Research Article

Salivary Biomarkers for Prostate Cancer: A Case-Control Study of PSA and S100P in Iranian Men

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ABSTRACT

Objectives: Early detection of prostate disease is crucial, yet current diagnostic methods have limitations. The S100P protein and saliva sampling present potential non-invasive diagnostic options. This study aimed to evaluate S100P and PSA as biomarkers for prostate cancer (PC) and to differentiate PC from benign prostatic hyperplasia (BPH). Additionally, it examined the suitability of saliva as a diagnostic medium for prostate disease.

Methods: This case-control study included 100 Iranian men aged 50 to 65 years, divided into two groups: 50 men with PC and 50 men with BPH. Serum and saliva samples were collected from each participant after obtaining informed consent. Serum and salivary PSA and S100P levels were measured using ELISA kits. The Mann–Whitney U test, Spearman's correlation coefficients, and receiver operating characteristic (ROC) analysis were applied to evaluate the data.

Results: Salivary and serum PSA and S100P levels were significantly higher in men with PC than in those with BPH ($P < 0.001$). A strong positive correlation was observed between serum and salivary levels of both biomarkers in both groups ($P < 0.001$). ROC curve analysis indicated that salivary PSA and S100P levels could effectively distinguish PC from BPH.

Conclusion: Salivary PSA and S100P show promise as non-invasive biomarkers for PC detection and differentiation from BPH. Further research with larger cohorts is needed to validate these findings and confirm the clinical utility of salivary PSA and S100P in PC and BPH diagnosis and management.

Keywords: Prostate cancer, benign prostatic hyperplasia, S100P, Saliva

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Introduction

Prostate cancer (PC) is a significant global health concern, ranking as the second most common cancer in men. In the United States alone, an estimated 288,300 new cases and 34,700 deaths occurred in 2023 (1). While PC can be life-threatening, most men diagnosed with it do not die from it. The 5-year relative survival rate for localized prostate cancer is nearly 100%, but it drops to 31% for metastatic cases (2). Treatment options vary depending on disease stage and risk, including active surveillance, surgery, radiation therapy, hormone therapy, chemotherapy, and immunotherapy. Early detection is critical for successful treatment and improved survival rates (3).

Current diagnostic methods, such as the digital rectal exam (DRE), prostate-specific antigen (PSA) testing, and biopsy, have limitations that may lead to overdiagnosis and overtreatment (4). Benign prostatic hyperplasia (BPH) is another common condition in older men, characterized by prostate enlargement and associated lower urinary tract symptoms (5). BPH affects approximately 50% of men aged 51–60, with prevalence increasing to 90% in men over 80 (6). Because BPH can mimic PC symptoms, diagnosis is often challenging. The need for more accurate and non-invasive diagnostic tools for prostate cancer is evident to ensure appropriate management and improve patient outcomes (7).

S100P is a member of the S100 family of calcium-binding proteins and plays a crucial role in various cellular processes, including cell growth, differentiation, and apoptosis (8). In the context of PC, S100P has garnered significant attention due to its potential as a non-invasive biomarker and therapeutic target. Studies have shown that S100P can promote cancer cell growth and proliferation, contribute to angiogenesis (the formation of new blood vessels), facilitate metastasis (the spread of cancer), and even contribute to treatment resistance (9).

The mechanisms by which S100P exerts these effects are complex and involve interactions with various signaling pathways and molecules within the cell. For instance, S100P can activate the receptor for advanced glycation end products (RAGE) signaling pathway, leading to increased cell growth, survival, and inflammation (10, 11). Additionally, S100P interacts with other proteins, such as matrix metalloproteinases (MMPs), which are involved in the breakdown of the extracellular matrix and contribute to cancer cell invasion and metastasis (12). The presence of S100P in biological fluids, including serum and saliva, has opened up the possibility of using it as a non-invasive biomarker for detecting prostate disease (13). This is particularly important given that current diagnostic methods, such as prostate biopsy, are invasive and carry potential complications.

