PSA levels among diabetic patients in our community. A cross-sectional study was conducted among diabetic patients older than 30 years of age in the city of Aden to assess PSA levels. Serum from 145 diabetic patients was collected after informed consent was obtained to examine total PSA levels by ELISA.

4.1. PSA levels

Serum PSA levels vary among individuals from different regions of the world; Asian men have lower levels than men of European descent and African Americans (30-32). The present study revealed that the mean PSA level was 2.5 ng/ml, which was higher than the mean reported among normal healthy Saudi men (1.24 ng/ml) (33), Iranian men (1.70 ng/ml) (34), Indian men (1.3 ng/ml) (31), Korean men (1.0 ng/ml) (35), Nigerian men (1.84 ng/ml) (36), Turkish men (1.56 ng/ml) (37), African-American men (2.1 ng/ml), and white American men (1.53 ng/ml) (38). These differences may be due to differences in the characteristics of the study population, the method of detection, and sample size. Our results were close to the values reported in Iraq (2.6 ng/ml) (39). Our results are lower than the finding in Egypt (3.5 ng/ml) (18). However, despite the growing awareness of the importance of PSA for early PCa diagnosis, reference values of serum PSA in Yemeni men have not yet been established. Therefore, Yemen should establish its own reference ranges because of the influence of environmental and genetic differences. On the Arab regional level, the mean PSA level in the current study is markedly higher than that reported in several studies among diabetic patients in Iraq (1.97 ng/ml) (39)and Morocco (1.31 ng/ml)(40). Our finding was close to the value of diabetic men in Egypt (2.3 ng/ml) (18).

Several studies found a lower serum PSA level among individuals with diabetes. A large population-based cohort study in Germany showed that severe forms of diabetes were related with lower PSA levels (22). In addition, a study showed that serum PSA levels were lower in patients with type 2 diabetes than in healthy men among Japanese males aged 40–79 years (21)). On the other hand, a study performed in Taiwan reported that the incidence of prostate cancer significantly increased with age in both diabetic and nondiabetic men (24). These differences may be attributed to environmental influences, changes in hormonal parameters (androgens, insulin, IGF-1, leptin, etc.), metabolic syndrome and genetic differences (41). Wallner and his colleagues assessed the associations between T2DM and changes in serum PSA levels, and suggested that Caucasian men with T2DM experienced smaller increases in serum PSA levels than those without diabetes (42).

4.2. PSA levels and age

It has been reported that PSA concentration is age-dependent and tends to increase with age because the prostate enlarges with age and contains more PSA-producing tissues (43). The current study revealed a significant association between age and serum PSA levels ($p<0.05$), and the PSA levels increased with age.

Our results are in line with those of previous reports which stated that the PSA level increased with age with a significant association (33),(34). It has been reported in Morocco that the PSA level increases with age in diabetic patients and is significantly lower in those aged 50-75 years (40). On the other hand, Cvitkoviae and colleagues reported that the values of PSA in diabetic subjects were less age-dependent than those in nondiabetic subjects, mainly among elderly patients. These variations could be attributed to the increase in prostate volume; the diminished capacity of the prostate to produce PSA; or, because of the prostate's decreased ability to preserve cell integrity, its increased permeability due to the breakdown of normal physiological barriers, thereby allowing PSA to leak into the general circulation (44-46).

Additionally, a study among diabetic men from Iraq showed

Table 1: Clinical characteristics of the study population (n=145)

Variables	No	%
Type of diabetic treatment		
Tablets	88	60.7
Injection	38	26.2
Both	11	7.6
No treatment	8	5.5
Duration of diabetes (years)		
1-10	96	66.2
11-20	39	26.9
21-30	10	6.9

Table 2: PSA level (ng/ml) in diabetic patients according to age, BMI and smoking

