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Assessment of Prostate-Related Biomarkers in Individuals with Metabolic Syndrome and Obesity: A Single-Center Study

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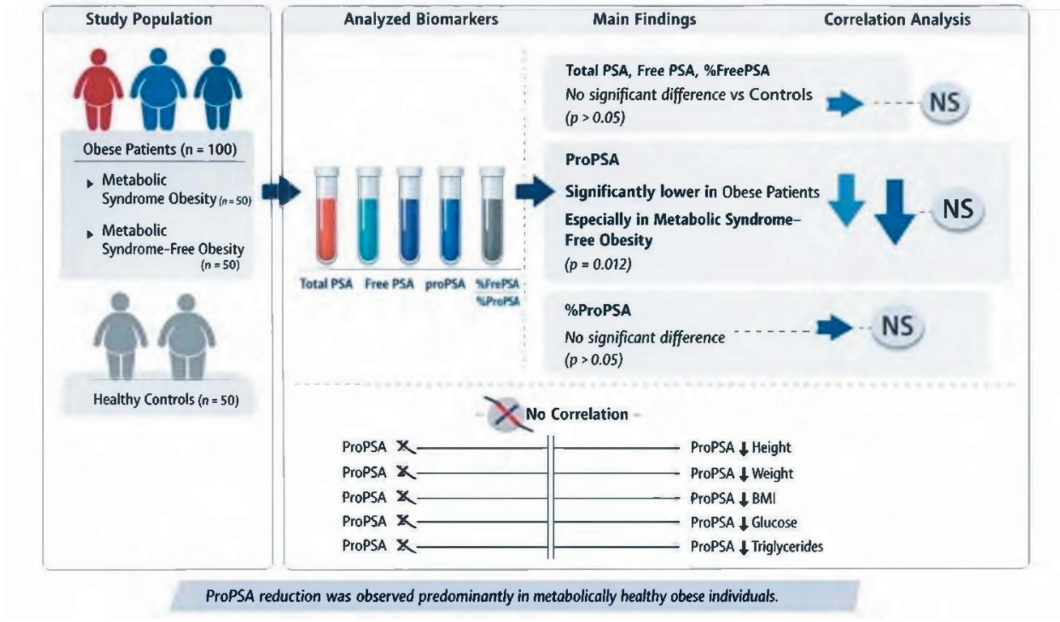
GRAPHICAL ABSTRACT



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ABSTRACT

Aim: The prevalence of obesity and metabolic syndrome is rapidly increasing worldwide. This study aimed to investigate the changes prostate-specific antigen (PSA) and its derivatives, commonly used as biomarkers in prostate cancer screening in individuals with obesity and metabolic syndrome.

Material and Methods: The study included 100 patients diagnosed with obesity at the Endocrinology Clinic of Zonguldak Bulent Ecevit Hospital between May 2023 and April 2024, along with 50 healthy volunteers. The patients were divided into 2 groups: metabolic syndrome obesity and metabolic syndrome-free obesity. NCEP-ATP III metabolic syndrome diagnostic criteria were used to assess

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whether they were metabolically healthy. According to these criteria, patients who meet any three of the five criteria are considered to have metabolic syndrome obesity; individuals who did not meet these criteria were evaluated in the metabolic syndrome-free obesity category. PSA, free PSA and proPSA levels were analyzed, %freePSA and %proPSA values were calculated. Group comparisons were performed using the Kruskal–Wallis test, and correlations were assessed using Spearman's rank correlation analysis.

