

The association of opium addiction with prostate volume: A cross-sectional study

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Abstract

Benign prostatic hyperplasia is a condition in which the prostate gland enlarges in a non-cancerous manner. Opioids can decrease prostate-specific antigen levels along with testosterone and can lead to changes in prostate volume. The main objective of the present study was to determine whether there is an association between opioid addiction and prostate volume. This observational cross-sectional study included 174 male patients admitted to Loghman Hakim Hospital in Tehran, Iran, between December 2023 and November 2024. Participants were categorized into 2 groups: opioid users (exposed group; N = 87) and non-users (non-exposed group; N = 87). Prostate volume was measured using ultrasound, and statistical analyses involved independent samples t-tests, Mann-Whitney U tests, and Spearman's correlation coefficient. A p-value of less than .05 was considered statistically significant. Among opioid users, 71.3% primarily consumed opium, while the remaining individuals used methadone, refined opium, or heroin. The average prostate volume for all participants was 29.5 cm³, with no significant difference observed between opioid users and non-users (p = .268). However, a significant positive correlation was found between the duration of opioid use and prostate volume (Spearman's rho = 0.353, p < .001). Additionally, age showed a strong correlation with prostate volume in both opioid users (Spearman's rho = 0.476, p < .001) and non-users (Spearman's rho = 0.591, p < .001). This study found no significant association between prostate volume and opium addiction, smoking, body mass index, and past medical history. Age and duration of opium consumption were the only significant factors associated with prostate volume. To achieve definitive results, prospective studies with larger sample sizes are needed.

Keywords: opioid-related disorders, opium, prostate, prostatic hyperplasia

Main points

- There was no statistically significant relationship between opioid dependency and prostate volume within this research.
- Age showed a positive and significant association with prostate volume among both opioid users and non-users.
- The extent of opioid usage was seen to be significantly and positively correlated with prostate size among opioid users but may be related to the user's age.
- Smoking status and body mass index factors failed to show any significant association with prostate volume within the population under study.

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Introduction

Benign prostatic hyperplasia, or benign prostatic hyperplasia (BPH), causes the prostate gland to enlarge in a non-cancerous manner. This enlargement occurs due to the uncontrolled growth of the epithelial and fibromuscular tissues in the transition zone and periurethral area (Devlin et al., 2021). It is the most common disease in older men (Pascual Mathey, 2022). The prevalence of BPH increases with age, so it is 8-10% in men over 40 years and 90% in men over 90 years (Pascual Mathey, 2022). According to the latest studies in 2019, globally, 94 million men aged 40 years and older are affected by BPH, with an age-standardized prevalence of 2480 per 100,000 (Awedew et al., 2022). The highest prevalence of BPH in the Middle East is reported to be 23.8%, and it is related to Egypt, Saudi Arabia, Kuwait, and the UAE (Noweir et al., 2022). Enlargement of the prostate due to BPH results in the manifestation of obstructive and irritative lower urinary tract symptoms (Joseph et al., 2002). Benign prostatic hyperplasia can also increase prostate cancer occurrence, probably due to common underlying pathophysiological factors (Miah & Catto, 2014).

Prostate-specific antigen (PSA) is a glycoprotein that plays a role in seminal fluid liquefaction (Wang et al., 2017). Some conditions can increase PSA levels, such as elderly age, African American race, low body mass index (BMI), larger prostate size, infection, inflammation, trauma, prostate-related medical procedures, and prostate cancer (Press et al., 2020). Other factors can also decrease PSA levels, such as non-steroidal anti-inflammatory drugs, thiazides, statins, less mental stress, lycopene and vitamin C-containing foods, soy bread, and sufficient physical activity (Chang et al., 2010; Hackshaw-McGeagh et al., 2016; Salleh, 2008). Opioids are another factor that can decrease PSA levels along with testosterone (Hosseini et al., 2012). However, PSA levels and prostate volume have a positive correlation (Deori et al., 2017; Kusuma Duarsa et al., 2021; Udoh et al., 2020). The mechanism by which opioids reduce PSA is not fully understood, but several mechanisms have been suggested, including suppression of the hypothalamic-pituitary-gonadal axis, reducing prostate gland activity, and indirect anti-inflammatory effects of opioids (Lec et al., 2020; Rubinstein et al., 2013; Smith & Elliott, 2012). Therefore, in the present study, the aim is to evaluate whether opioid consumption can change prostate volume or not.