Saliva has emerged as a promising diagnostic medium. It contains various proteins, nucleic acids, and other molecules that reflect physiological and pathological changes in the body, including the presence of cancer (14). Using saliva for diagnostics offers several advantages, such as non-invasive collection, ease of repeated sampling, and potential for point-of-care testing (15). Saliva-based tests have shown promise in detecting various cancers, including oral, breast, and pancreatic cancers, as well as other diseases like HIV and Sjögren's syndrome (16). The diagnostic potential of saliva extends beyond cancer, with ongoing research exploring its use in monitoring therapeutic drug levels, assessing hormonal imbalances, and detecting early signs of oral diseases (17).

To our knowledge, no study has examined the measurement of S100P in both serum and saliva of individuals with prostate disease. Therefore, this study investigates PSA and S100P levels in serum and saliva of patients diagnosed with PC and BPH. The primary objective is to evaluate S100P as a potential non-invasive biomarker for distinguishing PC from BPH. Additionally, this study aims to explore the correlation between S100P levels in serum and saliva.

The findings of this research have the potential to significantly advance our understanding of S100P in the context of prostate diseases and contribute to the development of novel diagnostic strategies. These advancements could enable earlier detection, facilitate more effective treatment decisions, and ultimately improve patient outcomes.

Materials and Methods

Participants

This case-control study included 100 Iranian men between the ages of 50 and 65. The participants were divided into two groups: a prostate cancer (PC) group with 50 men and a benign prostatic hyperplasia (BPH) group with 50 men. The men were recruited from Khansari Hospital in Arak, Iran. All participants provided written informed consent, and the study protocol was approved by the ethics committee of Arak University of Medical Sciences (ethics permission number IR.ARAKMU.REC.1398.218).

Eligibility Criteria

After the invitation and voluntary expression of individuals to participate in the study, to ensure the integrity of our study and minimize potential confounding factors, we carefully selected participants based on the following criteria:

Inclusion criteria for the PC group

I. Age: 50 to 65 years. This age range was chosen to

focus on men at higher risk for PC while allowing for a wider range of participants.

II. Histological Confirmation: Only patients with a histologically confirmed diagnosis of PC were included to ensure accuracy.

III. Treatment Status: Patients who had not received any prior treatment for PC, including chemotherapy, radiotherapy, or surgery, were eligible.

IV. General Health: Participants were required to be free of other malignant diseases, infections, and oral/dental diseases to minimize potential confounding factors.

Inclusion criteria for the BPH group

I. Age: 50 to 65 years. The same age range was used for both groups to ensure comparability.

II. Histological Confirmation: A histologically confirmed diagnosis of BPH was required for inclusion in this group.

III. Disease History: Participants with a history of malignant neoplasms or infections were excluded to minimize confounding factors.

IV. Oral Health: Participants were required to be free of oral/dental diseases to ensure that these conditions did not influence the salivary biomarkers.

Exclusion Criteria for Both Groups

I. Significant Comorbidities: Individuals with significant systemic diseases or salivary gland disorders were excluded to minimize potential confounding effects on the study results.

II. Prior Cancer Treatment: Participants with a history of cancer treatment, including chemotherapy or radiotherapy, were excluded to avoid potential influences on the biomarkers.

III. Metastatic Disease: Patients with metastatic PC were excluded to focus on localized disease and its impact on the biomarkers.

Blood and Saliva Specimen Collection

General participant characteristics were collected for ethical reasons. A 5 mL sample of whole blood was drawn from a peripheral vein of each participant. The blood was allowed to clot in a clean glass tube for 30 minutes at room temperature. Blood specimens were then centrifuged at 3,000 rpm for 5 minutes to obtain serum, which was stored at -70°C until analysis.

Unstimulated saliva was collected by instructing each participant to clean their lips and refrain from drinking, eating, smoking, or performing oral hygiene procedures for two hours prior to collection. Participants rinsed their mouths with plain water and sat for five minutes before providing a 5–10 mL saliva sample. Saliva specimens were centrifuged at 3,000 rpm for 10 minutes to obtain supernatant, which was stored at -70°C until analysis.

Analysis of Salivary and Serum PSA and S100P

Serum and salivary concentrations of PSA and S100P were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. The kits were designed to quantify PSA and S100P concentrations in biological fluids, including serum, saliva, cell lysate, and urine.