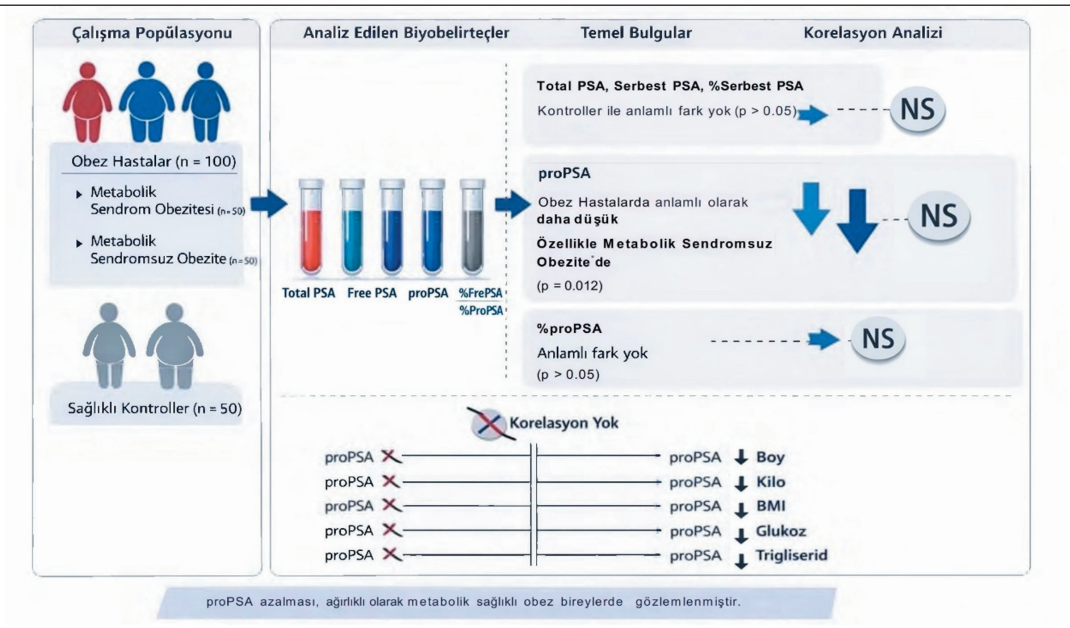
Results: Total PSA, free PSA and %freePSA levels were not difference in patients with obesity compared to the control group (p>0.05). ProPSA levels were significantly lower in patients with obesity, especially metabolic syndrome-free obesity (p=0.012), but no difference was observed in %proPSA levels (p>0.05). No correlation was observed between ProPSA and height, weight, BMI, fasting blood glucose, triglyceride and HDL-cholesterole levels.

Conclusion: The lack of change in %ProPSA despite lower ProPSA concentrations suggests that the decrease in ProPSA may be a proportional response to the reduction in total PSA observed in individuals with obesity. This study provides novel evidence on the effect of obesity and metabolic phenotype on ProPSA levels in prostate-healthy individuals, a population that has been underrepresented in previous PSA-related research.

Keywords: *Obesity, Metabolic syndrome, Prostate specific antigen and its derivatives*

Metabolik Sendrom ve Obezite Varlığında Prostat ile İlgili Belirteçlerin İncelenmesi: Tek Merkez Sonuçları

GRAFİKSEL ÖZET



Türkiye Diyabet ve Obezite Dergisi

Ismail Benice, Berrak Güven, Murat Can, A. Görkem Mungan, Taner Bayraktaroğlu

Benice İ ve ark. Metabolik Sendrom ve Obezite Varlığında ... Turk J Diab Obes 2026;10(1).

ÖZ

Amaç: Obezitenin ve metabolik sendromun prevalansı, dünya genelinde hızla yükselmektedir. Bu çalışmada obezite ve metabolik sendromu olan kişilerde prostat kanseri taramasında bir belirteç olarak kullanılan prostat spesifik antijen (PSA) ve türevlerinin nasıl değiştiğini incelemeyi amaçladık.