Although previous studies have mentioned the reducing effect of opioids on PSA (Hosseini et al., 2012), some of the other studies showed that PSA levels and prostate volume have a direct correlation (Aigbe et al., 2022; Putra et al., 2016). The number of studies investigating the correlation between opioid consumption and prostate volume is few. These study gaps, along with the small number of studies about the effect of opioids on prostate size, prompted to design this study to investigate the impact of opium and its derivatives on prostate volume.

Material and Methods

Patients' Selection

This observational cross-sectional study was conducted on all patients admitted to the Loghman Hakim Hospital in Tehran, Iran, from December 2023 to November 2024. It should be noted that written informed consent was obtained from all patients before the study. The exposed group contained the opioid-addicted patients who were admitted for non-prostatic problems, and the non-exposed group samples were selected among non-opioid-addicted patients who were referred for non-prostate causes. Each group contained 87 patients, and both were matched in age. The samples were chosen non-randomly by the census method from all the people referred to Loghman Hakim Hospital in December 2023-November 2024. The inclusion criteria were as follows: male patients 30-70 years old, patients with a history of addiction to opium or its derivatives for at least 1 year (for the exposed group), and those who lack addiction to other substances such as sedatives and alcohol. The exclusion criteria were as follows: presence of known prostate cancer or other malignancy, presence of urinary symptoms, abnormal findings in digital rectal examination, history of previous prostate surgery, history of pelvic radiotherapy, presence of bladder stones or urinary tract infection, prostate manipulation within the past 6 months, participants who do not provide informed consent for participation in the study, inability to speak or understand the language in which the study materials or interviews are conducted, and excluding participants who may provide incomplete or unreliable responses due to known dishonesty or difficulty understanding the research context.

Sample Size

The sample size was calculated for a cross-sectional study comparing the prevalence of the outcome between 2 independent groups: exposed and non-exposed. Based on prior data (Abolhasani Foroughi et al., 2023), a prevalence of 50% was assumed in the exposed group and 30% in the non-exposed group. The required sample size was estimated using the formula for comparing 2 proportions with pooled variance:

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}} \cdot \sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta} \cdot \sqrt{p_1(1-p_1) + p_2(1-p_2)} \right]^2}{(p_1 - p_2)^2}$$

Where $p_1 = 0.5$, $p_2 = 0.3$, and $\bar{p} = 0.4$. Using a 2-sided significance level of 0.05 ($Z_{1-\alpha/2} = 1.96$) and a statistical power of approximately 77% ($Z_{1-\beta} \approx 0.747$), the estimated minimum required sample size was 87 participants per group. This calculation ensures sufficient power to detect a 20-percentage point difference in prevalence between the 2 groups.

Data Collection

Prostate volume measurement was done for both exposed and non-exposed groups using transabdominal ultrasound by radiologists following standard protocols. The prostate volume was estimated using the oblate spheroid (Littrup et al., 1991; Toi, 2024), measuring each diameter in centimeters: width \times anteroposterior plane \times length \times 0.5. The bladder of all patients was approximately at 50% capacity.

Demographic information and clinical data, including medical history, history of opium addiction, presence of underlying diseases, history of smoking and tobacco addiction, and any related clinical variables, are collected from the interview with the patient.