Briefly, samples and standards (100 µL) were incubated in the wells for 2.5 hours. After incubation, the wells were washed four times with a washing buffer. Subsequently, 100 µL of biotinylated antibody was added to each well and incubated for 1 hour. The wells were washed again four times, followed by the addition of 100 µL of streptavidin, which was incubated at room temperature for 45 minutes with shaking. After another round of four washes, 100 µL of TMB One-Step substrate reagent buffer was added to each well and incubated for 30 minutes at room temperature with shaking. Finally, 50 µL of stop solution was added, and absorbance was measured at 450 nm using an ELISA reader (ELX 800 TM; BioTek Instruments, Inc.).

Statistical Analysis

Descriptive information was analyzed using Fisher's exact test and Pearson's chi-squared test. The D'Agostino test was used to assess the normality of data distribution. The Mann–Whitney U test was employed to compare the means (SEMs) of saliva and serum parameters between the two groups. Spearman's correlation coefficient was calculated to determine the relationship between serum and salivary parameters.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic potential of salivary PSA and S100P concentrations compared to serum for distinguishing PC from BPH. Cutoff values were determined based on the best trade-off between sensitivity and specificity. The overall performance of the test was assessed by calculating the total area under the ROC curve (AUC). A p-value of less than 0.05 was considered statistically significant.

Statistical analyses were conducted using GraphPad Prism (version 10.00; GraphPad Software) and MedCalc (version 23.1.6; MedCalc Software).

Results

Demographic Information

The groups (PC group: 53.64 ± 3.32, BPH group: 54.11 ± 4.12) did not significantly differ in terms of age ($P > 0.05$). Also, both groups (PC group: 21.1 ± 0.3, BPH group: 21.8 ± 0.2) were well matched, with no significant difference between them in terms of their body mass index (BMI). 12% of the PC and 16% of the BPH groups had a certain level of higher education. 44% of the PC

group and 18% of the BPH group had an intermediate level education. Also, 64% of the PC group and 68% of the BPH group had a primary school level. In the PC group, 40% of individuals were current smokers, while in the BPH group, 30% were current smokers. All individuals in both groups were married, and none reported daily alcohol consumption.

PSA and S100P concentrations in saliva and serum

The mean serum PSA concentrations were significantly higher in the PC (8.3 ± 1.1) group than in the BPH (2.3 ± 1.2) group (P<0.001). Salivary PSA concentrations were significantly higher in the PC (3.8 ± 0.2) group than in the BPH (1.1 ± 0.3) group (P<0.001). Also, Elevated levels of S100P were observed in both serum and saliva samples from the PC (serum S100P: 24.3 ± 1.1, salivary S100P: 10.2 ± 0.4) group compared to the BPH (serum S100P: 8.4 ± 0.6, salivary S100P: 2.7 ± 0.2) group, with a statistically significant difference (P<0.001).

Correlation between salivary and serum PSA, S100P concentrations in the groups

The Spearman correlation coefficients showed a significant positive correlation between the serum and salivary PSA (PC group: r= 0.88, BPH group: r= 0.75) and S100P (PC group: r= 0.82, BPH group: r= 0.71) concentrations in both groups (P<0.05), Table 3.

ROC Curve Analysis Results

We performed ROC curve analysis to assess the diagnostic potential of salivary PSA and S100P compared with serum PSA and S100P, Table 4. The area under the ROC curve (AUC) for PSA was 0.954 (95% CI, 0.77-0.93), with a sensitivity of 95% and a specificity of 90% at a cutoff value of 0.5 ng/mL. The AUC for S100P was 0.928 (95% CI, 0.75–0.90), with a sensitivity of 90% and a specificity of 85% at a cutoff value of 7.1 ng/mL.

Table 1. The demographic characteristics of the study groups.

Characteristic [a]	PC Group [b]	BPH Group	P-value [c]
Age (years, mean ± SEM)	53.64 ± 3.32	54.11 ± 4.12	0.70
BMI (kg/m², mean ± SEM)	21.1 ± 0.3	21.8 ± 0.2	0.90
Education Level (%)	6 (12%)	8 (16%)	
- High School			
- Intermediate	22 (44%)	18 (36%)	
- Primary School	32 (64%)	34 (68%)	
Smoking (%)	20 (40%)	15 (30%)	0.40
Marital Status (married) (%)	50 (100%)	50 (100%)	>0.99
Alcohol Use (%)	0 (0%)	0 (0%)	>0.99

PC, prostate cancer; BPH, benign prostatic hyperplasia; BMI, body mass index. [a] The Fisher exact and Pearson χ 2 tests were used to analyze the demographic information.[b] n = 50. [c] P <0.05 was considered as statistically significant.