Gereç ve Yöntemler: Araştırmaya Mayıs 2023 – Nisan 2024 tarihleri arasında Zonguldak Bülent Ecevit Hastanesi Endokrinoloji polikliniğinde obezite tanısı alan ve çalışma kriterlerini karşılayan 100 hasta ve 50 sağlıklı gönüllü dahil edildi. Hastalar metabolik sendromlu obezite ve metabolik sendromsuz obezite olmak üzere 2 gruba ayrıldı. Metabolik olarak sağlıklı olup olmadıklarını değerlendirmek amacıyla NCEP-ATP III metabolik sendrom tanı kriterleri kullanıldı. Bu kriterlere göre, beş kriterden herhangi üçünü karşılayan hastalar metabolik sendromlu obezite olarak kabul edilirken; bu kriterleri karşılamayan bireyler metabolik sendromsuz obezite kategorisinde değerlendirildi. Çalışma gruplarında PSA, freePSA ve proPSA düzeyleri bakılırken, %freePSA ve %proPSA düzeyleri hesaplandı.

Bulgular: Obeziteli yaşayan hastaların total PSA, serbest PSA ve % free PSA düzeyleri kontrol grubundan farklı değildi (p>0.05). ProPSA düzeyleri obeziteli hastalarda, özellikle metabolik sendromsuz obezite hastalarında anlamlı derecede düşüktü (p=0.012), ancak %proPSA düzeylerinde herhangi bir fark gözlemlenmedi (p>0.05). ProPSA ile boy, vücut ağırlığı, VKİ, açlık kan şekeri, trigliserid ve HDL düzeyleri arasında bir korelasyon gözlenmedi.

Sonuç: Daha düşük ProPSA konsantrasyonlarına rağmen %ProPSA'da değişiklik olmaması, ProPSA'daki azalmanın obeziteli hastalarda gözlenen toplam PSA'daki azalmaya orantılı bir yanıt olabileceğini düşündürmektedir. Ayrıca metabolik parametreler obezite ile ProPSA düzeyleri arasındaki ilişkiye katkıda bulunmamıştır. Bu özel popülasyonda ProPSA'nın tanısal faydasını ve klinik etkilerini değerlendirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: *Obezite, Metabolik sendrom, Prostat spesifik antijen ve türevleri*

INTRODUCTION

Obesity is a major health problem that can negatively affect men's quality of life and overall health (1). According to the data of the National Health and Nutrition Examination Survey (NHANES) published in the United States in 2017, 39.6% of the society lives with obesity , while this rate is 37.9% in men (2). Studies have shown that men are less likely than women to consider body weight and weight as a health risk (3,4). Obesity is considered an important factor in the development of various men health problems such as benign prostatic hyperplasia, lower urinary tract symptoms, erectile dysfunction, hypogonadism, infertility and prostate cancer (1). Prostate cancer is is the most commonly diagnosed cancer in men (5)and the fifth most common cause of cancer death (6). Obesity-related inflammation, hormonal changes caused by obesity, and insulin resistance may increase the risk of prostate gland enlargement and cancer (1,7,8). In this context, several studies have distinguished between metabolically active (or unhealthy) and metabolically inactive (or healthy) forms of obesity, highlighting that the contribution of obesity to prostate cancer risk may vary depending on its metabolic profile (9,10). Therefore, early diagnosis and management of obesity is vital in the prevention and treatment of men's health problems.

Prostate-specific antigen (PSA) is the most commonly used blood test for prostate cancer screening (11,12). In recent years, additional PSA-derived tests such as free PSA, proPSA and its derivatives have gained popularity to increase accuracy due to low specificity for cancer (13,14). The [-2] form of proPSA ([-2]proPSA) is used to calculate prostate health index (PHI), which is used to estimate cancer risk in risk groups. Thus, scientific studies investigating the relationship between obesity and these derivatives have attracted considerable attention. Although several studies have investigated the effect of obesity on total PSA levels (15,16), the impact of obesity and metabolic phenotype on ProPSA in prostate-healthy individuals remains largely unexplored. Most previous research has focused on patients with suspected or confirmed prostate cancer, limiting the understanding of PSA-derived biomarkers in non-cancer populations. Therefore, the present study aims to evaluate ProPSA, total PSA, and free PSA levels in individuals with obesity stratified by metabolic status and to compare them with healthy controls, thereby addressing an underexplored aspect of obesity-related alterations in prostate biomarkers.