Statistical Analysis

We conducted statistical analyses with a primary focus on prostate volume as the outcome variable. To compare the demographic and clinical characteristics of opioid users and non-users, descriptive statistics was utilized. For group comparisons, independent samples *t*-test were applied for variables that followed a normal distribution, while the Mann-Whitney *U*-test was used for those that did not. To examine correlations between prostate volume and continuous variables such as age, BMI, and opioid use duration, Spearman's rank correlation coefficient was employed. Statistical significance was defined as a *p*-value of less than .05. All analyses were carried out using SPSS version 28.

The research obtained approval from the Research Ethics Committee of the School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, under the Approval ID IR.SBMU.MSP.REC.1402.431 on November 28, 2023.

Results

Patients Characteristics

This study analyzed 174 male patients who met the criteria for participation. Of the 174 participants who completed the study, 87 belonged to the opium consumer group (exposed group), and the other 87 belonged to the no opium group (non-exposed group). Within the exposed group, 71.3% used opium ($n = 62$), while others used methadone (9.2%, $n = 8$), refined opium or opium sap (14.9%, $n = 13$), or heroin (4.6%, $n = 4$). Refined opium, also known as opium sap, is the processed form of opium that is produced by simmering opium dross, either alone or in combination with raw opium, in water for an extended period.

Among the non-exposed group, 59.8% ($n = 52$) did not report any previous medical history or underlying disease, while 8.04% ($n = 7$) reported diabetes mellitus (DM), 9.2% ($n = 8$) reported hypertension (HTN), and 3.4% ($n = 3$) reported both HTN and DM. The remaining 19.5% ($n = 17$) reported other medical problems. In the exposed group, 72.4% ($n = 63$) did

not have any previous medical history, while 2.3% ($n = 2$) had DM, 12.6% ($n = 11$), and 2.3% ($n = 2$) had both HTN and DM. Moreover, 10.3% ($n = 9$) of the people had other medical problems. In the opium user group, the mean duration of opioid use was 18.37 years (standard deviation = 11.59).

In this study, out of 174 participants, 58.62% ($n = 102$) reported smoking cigarettes. Among the exposed group, 14.9% ($n = 13$) consumed opium or its derivatives orally, while 3.4% ($n = 3$) used the injection method. Additionally, 48.3% ($n = 42$) smoked the product to use opium or its derivatives, and 33.3% ($n = 29$) used opium or its derivatives in various ways. According to the study, the majority of participants, specifically 76.44% ($n = 133$), did not utilize any therapeutic drugs during the study (Table 1).

Prostate-Related Characteristics

In this study, the prostate volume was measured and found to range from 15 cm³ to 85 cm³. The mean prostate volume was 30.49 cm³ for all participants, with the non-exposed group having a mean prostate volume of 29.9 cm³. The opium consumer group had a lower mean prostate volume (29.2 cm³ vs 29.9 cm³) than the non-exposed group. Among the exposed group, the highest average prostate volume was observed in people who consumed opium (32.9 cm³), while the lowest average was observed in people who consumed refined opium (24.4 cm³). People with HTN in the no opium group had the highest mean prostate volume (41.6 cm³).

In contrast, people with other medical problems had the highest mean prostate volume (41.5 cm³) in the opium consumer group. Smokers had a larger mean prostate volume (32.3 cm³) than non-smokers (27.9 cm³) in all 174 patients. This pattern was also observed in the exposed group, where smokers had a larger mean prostate volume compared to non-smokers (29.2 cm³ vs 29 cm³). Furthermore, people who consumed opium and its derivatives through a combination of smoking, inhalation, and oral methods had the highest mean prostate volume (35.25 cm³) compared to those who used a single method of consumption. Statistically, no significant differences in mean prostate volume were observed across the exposed group and the non-exposed group ($p = .268$) (Table 1).

Risk Factors for Prostate Volume

The mean of BMI in opium users and non-users was 24.28 kg/m² and 26 kg/m², respectively. These values in the 2 groups were significantly different ($p = .002$). The between-subjects effects analysis showed that there was no significant interaction between opioid consumption and BMI on the prostate volume (Table 2). In contrast, a statistically significant positive correlation was observed between the duration of opioid use and prostate volume among opium users (Spearman's rho = 0.353, $p < .001$).