Table 2. The results of salivary and serum concentrations of PSA and S100P

Variable [a]	PC Group (mean ± SEM) [b]	BPH Group (mean ± SEM) [b]	P-value [c]
Serum PSA (ng/mL)	8.3 ± 1.1	2.3 ± 1.2	<0.001
Salivary PSA (ng/mL)	3.8 ± 0.2	1.1 ± 0.3	<0.001
Serum S100P (ng/mL)	24.3 ± 1.1	8.4 ± 0.6	<0.001
Salivary S100P (ng/mL)	10.2 ± 0.4	2.7 ± 0.2	<0.001

PC, prostate cancer; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; S100P, S100 calcium-binding protein P. [a] The normal distribution of data was assessed using the D'Agostino test. The Mann-Whitney U test was employed to calculate and compare the means of data. [b] n = 50. [c] P <0.05 was considered statistically significant.

Table 3. The results of correlation between salivary and serum concentrations of PSA and S100P.

Variable [a]	Spearman's Correlation Coefficient (r) [b]	P-value [c]
PSA (PC group)	0.88	<0.01
PSA (BPH group)	0.75	0.02
S100P (PC group)	0.82	<0.01
S100P (BPH group)	0.71	0.01

PC, prostate cancer; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; S100P, S100 calcium-binding protein P. [b] Spearman correlation coefficients was used to determine the relationship between serum and salivary PSA and S100P. [c] P <0.05 was considered to be statistically significant.

Table 4. ROC Curve Analysis Results [a]

Variable	Cut-off value [b]	Sensitivity (%)	Specificity (%)	AUC	SE	95% Confidence Interval
Salivary PSA, mg/dl	0.5	95	90	0.954	0.0634	0.77-0.93
Salivary S100P, ng/ml	7.1	90	85	0.928	0.08549	0.75–0.90

PSA, prostate-specific antigen; S100P, S100 calcium-binding protein P; AUC, area under the curve; ROC, receiver operating characteristic. SE; Standard error. [a] The ROC analysis was applied to appraise the diagnostic potential of salivary PSA and S100P compared with serum and to correctly separate the participants into the case and control groups. [b] The cut-off values were assessed based on the best trade-off between sensitivity and specificity.

Discussion

Early detection of prostate disease is crucial for reducing mortality (18), emphasizing the need for effective diagnostic markers in serum and saliva (19). This study investigated PSA and S100P levels in the serum and saliva of men with PC and BPH. The findings revealed significantly elevated salivary and serum PSA and S100P levels in men with PC compared to those with BPH. Additionally, the results demonstrated a significant positive correlation between serum and salivary levels of both PSA and S100P. These findings suggest that salivary PSA and S100P measurements may offer comparable sensitivity and specificity to serum PSA and S100P levels in distinguishing PC from BPH.

Traditionally recognized for its role in digestion and oral health, saliva has emerged as a promising diagnostic medium due to scientific and technological advancements (20). This easily obtainable and non-invasive biofluid contains a wide range of biomarkers, such as DNA, RNA, proteins, hormones, and microorganisms, providing valuable insights into an individual's health (16). Saliva has demonstrated its utility in diagnosing various conditions, including infectious diseases (e.g., HIV, hepatitis), autoimmune disorders (e.g., rheumatoid arthritis), hormonal imbalances (e.g., diabetes), and cancers such as oral and breast cancer (21). Given its advantages, saliva is expected to play an increasingly important role in personalized medicine and early disease detection.

