

Association between body mass index and hemoglobin A1c with serum prostate-specific antigen level

A retrospective cohort study

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ABSTRACT

الأهداف: تقييم العلاقة بين مؤشر كتلة الجسم (BMI) والهيموجلوبين HbA1c ومستوى المستضد الخاص بالبروستاتا في الدم (PSA).

المنهجية: أجريت دراسة أترابية بأثر رجعي في مستشفى الملك فيصل التخصصي ومركز الأبحاث في الرياض، المملكة العربية السعودية، في الفترة من يناير 2016م إلى ديسمبر 2021م. جمعنا البيانات من السجلات الطبية للمرضى الذين زاروا عيادات طب الأسرة، بما في ذلك التركيبة السكانية والتدخين الحالية، وقيمة مؤشر كتلة الجسم، ومؤشر مستوى PSA، ومستوى التستوستيرون، ونتائج فحص المستقيم الرقمي، وحالة خزعة البروستاتا، وجلوكوز الدم الصائم (FBG)، ونسبة HbA1c، ومدّة مرض السكري، والأمراض المصاحبة المزمنة (أي ارتفاع ضغط الدم، أو اضطراب شحوم الدم، أو مرض الكلى المزمن)، وتاريخ الأدوية.

النتائج: كان متوسط مستوى PSA المستضد الخاص بالبروستاتا في الدم 1.89 ± 4.02 نانوغرام/ديسيلتر ومتوسط HbA1c كان $6.59 \pm 2.69\%$. وكان 41.8% من المشاركين يعانون من زيادة الوزن، و 54.3% غير مصابين بالسكري، و 85.3% غير مدخنين. خضع 11 مشاركًا فقط (1.6%) لخزعة البروستاتا بعد إجراء اختبار PSA. كان هناك ارتباط إيجابي بين مستوى PSA والعمر، وارتباط سلبي بين مستوى PSA ومؤشر كتلة الجسم، ولا يوجد ارتباط بين مستوى PSA و HbA1c أو FBG.

الخلاصة: كانت مستويات المستضد الخاص بالبروستاتا أعلى لدى كبار السن وأولئك الذين لديهم مؤشر كتلة الجسم منخفض. لم تظهر ارتباطات بين مستويات PSA و HbA1c أو FBG، حتى بعد ضبط المتغيرات الأخرى. علاوة على ذلك، لم يتم العثور على ارتباطات بين مستويات PSA والأمراض المصاحبة الأخرى مثل دسليبيديا وأمراض الكلى المزمنة وارتفاع ضغط الدم.

Objectives: To assess the association between body mass index (BMI) and hemoglobin A1c (HbA1c) with serum prostate-specific antigen (PSA) level.

Methods: A retrospective cohort study was carried out at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia, from January 2016 to December 2021. Data were collected from the medical records of patients who visited the family medicine clinics, including demographics, smoking status, BMI value, index PSA level, testosterone level, digital rectal exam findings, prostate biopsy status, fasting blood

glucose (FBG), HbA1c, diabetes duration, chronic comorbidities (namely, hypertension, dyslipidemia, or chronic kidney disease), and medication history.

Results: The mean PSA level was 1.89 ± 4.02 ng/dL and mean HbA1c was $6.59 \pm 2.69\%$. Of the participants, 41.8% were overweight, 54.3% were non-diabetics, and 85.3% were nonsmokers. Only 11 (1.6%) participants had undergone a prostate biopsy after taking a PSA test. There was a positive correlation between PSA level and age, a negative correlation between PSA level and BMI, and no correlation between PSA level and HbA1c or FBG.

Conclusion: Prostate-specific antigen levels were higher in older people and those with low BMIs. No correlations were found between PSA levels and HbA1c or FBG, even after adjusting for other variables. Moreover, no correlations were found between PSA levels and other comorbidities such as dyslipidemia, chronic kidney disease, and hypertension.