The results also showed a significant positive correlation between age and prostate volume in both opium users

Table 1. Demographic characteristics of study population

Variables	Addict Patients or Exposed Group (N = 87)	Non-addict Patients or Control Group (N = 87)	p
Age, mean (SD)	52.03 (11.81)	48.83 (13.63)	.098*
Past medical history, n (%)	Diabetes	2 (2.3)	.138#
	HTN	11 (12.6)	
	Diabetes and HTN	2 (2.3)	
	Other	9 (10.3)	
	Patients without past medical history	63 (72.4)	
Type of addiction, n (%)	Opium	None	–
	Methadone	8 (9.2)	
	Refined opium or opium sap	13 (14.9)	
	Heroin	4 (4.6)	
Way of consumption, n (%)	Oral	None	–
	Injection	3 (3.4)	
	Smoking	42 (48.3)	
	Mixed-method opium consumers	29 (33.3)	
Cigarette smoking, n (%)	Yes	23 (26.4)	<.001#
	No	64 (73.6)	
Duration of addiction, mean (SD)	18.37 (11.59)	None	–
BMI, mean (SD)	24.28 (4.25)	26 (3.06)	.002*
Prostate volume, mean (SD)	29.2 (11.06)	29.9 (15.59)	.268*

Note: BMI = Body mass index; HTN = Hypertension; SD = Standard deviation.

*Mann–Whitney U-Test

#Chi-square test.

Table 2. Correlation between variables and prostate volume in opium users and non-users

Group	Variable	Spearman's Rho Correlation Coefficient	p (2-tailed)
Opium users	Age	0.476	<.001
	Duration of use	0.353	<.001
	BMI	–0.019	.863
Non-users	Age	0.591	<.001
	BMI	–0.018	.868

Note: BMI = Body mass index.

(Spearman's rho = 0.476, $p < .001$) and non-users (Spearman's rho = 0.591, $p < .001$). This suggests that independent of opioid use, age has a key influence on prostate volume (Table 2).

Discussion

The statistical analysis of the study revealed that none of the previously mentioned variables had a significant association with prostate volume, except for age and the duration of opioid use, which were identified as the only significant predictors of prostate volume.

According to epidemiological research conducted in Iran, prostate cancer is the most frequently diagnosed cancer in men. In 2000, it ranked as the tenth most commonly diagnosed cancer, while in 2016, it had risen to the fifth position (Khanali & Kolahi, 2021). This highlights the significant health challenge posed by prostate cancer in Iran.

Prostate volume has been proven to be a significant indicator of the likelihood of prostate cancer in multiple studies (Haj-Mirzaian et al., 2024). Therefore, identifying the factors

that affect Prostate volume is crucial to efficiently identify individuals at risk of developing prostate cancer. A recent study conducted by Mingyang Sun et al. found an association between long-term opioid use and cancer risk. The incidence rate ratios and hazard ratio of prostate cancer in the opioid group compared to the non-opioid group were 2.00 (1.35–3.03) and 2.85 (1.92–4.00), respectively (Sun et al., 2022). Hence, it is critical to investigate the relationship between opioid consumption and prostate volume. However, the research on the relationship between the consumption of opium and its derivatives and prostate volume is limited, with only 3 studies found on this topic (Abolhasani Foroughi et al., 2023; Hosseini et al., 2012; Safarinejad et al., 2013). In a study conducted by Foroughi et al., the relationship between opium abuse and prostate enlargement was investigated. The results showed that the mean prostate size in the addict group was significantly higher than in the healthy group ($p = .005$). Although the findings were contrary to theirs ($p = .268$), Foroughi et al. found a significant relationship between age and prostate volume ($p < .001$) using logistic regression, which was similar to the findings based on correlation coefficient analysis ($p < .001$). Both sets of findings suggest a direct correlation between age and prostatic volume (Abolhasani