MATERIAL and METHODS

Subjects

Our study included male individuals diagnosed with obesity at the Zonguldak Bülent Ecevit University Hospital Endocrinology Clinic. Participants were between 40 and 60 years old and had normal PSA test results (PSA < 4 ng/mL) within the last six months. Our study was approved by our institution's Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients' body mass index (BMI) >30 kg/m2 was used as a criterion for obesity. During the participants' examinations, height, weight, waist circumference and systolic blood pressure (SBP) and diastolic blood pressure (DBP) data were recorded. The obesity group was designed to consist of 2 groups: those who meet the criteria for metabolic syndrome and those who do not have metabolic syndrome. For the metabolically healthy criterion, NCEP-ATP III metabolic syndrome diagnostic criteria were used. The diagnosis of metabolic syndrome was based on meeting three of the following five criteria: (i) Waist circumference >102 cm; (ii) Fasting blood glucose (FBG) ≥100 mg/dl or previously diagnosed with diabetes; (iii) Fasting triglycerides (TG) ≥150 mg/ dL or receiving antilipemic treatment; (iv) High density lipoprotein-cholesterol (HDL-C)< 40 mg/ dL (in men); and (v) high blood pressure (SBP ≥130 mm Hg, DBP ≥85 mm Hg or previously diagnosed hypertension or receiving antihypertensive treatment). Healthy male individuals of the same age group who were metabolically healthy and without obesity were used as the control group. For all participants, having a urological complaint, a history of prostate disease in the patient file, acute infection, heart, liver and kidney disease, and a history of cancer were used as exclusion criteria from the study.

Sampling and Analysis

Blood samples taken for routine biochemical metabolic parameters from the patient and control groups participating in the study were subjected to separation by centrifuging at 4000 rpm for 10 minutes within 2 hours. The obtained serum was aliquoted into 2 ml Eppendorf tubes and stored at -80 C until the study was performed. Serum levels of PSA and fPSA were analyzed using DXI800 Access immunoassay system (Beckman Coulter Inc. USA). Metabolic parameters such as fasting blood glucose, triglycerides, and HDL performed using an AU5800 clinical chemistry system (Beckman Coulter, Inc USA).). The obtained serum ProPSA levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations (Atlas Biotech. Türkiye). %freePSA and %proPSA values were calculated from the studied tests *(% freePSA =100* freePSA /PSA, % proPSA = 100* proPSA / freePSA).*

Statistical Analysis

Sample size estimation was performed using G*Power version 3.1.9.4 (Franz Faul, Kiel University, Germany). Assuming a moderate effect size (f = 0.25) and an alpha level of 0.05, the available sample size of 150 participants provided approximately 80% power for detecting between-group differences across three groups. Total PSA, free PSA and ProPSA were compared between the groups and their relationships were statistically performed by 'SPSS 19.0' (SPSS Inc., Chicago, IL, USA). The conformity of numerical variables to normal distribution was examined using the Shapiro-Wilk test Kruskal–Wallis variance analysis was used to compare the study groups. When a statistically significant difference was detected, pairwise group comparisons were performed using Dunn's post-hoc test to identify the source of the difference. The linear relationship between two numerical variables was examined with Spearman correlation analysis. For all evaluations, p<0.05 was considered significant.