Keywords: prostate specific antigen, body mass index, diabetes, Saudi Arabia

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Prostate-specific antigen (PSA) level is usually initially used for prostate cancer screening.¹ According to the American Urology Association and the European Association of Urology, a prostate biopsy is warranted when PSA levels exceed 3–4 ng/dL.^{2,3} However, multiple factors, including age, catheterization, medications, acute prostatitis, and other comorbidities, affect PSA levels, limiting the validity of the test.⁴ Particular attention has been paid to the effect of obesity and diabetes on PSA level.

The relationship between obesity and PSA level remains controversial. Obese men have a larger plasma volume which might decrease serum concentration of the soluble tumor marker.⁵ Chia et al,⁶ Price et al,⁷ and Kubota et al⁸ found an inverse relationship between body mass index (BMI) and PSA. On the other hand, several studies showed no statically significant association between PSA and BMI.^{9–11}

A systematic review with compelling evidence concluded that there is an inverse relationship between diabetes and prostate cancer.¹² Another meta-analysis found that this inverse association was believed unlikely to affect prostate cancer screening.¹³ On the other hand, several studies have observed that diabetes increases the risk of more aggressive prostate cancer. An Asian meta-analysis found that having diabetes increases the incidence and risk of death from prostate cancer.¹⁴

Overall, the literature offers inconsistent findings on the relationship between PSA level and BMI or hemoglobin A1c (HbA1c). There have also been few local studies on this topic. Therefore, in a primary care setting at the family medicine clinic at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia, this study aimed to assess the association between BMI and HbA1c with serum PSA level.

Methods. A retrospective cohort study was carried out at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia, from January 2016 to December 2021. All adult patients aged 40 years and older who visited the family medicine clinic for PSA screening for prostate cancer were included in the study. Patients who had conditions that might affect PSA levels, such as cirrhotic liver disease or acute prostatitis, or who had already been diagnosed with prostate cancer were excluded from the study.

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Data recorded included demographic information (namely, age and nationality), BMI value, index PSA level (the first PSA reading), testosterone level, digital rectal exam findings, prostate biopsy status, fasting blood glucose (FBG), HbA1c, diabetes duration, and chronic comorbidities (namely, hypertension, dyslipidemia, and chronic kidney disease). Prostate-specific antigen levels of >4 ng/dL were considered abnormal. The American Diabetes Association's guidelines were used to determine the presence of prediabetes and diabetes.¹⁵ Fasting blood glucose and HbA1c results were included if they had been obtained within 3 months before or after the index PSA. If no data were available within 3 months, the reading obtained closest to the index PSA was used. Hypertension and dyslipidemia were defined according to the American Heart Association's guidelines and based on whether a patient was taking antihypertensive drugs or statins.^{16,17}

Medications likely to interact with the interpretation of PSA levels, including insulin, metformin, amlodipine, aspirin, warfarin, allopurinol, betamethasone, candesartan, statins, and diuretics, were collected to account for confounding factors.^{18,19}

Data were collected anonymously. Serial numbers and coding were utilized to ensure privacy and confidentiality. Ethical approval was received, and a waiver of informed consent was obtained from the Research Ethics Committee at King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia (RAC# 2221030).

Statistical analysis. Data was analyzed using the Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA). In descriptive statistics, percentages (%) and frequencies (n) were used to summarize categorical variables, and the mean \pm standard deviation (SD) was reported for continuous variables. The difference in the distribution between the categorical variables was tested through Chi-square tests. For analyzing the continuous variables, an independent T-test and ANOVA were used, as the main outcome of the study (PSA) was normally distributed. Pearson's correlation was used to test for collinearity between continuous variables. Linear regression was carried out to assess the role of different variables on PSA level. All statistical analyses were carried out at a *p*-value of 0.05 with a 95% confidence interval (CI).