Foroughi et al., 2023). Two other research studies found there is no significant relation between opioid consumption and prostate volume. In the article by Safarinejad et al., the p -value between opioid consumption and prostate volume was .28 for the transition zone volume and .26 for the prostate gland (Safarinejad et al., 2013). Both of the p -values were above .05. In another study conducted by Hosseini et al., there was no significant relation between opioid consumption and prostate volume ($p = .053$) (Hosseini et al., 2012). The articles investigating the link between substance use and prostate volume show varying findings, which could be explained by differences in the molecular pathways. Studies on prostate cancer have found that Kappa opioid receptors are involved in both promoting and inhibiting the growth of prostate cancer cells in vitro and may interact with the androgen cascade. Similarly, the opioid growth factor receptor is highly expressed in prostate cancer cells but repressed by androgens. Mu opioid receptors are found more frequently in prostate cancer tissue and are associated with poor oncologic outcomes (Lec et al., 2020). These findings suggest that opioids can have both promoting and inhibiting effects on prostate cancer cell growth, which may contribute to the differences in prostate volume observed in individuals who consume opioids.

The research suggests that there is no significant correlation between BMI and prostate volume ($p > .05$), which aligns with the findings of a study by Mampa et al., 2021 ($p = .195$). Their study involved 178 men with BPH aged between 50 and 75 years who were seen at Charlotte Maxeke Johannesburg Academic Hospital Urology Outpatient Department between September 2018 and February 2019 (Mampa et al., 2021). However, a study conducted in Zhengzhou on men aged 40 years or older found that prostate volume increased as BMI increased ($r = 0.110$, $p < .001$, p -trend = .045) (Yue et al., 2020). Variations in research findings could be attributed to differences in the racial demographics of the study participants. Additionally, some studies focused on individuals with BPH, while others did not.

One of the aims was to examine the relationship between the duration of opioid consumption and prostate volume. The analysis found a statistically significant correlation between the duration of opioid use and prostate volume ($p < .001$). However, the significant relationship between duration of opium consumption and prostate volume in this study may be due to the longer duration of opioid use in older people, because there is a positive correlation between age and duration of use in this study. In other words, the observed relationship between duration of use and prostate volume may be affected by old age and not duration of use, because the partial correlation analysis showed that there is no significant correlation between duration of opioid use and prostate volume.

Limitations and Directions/Suggestions for Future Research

The study conducted had certain limitations that need to be taken into account. The primary limitation was the relatively

low sample size in subgroups. Besides, the statistical power was approximately 77%, which is slightly below the conventional threshold of 80%. As a result, the study may have been underpowered to detect smaller differences between groups. Furthermore, the study was performed only on Iranian men, and hence, the results cannot be applied to other patient populations. As with many previous studies, this study also had certain limitations, being a single-center study. For definitive evidence of the effects of opium consumption on prostate volume, larger multicenter studies need to be conducted. Regrettably, due to budget constraints, PSA measurements could not be conducted in the patients as part of the research project.

The present study found no statistically significant association between opium addiction and prostate volume. Similarly, no significant relationship was observed between prostate volume and various factors like smoking status, BMI, and past medical history. However, age and the duration of opium consumption were identified as the only significant factors associated with prostate volume.

Author contributions

Conception: T.O., R.N., M.S.M.; Design: M.T., M.H.M., M.S.M.; Supervision: T.O., R.N., S.M.H.; Data acquisition: T.O., M.T., M.H.M., S.R.A., S.B.S., M.R.A.; Data interpretation: T.O., S.M.H., Z.R., M.S.M., M.R.A.; Drafting of the manuscript: T.O., S.M.H., M.S.M., M.R.A.; Critical revision of the manuscript: R.N., M.T., M.H.M., S.R.A., S.B.S., Z.R. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the The Research Ethics Committees of the School of Medicine at Shahid Beheshti University of Medical Sciences (Date: January 1, 2025, Decision/Protocol No: IR.SBMU.MSP.REC.1402.431). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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