While prostate-specific antigen (PSA) is a common biomarker for PC detection, it has limitations, including low specificity and the potential for false positives (22). Our study, consistent with other research (23-26), found significantly elevated serum and salivary PSA levels in PC patients compared to those with BPH. As observed in previous work (27, 28), salivary PSA concentrations were generally lower than serum concentrations in both groups. Furthermore, we identified a statistically significant positive correlation between serum and salivary PSA concentrations in both the PC group and the BPH group. Our findings align, in part, with Shiiki et al.'s observation of a direct correlation between serum and salivary PSA in individuals with elevated serum PSA. However, they did not find this correlation in patients with lower serum PSA levels (27). Also, Turan et al. (29) examined free and total PSA in serum and saliva across BPH, PC, and healthy individuals. They reported a significant correlation between free and total PSA in both sample types for all participants, along with significant differences in serum free and total PSA between the three groups. Interestingly, they did not find significant differences in salivary PSA concentrations between the groups. In general, these results indicate that PSA in saliva acts as a reliable biomarker, but further research is needed to confirm its definitive role.

S100P, a calcium-binding protein, participates in various cellular processes, including cell growth, proliferation, differentiation, apoptosis, and migration (30). Previous studies have reported that S100P is significantly elevated in prostate tumor tissue and is associated with disease progression and metastasis (31).

The molecular mechanisms through which S100P exerts its effects in cancer are complex and multifaceted. It has been shown that S100P can interact with cell surface receptors such as RAGE or activate intracellular signaling pathways, including MAPK and NF-κB. In summary, S100P plays diverse roles in cancer development: it interacts with RAGE, activates intracellular signaling pathways, regulates the cell cycle, inhibits apoptosis, stimulates angiogenesis, facilitates metastasis, induces inflammation, influences immune responses, and modulates the expression of MMPs (32, 33).

These findings underscore the multifaceted role of S100P in cancer, particularly in PC development and progression, positioning it as a potential therapeutic target.

Serum S100P measurement has shown promise as a viable biomarker. In this regard, our study demonstrated that S100P levels in the serum of the PC group were significantly elevated compared to those in the BPH group. Consistent with our findings, studies by Zhiliang et al. (34) (n = 78) on opisthorchiasis-associated cholangiocarcinoma (CCA) and Wang et al. (n = 96) on colorectal cancer (CRC) revealed that elevated serum S100P levels correlate with poorer prognosis, advanced disease stage, and metastasis (35). Collectively, these studies suggest that S100P is elevated in both tumor

tissue and serum of cancer patients, correlating with unfavorable disease characteristics. Therefore, S100P may serve as a promising biomarker for cancer diagnosis, prognosis, and potentially treatment.

Additionally, a significant positive correlation was observed between serum and salivary S100P concentrations in both groups. While serum PSA remains the standard biomarker for PC, ROC curve analysis highlighted the promising diagnostic potential of salivary S100P. Furthermore, salivary S100P concentrations were significantly lower in both groups compared to serum. These results suggest that salivary S100P levels may reflect systemic S100P levels, supporting its potential use as a salivary marker for PC and BPH detection and differentiation.

To our knowledge, this is the first study to investigate both serum and salivary S100P levels. The study has several strengths, including the use of saliva as a non-invasive sample collection method, careful matching of PC and BPH groups based on factors such as age, BMI, and lifestyle, and the application of standardized methods for measuring S100P in serum and saliva. However, limitations include the relatively small sample size and the lack of investigation into advanced stages of prostate cancer (metastatic). Further research is required to validate these findings and generalize them to larger populations and different disease stages.

Conclusion

This study highlights the potential of salivary PSA and S100P as non-invasive biomarkers for PC detection and differentiation from BPH. Elevated levels of both markers in PC patients, coupled with a strong correlation between serum and salivary levels, suggest that salivary S100P, particularly with PSA, offers a promising biomarkers for early detection. While serum PSA remains the standard, these findings, despite study limitations, warrant further research with larger cohorts to validate the clinical utility of salivary PSA and S100P in PC and BPH diagnosis and management.

Declarations

Competing interests

The authors declare that they have no conflicts of interest.

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Author contributions

Jamal Amri, Davood Goodarzi, and Mona Alaee conducted the investigation and developed the methodology for the study. Jamal Amri and Mehdi Salehi were responsible for validating the study methods and refining the methodology. Jamal Amri and Mohammad Reza Zare managed the software aspects of the study and performed data analysis. Mehdi Salehi played a crucial role in securing funding for the project and overseeing its administration.

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