RESULTS

A total of 100 male patients with obesity (50 metabolic syndrome obesity, 50 metabolic syndrome-free obesity) and 50 healthy male volunteers without obesity as a control group were evaluated in this study. The obesity group was designed to consist of 2 groups: those who met the criteria for metabolic syndrome and those who did not have metabolic syndrome. There was no difference between the study groups in terms of age and height. The body weight and BMI of the control group were significantly lower than those of the obesity groups (p<0.001). Fasting blood glucose and triglyceride levels of the obesity group with metabolic syndrome were significantly higher than the other groups (p<0.001), while HDL cholesterol levels were significantly lower (p<0.001). The comparison of demographic characteristics and biochemical results of obesity patients with/without metabolic syndrome and the control group is presented in Table 1.

When the compare of prostate biomarkers all patients with obesity, the serum PSA median value of the obesity group was determined as 0.64 (0.21-2.47), while this value was found to be 0.735 (0.22-3.35) in the control group. Serum freePSA median value of the obesity group was 0.175 (0.05-0.94) in the obesity group, while it was 0.195 (0.06-0.87) in the control group. Serum %freePSA median value of the obesity group was 25 (11.3-69.0), while it was 26.5 (4.5-57.1) in the control group. No significant difference was found between the study groups in terms of PSA, freePSA and %freePSA levels (p>0.05). However, the median serum proPSA value of the obesity group was 4.62 (1.33-32.48), while it was measured as 5.67 (1.33-17.06) in the control group, and compared to the control group, the serum proPSA levels of the patients with obesity were significantly lower (p=0.032). However, serum %proPSA median value of the obesity group was 2,43 (0.49-24.98), while it was 2.85 (0.66-20.67) in the control group, and decrease of proPSA

Table 1: Demographic characteristics and biochemical findings of obesity subgroups and control group

Characteristics	Metabolic syndrome obesity (n=50)	Metabolic syndrome-free obesity (n=50)	Control (n=50)	*p* value
Age (years)	50.0 (40-59)	48.0 (40-60)	48.0 (40-60)	0.215
Weight (kg)	104.4 (81.5-149.4)	99.0 (50-154.7)	78.65 (59.5-99.1)	**<0.001**
Height (cm)	172 (159-183)	172 (121-186)	174 (160-189)	0.333
BMI (kg/m^2)	34.4 (30.1-53.6)	33.2 (30-47.2)	26.0 (20.3-28.4)	**<0.001**
FBG (mg/dL)	111 (86-366)	97 (80-121)	98 (83-147)	**<0.001**
TG (mg/dL)	212 (74-882)	114 (59-294)	102 (35-314)	**<0.001**
HDL-c (mg/dL)	37 (23-75)	46 (34-72)	49 (34-69)	**<0.001**

Descriptive data in the table are given as mean /median and min-max . **BMI,** body mass index; **FBG,** fasting blood glucose; **TG,** triglicerides; **HDL-c,** high-density lipoprotein cholesterole.