Variables	n	Mean ± SD	P-value	Test
Age (years)			0.000**	One-way Anova
30-39	26	1.85+0.31		
40-49	44	2.17+0.25		
50-59	49	3.02±0.33		
60-69	19	3.05±0.40		
70-79	7	3.18±0.62		
BMI (kg/m2)			0.600	One-way Anova
Normal	11	2.33±0.55		
Underweight	42	2.55±0.57		
Overweight	71	2.59±0.69		
Obese	21	2.60±0.51		
Smoking status			0.035*	T-test
Yes	34	3.04±0.42		
No	111	2.88±0.27		

*Significant $p < 0.05$; **Significant $p < 0.001$

that there was no significant association between serum PSA level and age (37, 39). Nonetheless, Oesterling proposed that the recommended age-specific reference ranges for healthy persons based on Olmsted County, Minnesota, data for serum PSA were 0–2.5 ng/ml, 0–3.5 ng/ml, 0–4.5 ng/ml, and 0–6.5 ng/ml for men aged 40–49, 50–59, 60–69, and 70–79 years, respectively (43). In addition, a previous study reported a higher age-specific PSA of 0.83, 1.23, 1.83, and 2.31 ng/ml, for African American men aged 40–49, 50–59, 60–69, and 70–79 years, respectively (30). For Saudi Arabia, men had PSA values of 0.87, 0.93, 1.17, 1.44, and 2.05 ng/ml, for those aged 30-40, 41-50, 51-60, 61-70, and ≥71 years, respectively (33). Our results indicated that the mean PSA level in our group of Yemeni diabetic patients was lower than the normal reference range, which is specific to healthy individuals in different geographical areas.

4.3. PSA levels and BMI

Our study indicated that there was no significant association between PSA levels and BMI. Our findings were consistent with those of some previous reports ((34), (14, 15, 47)). On the other hand, other studies reported that BMI was inversely related with PSA levels (48-50), indicating an inverse relationship between BMI and PSA levels, especially among 70- to 79-year-old Chinese men with a BMI >25.0. In addition, Price and his colleagues found that obesity (BMI >30) was associated with decreased PSA levels in a multiethnic cohort of participants (12). Kubota found an inverse but weak relationship between BMI and PSA levels in Japanese participants from a large cohort study based on health check-up data (51). They ascribed this variation in men with a higher BMI as being due to the larger plasma volumes, which could decrease serum concentrations of soluble tumor markers (23, 50). Another study found that obesity was possibly associated with a reduction in PSA levels (p=0.096) (22). A study reported that PSA levels were increased among men with a normal BMI, and there were no significant differences among BMI categories in diabetic patients (52). A study found that both the overweight and obese BMI groups showed lower predicted PSA levels than the comparison group (BMI<25); however, it has been reported that diabetes and overweight BMI were independently associated with lower PSA levels (48). Several epidemiological studies have suggested that obesity is associated with an increased risk for the development of

Table 3: PSA level (ng/ml) in diabetic patients according to type of treatment and duration of diabetes

Variables	PSA			Test
	n	Mean ± SD	P-value	
Type of diabetic treatment			0.194	One-way Anova
Tablets	88	3.05±0.42		
Injection	38	2.96±0.36		
Both	11	2.99±0.25		
No treatment	8	2.76±0.27		
Duration of DM (years)			0.098	One-way Anova
1-10	96	3.05±0.42		
11-20	39	2.93±34		
21-30	10	2.83±0.26		
Level of Glucose (mg/dl)				
Below 140 (normal)	28	2.64 ± 0.72	0.462	T-test
140 and more (not normal)	117	2.54 ± 0.59		

prostate cancer (52, 53). In contrast, other studies have been somewhat inconsistent, as some have suggested that there was an association between obesity and prostate cancer that may differ by tumor aggressiveness (54, 55), and others have stated a protective effect of obesity (56, 57). Therefore, this association remains controversial and may vary according to population characteristics and could be due to the small sample size or poor representations of study populations (58).