Results. A total of 750 participants underwent both PSA and HbA1c tests and were included in this study. Their mean age was 61.36 \pm 10.82 years, and the majority of the participants (32.7%) were aged 50–59. The mean PSA level of the participants was 1.88 \pm 3.88 ng/dL,

and the mean HbA1c (within 6 months of the PSA reading) was $6.58 \pm 2.60\%$. Additionally, 69.2% of the participants were Saudi, 41.6% were overweight, and 83.0% were nonsmokers. Only 11 (1.6%) participants underwent a prostate biopsy after PSA testing. Additional descriptive statistics regarding the study sample are reported in [Table 1](#). Medications used among the participants are shown in [Figure 1](#).

No correlation was found between PSA level and HbA1c or FBG, as shown in [Table 2](#). However, the analysis showed that mean PSA levels were significantly higher among patients who were aged 80 years and older (3.41 ± 4.67 ng/dL) or underweight (9.74 ± 27.23 ng/dL; $p < 0.05$). The mean PSA level did not differ significantly among relevant comorbidities ([Table 3](#)) or medications

Table 1 - General characteristics of participants (N=750).

Variables	n (%)
Age, mean±SD	61.36±10.82
<40	2 (0.3)
40-49	95 (12.7)
50-59	245 (32.7)
60-69	238 (31.7)
70-79	126 (16.8)
≥80	44 (5.9)
PSA, mean±SD	1.88±3.88
HgA1c, mean±SD	6.58±2.60
FBG, mean±SD	6.90±2.63
BMI	
Underweight	11 (1.5)
Normal weight	127 (17.6)
Overweight	300 (41.6)
Obese	283 (39.3)
Smoking	
Yes	111 (15.8)
No	584 (83.0)
Prostate biopsy	
Yes	15 (2.0)
No	734 (98.0)
Diabetes	
Yes	349 (46.7)
No	398 (53.3)
Dyslipidemia	
Yes	390 (52.6)
No	351 (47.4)
Chronic kidney disease	
Yes	40 (5.4)
No	701 (94.6)
Hypertension	
Yes	331 (44.5)
No	412 (55.5)

Values are presented as numbers and percentages (%).
 SD: standard deviation, PSA: prostate-specific antigen,
 HgA1c: hemoglobin A1c, FBG: fasting blood glucose,
 BMI: body mass index

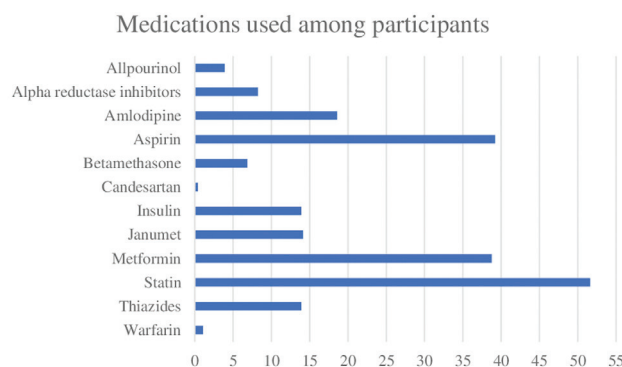


Figure 1 - Frequency of medications used among participants.

used ($p > 0.05$). Linear regression results were not reported because no significant association was found between PSA level and HbA1c, even after adjusting for all included variables.

Discussion. In this study, the association between BMI, HbA1c, and PSA level, was investigated. Prostate-specific antigen level is correlated with age and as age increases, PSA level also becomes higher.²⁰ This relationship can be explained by the fact that there is age related increase in the prevalence of benign prostatic enlargement.²¹ Our study found that the mean PSA level increased with age (3.41 ± 4.67 ng/dL), especially in those aged 80 years and older. Obesity increases intravascular volume, which dilutes the amount of PSA in the body. However, it is not clear whether this effect should be adjusted when determining PSA level.²² We found that those with a lower BMI had a higher mean PSA level (9.74 ± 27.23 ng/dL; $p < 0.05$). This finding is in line with that of another study, BMI was found to be inversely associated with PSA level; that is, participants whose BMI was >27 had lower PSA levels than those whose BMI was <27 .²³