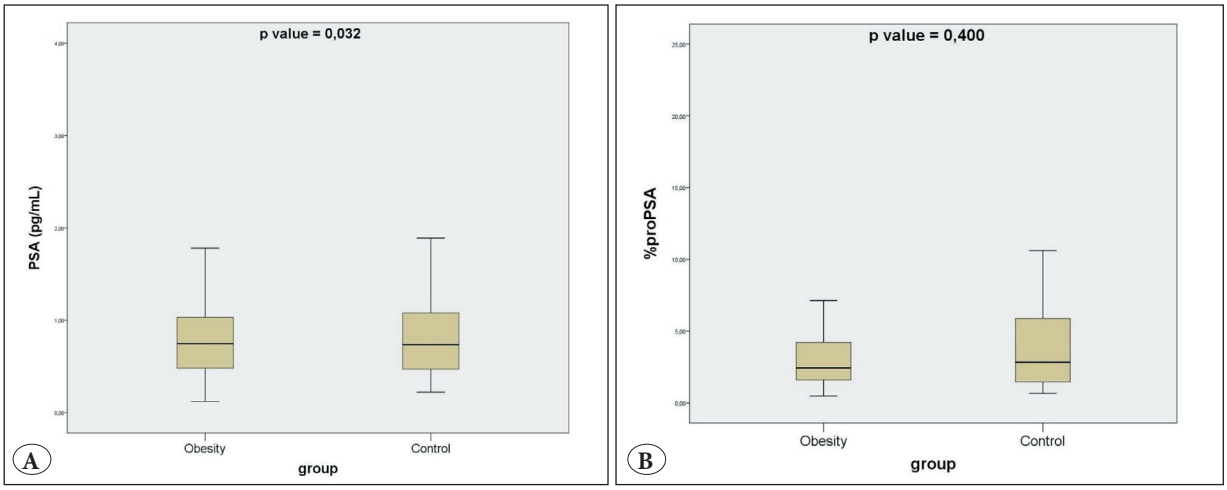


Figure 1: Comparison of ProPSA **(A)** and % proPSA **(B)** levels between patients with obesity and the control group.

Table 2: Comparison of PSA-related biomarkers of the study groups

	Metabolic Syndrome obesity (n=50)	Metabolic syndrome-free obesity (n=50)	Control (n=50)	*p* value
PSA (ng/mL)	0.610 (0.21-3.92)	0.845 (0.21-3.87)	0.735 (0.22-3.35)	0.193
freePSA (ng/mL)	0.170 (0.07-0.94)	0.180 (0.05-0.52)	0.195 (0.06-0.87)	0.725
% freePSA	26.96 (14.17-69.05)	21.56 (11.32-46.43)	26.82 (14.29-57.14)	0.136
ProPSA (ng/L)	4.98 (2.5-32.48)	4.51 (1.33-14.0)	5.67 (1.33-17.06)	**0.012**
% proPSA	3.51 (0.49-12.48)	3.17 (0.51-11.9)	4.17 (0.66-20.67)	0.353

Descriptive data in the table are given as median and min-max . p value derived from Kruskal–Wallis test. Post-hoc pairwise comparisons were performed using Dunn's test when applicable.

levels did not create a significant difference in %proPSA levels (p=0.400). Comparison of ProPSA and % proPSA of all patients with obesity and the control group is presented in Figure 1. Also, we presented median and min-max values and statistical evaluation of PSA-related tests in metabolic syndrome obesity, metabolic syndrome-free obesity and control groups in Table 2. Although no significant differences were observed among the study groups with respect to total PSA and free PSA levels, ProPSA levels differed significantly across the three groups (Kruskal–Wallis test, p = 0.012). Post-hoc pairwise comparisons using Dunn's test demonstrated that this difference was primarily driven by significantly lower ProPSA levels in the metabolically healthy obesity group compared with the control group (adjusted p = 0.012).

Correlation analysis was applied between PSA, free PSA and ProPSA levels and metabolic parameters of the study groups and the data related to the analysis are presented in Table 3. No correlation was observed between ProPSA levels and fasting blood glucose, Triglyceride, HDL-cholesterol and BMI (p>0.05).

Table 3: Correlation analysis of PSA, free PSA, and ProPSA with anthropometric and metabolic parameters in the entire study population

Correlation analysis	Findings (n=100)	
	r values	*p* values
PSA- Height	0.019	0.937
PSA- Weight	-0.67	0.403
PSA-BMI	-0.59	0.457
PSA- Fasting blood glucose	-0.130	0.100
PSA- Triglyceride	-0.102	0.201
PSA- HDL	0.129	0.104
FreePSA - Height	0.006	0.937
FreePSA - Weight	-0.106	0.182
FreePSA - BMI	-0.101	0.203
FreePSA - Fasting blood glucose	-0.88	0.269
FreePSA - Triglyceride	-0.67	0.399
FreePSA -HDL	0.047	0.554
ProPSA - Height	-0.017	0.832
ProPSA - Weight	-0.110	0.169
ProPSA - BMI	-0.130	0.104
ProPSA - Fasting blood glucose	0.106	0.184
ProPSA - Triglyceride	0.002	0.983
ProPSA - HDL	-0.42	0.604

DISCUSSION

Prostate-specific antigen (PSA) is one of the tumor markers used in the diagnosis and post-treatment monitoring of prostate cancer (17). However, it has low specificity in detecting the presence of cancer (18), therefore, more accurate biomarkers are needed to increase the ability to detect prostate cancer and to reduce the number of unnecessary biopsies. Free PSA isoforms in particular are attracting attention as diagnostic and risk markers.