4.4. PSA levels and diabetes duration

In the current study, there was no statistically significant association between the duration of diabetes and PSA levels. Our finding agrees with that of Muller et al., who reported that PSA levels were not associated with the duration of diabetes (22). On the other hand, a study conducted in the USA found an inverse association between diabetes duration and PSA levels, and the predicted geometric mean PSA value was low in men who were diagnosed with diabetes for more than 10 years previously (48).

4.5. PSA levels and the type of diabetic treatment

The findings of the current study showed that there was no significant difference in PSA levels among diabetic patients receiving different types of diabetic treatment. Our findings seem to be in line with those of a previous report (23). Moreover, a cohort study reported that there was no evidence that antidiabetic medications were associated with lower PSA levels (59). In contrast, a study in Germany showed that PSA values were significantly reduced in men with insulin treatment (p=0.006) and oral diabetic medication (p=0.030) (22). However, diabetic men who took medication appeared to have lower PSA levels than diabetic men who did not take medication (48). Other studies have reported higher PSA concentrations among men using metformin (60, 61). Regarding insulin use, significant differences in post-medication PSA levels were detected for exposure within 6 months of PSA being measured (59). However, differences in findings may be due to variations in study design and comparison populations.

4.6. PSA levels and smoking status

The present study reported a significant association between smoking status and PSA levels. In accordance with our findings, Koc and colleagues reported that younger and older smokers displayed higher PSA levels than nonsmokers, although the difference was not statistically significant (62). In contrast, Gray and colleagues have reported no difference in PSA levels between smokers and nonsmokers (63). However, a study of PSA levels in men over the age of 55 found that PSA levels were significantly lower in smokers than in nonsmokers in men over 55 (15, 64). Moreover, Li and colleagues found significantly lower PSA levels in smokers than in nonsmokers in men over 40 (65). However, previous studies reported that the relationship between PSA levels and smoking is not yet clearly established (62).

4.7. PSA levels and FBG levels

The findings of this study suggested that there was no correlation between FBG levels and serum PSA levels. A study conducted by Mohammad et al. showed a negative relationship between serum PSA levels and FBG levels (66). In contrast, Cvitkovic et al. reported a negative relationship between FBG levels and serum PSA levels (44). Additionally, a study from Iran reported that there was no significant relationship between serum PSA levels and FBG levels (34). They attributed these variations to total testosterone levels in people with type 2 diabetes being lower than those in healthy people, and this differÂňence could be due to low levels of sex hormone binding globÂňulin (SHBG) (34, 67).

4.8. Study limitations

The main limitations of this study are due to financial constraints. This study did not include a large-scale population or a control group (healthy people), and it did not go further to include some important investigations, such as free PSA levels, the free/total PSA ratio, HbA1c levels, as well as androgen and testosterone levels. Additionally, a number of factors such as manipulations to measure prostate weight and volume might affect PSA levels. In addition, information on cycling and sexual intercourse was not revealed by the men who participated in the study. It is possible that men with underlying prostate disease could have been included in this study, although we excluded subjects with evident prostate disease. We did not consider types of oral diabetes medications in our analyses, although metformin and sulfonylurea are the most common medications used in Yemen for the treatment of diabetes. Another limitation was the lack of adjustment for other common medications, such as antihypertensives, 5α-reductase inhibitors, and lipid-lowering medications, which may potentially affect PSA levels.

5. Conclusion

The current study revealed that PSA levels were significantly associated with age and smoking status. No relaÂňtionship was observed between PSA levels and BMI, the type of diabetic treatment, or FBG levels. Therefore, special consideration should be warranted in the evaluation of PSA in elderly diabetic patients, and further investigation is needed when prostate cancer is suspected. PSA levels are affected by many factors that may be unrelated to diabetes, including age and smoking. Our results may help clinicians take these factors into account when setting the PSA cutoff value at screening. Further studies are needed to confirm our results and to explain the underlying variations.

6. Appendix

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6.2. Author contribution

All authors have equally contributed in the study, data analysis and writing the manuscript.

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None.

6.4. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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