Prostate epithelial cells produce PSA in response to androgens which play an important role in prostate tumorigenesis. Diabetic men tend to have low androgens concentration.²⁴ Our study revealed no correlation or significant association between HbA1c, FBG, and PSA level, even after adjusting for other variables. Similarly, a Moroccan study found that PSA levels were similar between diabetics and non-diabetics.²⁵ However, a study carried out in Japan found that PSA levels were lower among diabetics after adjusting for the ages of the study's participants.²⁶ Similarly, another study carried out in Germany found that PSA levels were lower in those with high HbA1c results.²⁷ This positive correlation might be explained by the fact that the

Table 2 - Mean prostate-specific antigen levels among different subgroups.

Variables	Mean±SD	P-values
Age		
<40	1.03±0.60	0.001
40-49	1.05±1.04	
50-59	1.31±1.27	
60-69	1.94±1.92	
70-79	2.99±8.29	
≥80	3.41±4.67	
BMI		
Underweight	9.74±27.23	0.001
Normal weight	2.07±2.47	
Overweight	1.70±2.11	
Obese	1.68±1.84	
Smoking		
Yes	1.79±2.76	0.742
No	1.93±4.21	
Prostate biopsy		
Yes	4.07±2.71	0.027
No	1.83±3.89	
Diabetes		
Yes	1.73±1.94	0.327
No	2.01±5.01	
Dyslipidemia		
Yes	1.77±2.01	0.739
No	2.01±5.26	
Chronic kidney disease		
Yes	3.20±4.66	0.07
No	1.81±3.85	
Hypertension		
Yes	1.99±2.42	0.49
No	1.79±4.77	

Values are presented as mean ± standard deviation (SD).
BMI: body mass index

prevalence of diabetes among the participants was low unlike our study in which the diabetic subjects were 46.7%.^{28,29}

This study found that PSA level is not correlated with other comorbidities (namely, dyslipidemia, chronic kidney disease, and hypertension). A study carried out in the United States of America found that serum triglycerides are negatively correlated with serum PSA levels in those diagnosed with prostate cancer.³⁰ Another prior study showed that patients with chronic kidney disease had higher PSA levels than those in the control group.³¹ Like our study, one study found that hypertension was not correlated with PSA.²⁶ As presented in **Figure 1**, we found that the medication used by the participants was not correlated with PSA levels. However, Müller et al²⁷ found that PSA levels were lower in those using oral antidiabetic medications and insulin. Another study concluded that, although statins are associated with lower PSA levels, their

Table 3 - Correlation between prostate-specific antigen level, hemoglobin A1c, and fasting blood glucose.

Protein	Correlation	HbA1c	FBG
PSA	r	0.04	0.04
	p	0.30	0.34

PSA: prostate-specific antigen, HgA1c: hemoglobin A1c, FBG: fasting blood glucose

presence should not affect screening interpretation.³² Similarly, Chang et al¹⁹ found that both statins and thiazide diuretics lower PSA level. Finally, a prospective study found that aspirin use is associated with lower PSA levels and cancer risk.³³

Study strengths & limitations. A key strength of this study is that it is a population-based study. In addition, only few local studies have examined the association between PSA level, HbA1c, or BMI. Moreover, most of the potential confounding factors that might have an impact on PSA levels such as other chronic medical conditions and medications were addressed. On the other hand, those subjects who might have early prostate cancer but were missed due to low serum PSA level were not fully excluded through prostate biopsy which could be a limitation in our study. Another potential limitation is the lack of precise data regarding diabetes such as diabetes duration, treatment duration, and level of adherence and control, which might also affect PSA values.

In conclusion, PSA levels were higher in older people and those with low BMIs. Modified PSA thresholds for obese men and considering BMI readings while interpreting age-specific PSA levels is therefore recommended. No correlations were found between PSA levels and HbA1c or FBG, even after adjusting for other variables. Future local studies with a larger sample size and detailed information on diabetes duration and management is recommended. Moreover, no correlations were found between PSA levels and other comorbidities such as dyslipidemia, chronic kidney disease, and hypertension.

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