We observed that the median values of total PSA and free PSA in the entire obesity group were lower than the control group, but the difference between the groups was not statistically significant. Many studies have demonstrated that serum PSA levels tend to be lower in individuals with obesity than in normal-weight individuals. This tendency may cause screening and prostate cancer diagnosis to be missed in individuals with obesity, negatively affecting the overall performance of the test. For example, Baillargeon et al. found that PSA levels were lower in paitents with obesity and overweight men without prostate carcinoma in their study (19). Fowke et al. reported that both PSA and free PSA decreased with increasing BMI in patients under 60 years of age (20). Bañez et al. suggested that this decrease in PSA was due to increased blood volume and PSA hemodilution in individuals with obesity (21). However, some studies have found that PSA levels were not affected. Thompson et al reported that BMI data from 1565 men in their study had no effect on PSA (22). Similarly, Capitanio et al. observed that BMI had no effect on PSA and %freePSA in men without known prostate cancer. The researchers concluded that the relationships between BMI and various prostate cancer characteristics may differ from one population to another (23). Sanchis-Bonet et al. investigated the accuracy of PSA compared with BMI in detecting prostate cancer in spanish men with a first indication for prostate biopsy. In the study, PSA levels did not differ between BMI groups (24). In a prospective multicenter study of patients with localized prostate cancer published in 2021 by Meunier et al., they reported that there was no significant relationship between BMI, weight, waist circumference or fat percentage and PSA concentration (25). Our results showed that BMI has no effect on both total and free PSA.

ProPSA is one of the inactive PSA derivatives that constitute free PSA and was identified in the serum of prostate cancer patients (26). Studies on derivative tools such as ProPSA and %proPSA generally aim to demonstrate the effectiveness and accuracy of the tests in cancer detection (27,28). Khan et al., in their study on men with total PSA between 4 and 10 ng/mL to avoid unnecessary biopsies, suggested that the combination of PSA, %freePSA and ProPSA increased specificity in detecting early prostate cancer compared to measuring each PSA form separately (13). Sokoll et al., on the other hand, investigated the clinical benefit of using proPSA in the early diagnosis of prostate cancer in PSA levels between 2.5 and 4.0 ng/mL. They suggested that 75% of cancers could be detected and 59% of unnecessary biopsies could be prevented by using %proPSA in PSA levels between 2.5 and 4.0 ng/mL (29).

In recent years, studies evaluating the performance of PSA-derived tests in predicting prostate cancer in individuals with obesity have drawn attention. For example, Zhu et al. found in their study that prostate cancer-related tumor markers (total PSA, free PSA/total PSA ratio (freePSA/PSA), proPSA, %proPSA and PHI) had lower predictive value in individuals with obesity compared to normal weight individuals in patients with PSA levels of 2-10 ng/mL. In the same study, there was no statistically significant difference between individuals with obesity and normal individuals in terms of total PSA, free-total PSA ratio, [-2]proPSA, %[-2] proPSA, and PHI values (30). Abrate et al. reported that %proPSA and PHI values were significantly more accurate than PSA, free PSA and %freePSA in determining the presence of prostate cancer in patients with obesity referred for biopsy with suspicion of prostate cancer. In the same study, they found significant differences in terms of PSA and PHI between obesity, overweight, and normal patient groups. However, there was no difference between the groups in terms of free PSA, %freePSA, proPSA and %proPSA (31). Most of these studies were designed to evaluate the diagnostic performance of the tests in patients with cancer and/or in cases where the PSA level was in the diagnostic gray zone (in patients with PSA levels between 4-10 ng/mL) (15,30,32–34). There are limited studies on healthy individuals with obesity who have total PSA levels below 4 ng/mL. In this context, our study is the first to examine the relationship between obesity and proPSA in prostate-healthy individuals and the contribution of metabolic parameters to this relationship. We found that ProPSA levels were significantly lower in patients with obesity compared to individuals without obesity. When ProPSA levels in patients with obesity were evaluated according to the presence of metabolic syndrome, ProPSA levels were found to be significantly lower only in metabolic syndrome-free patients with obesity. However, this difference did not create a difference that would affect the %ProPSA evaluation between the obesity groups and the control group. Additionally, no association was observed between metabolic parameters and ProPSA levels. Correlation coefficients were weak and did not indicate clinically meaningful associations, suggest-

ing that metabolic parameters are unlikely to have a strong linear relationship with ProPSA levels in this population. This finding suggests that the relationship between obesity and PSA-derived biomarkers may not be uniform across different metabolic phenotypes. Rather than obesity alone, the underlying metabolic profile may play a role in modulating ProPSA levels.

This study has several limitations that should be acknowledged. First, its single-center design may limit the generalizability of the findings to broader populations. Second, the relatively modest sample size and the exploratory nature of the study may have reduced the ability to detect smaller between-group differences. In addition, potential confounding factors such as smoking status, medication use, and hormonal parameters were not systematically available in the study records and therefore could not be included in statistical adjustments. Multivariable regression analysis was not performed in line with the exploratory design of the study. Furthermore, ProPSA measurements were performed using an ELISA-based assay rather than standardized [-2]proPSA methods, which may limit direct comparability with studies using prostate health index–based approaches. Finally, although participants had no known prostate disease and PSA levels were below 4 ng/mL, the absence of prostate cancer was not confirmed by histopathological evaluation; therefore, the presence of undetected subclinical prostate cancer cannot be completely excluded.

In this study, we examined the possible effects of obesity on PSA and its derivatives in healthy individuals with PSA levels below 4 ng/mL. As a result of our study, although a decrease in total PSA and free PSA levels was observed in patients with obesity compared to the control group, this decrease was not statistically significant. However, this minimal decrease may have caused a significant decrease in ProPSA levels relatively. The lack of a significant change in %ProPSA values with obesity supports the fact that this decrease is proportional. Importantly, the lack of a similar reduction in the metabolic syndrome obesity group highlights the heterogeneity of obesity and underscores the relevance of metabolic phenotype when interpreting PSA-derived biomarkers. Given the exploratory nature of the study and the limited number of predefined comparisons, no formal adjustment for multiple testing was applied; therefore, the results should be interpreted with appropriate caution. Further studies are needed to compare the levels for proPSA marker in subjects with obesity and in healthy subjects.

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Author's Contributions
Conception and Design: **İsmail Benice, Berrak Güven,** Materials, Data Collection or Processing: **İsmail Benice, Berrak Güven, Murat Can, Ayça Gorkem Mungan, Taner Bayraktaroğlu,** Analysis or Interpretation: **İsmail Benice, Berrak Güven,** Literature Search: **İsmail Benice, Berrak Guven,** Writing: **İsmail Benice, Berrak Güven,** Critical Review: **Berrak Güven, Murat Can, Ayça Gorkem Mungan, Taner Bayraktaroğlu.**

Conflict of Interest
All authors have declared no conflicts of interest.

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Ethics Committee Approval
The research protocol received approval from the Ethics Committee on Clinical Research at Zonguldak Bülent Ecevit University, Faculty of Medicine with approval granted on September 03, 2023 (approval number: 23-09).

Peer Review Process
Extremely and externally peer-reviewed.

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