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Elevated PSA in patients with combination of chronic prostatitis and benign prostatic hyperplasia: management options and improving prostate cancer detection (Review article)

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The relationship between chronic prostatitis (CP), which often coexists with benign prostatic hyperplasia (BPH), and elevated prostate-specific antigen (PSA) levels presents a clinical challenge, often complicating the decision-making process regarding prostate cancer (PCa) diagnosis. This overlap creates significant clinical challenges, as distinguishing between benign inflammatory conditions and malignancy is critical for determining the appropriate course of action. The treatment options for elevated PSA in the context of CP are not clearly defined in current guidelines.
While most studies suggest that antibiotics are the most typical management strategy in such cases, the choice of antibiotic and optimal treatment duration remain unclear. Some research has explored the use of fluoroquinolones and other broad-spectrum antibiotics, but consensus on the most effective regimen is lacking. Additionally, there is limited evidence regarding the long-term outcomes of antibiotic therapy in these cases. Although most studies have shown that PSA levels decrease following antibiotic treatment, it remains uncertain whether this reduction improves the accuracy of PCa diagnosis. A drop in PSA may reflect the resolution of inflammation rather than the absence of cancer, posing a risk of overlooking malignancies.
Another significant challenge is that inflammatory processes in the prostate can deteriorate and complicate histological analysis, further obscuring PCa diagnosis. Inflammation may alter tissue architecture, making it harder to detect malignant cells and increasing the risk of both false-positive and false-negative findings. This complicates the interpretation of prostate biopsies and may delay appropriate cancer treatment.
Emerging research has started to focus on novel biomarkers, such as Prostate Health Index (PHI), 4Kscore, and urinary markers like PCA3 and TMPRSS2:ERG, which may offer additional diagnostic value beyond PSA alone. These markers have shown promise in differentiating CP from PCa, but their clinical utility requires further validation through large-scale studies.
In conclusion, the relationship between CP, PSA levels, and PCa remains complex and poorly defined. Future research should aim to establish standardized treatment protocols for PSA elevation in patients with CP and BPH, clarify the role of antibiotics, and explore the integration of new biomarkers into routine clinical practice. This review highlights the importance of individualized diagnostic strategies and the integration of novel biomarkers to optimize patient management, reduce unnecessary biopsies, and improve clinical outcomes. Ongoing research remains crucial for refining these approaches and establishing evidence-based guidelines for the diagnosis and treatment of CP and PCa.
Keywords: *chronic prostatitis, prostate-specific antigen, prostate cancer, prostate biopsy, benign prostatic hyperplasia.*

Підвищений рівень ПСА у пацієнтів із поєднанням хронічного простатиту й доброякісної гіперплазії передміхурової залози: варіанти лікування та оптимізація діагностики раку (Огляд літератури)

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Взаємозв'язок між хронічним простатитом (ХП), який часто зустрічається у пацієнтів із доброякісною гіперплазією передміхурової залози (ДГПЗ), та підвищеним рівнем простатоспецифічного антигену (ПСА) становить клінічну проблему, яка часто ускладнює процес прийняття рішень щодо діагностики раку передміхурової залози (РПЗ). Це створює значні клінічні труднощі, оскільки розмежування між доброякісними запальними захворюваннями та злоякісними процесами є критичним для визначення відповідної стратегії лікування, а тактика лікаря при підвищенні рівня ПСА в контексті ХП не є чітко визначеною в сучасних настановах.
Хоча більшість досліджень вказує на те, що антибіотики є найтиповішою стратегією лікування в таких випадках, вибір антибіотика та оптимальна тривалість лікування залишаються нез'ясованими. У деяких дослідженнях вивчали використання фторхінолонів та інших антибіотиків широкого спектра, але консенсус щодо найефективнішого режиму лікування відсутній. Крім того, є обмежені дані щодо довгострокових результатів антибіотикотерапії в таких випадках. Хоча більшість досліджень показала зниження рівня ПСА після антибіотикотерапії, залишається незрозумілим, чи

покращує це точність діагностики РПЗ, адже зниження ПСА при цьому може бути відображенням зменшення запалення, а не відсутності раку, що створює ризик не помітити злоякісні пухлини.
Ще однією важливою проблемою є те, що запальні процеси в передміхуровій залозі можуть погіршувати й ускладнювати гістологічний аналіз, що створює ще більше проблем у діагностиці РПЗ. Запалення може змінити архітектуру тканини, ускладнюючи виявлення злоякісних клітин і підвищуючи ризик як хибнопозитивних, так і хибнонегативних результатів. Це також ускладнює інтерпретацію біопсії передміхурової залози й може затримувати правильне лікування раку.
Нові дослідження почали зосереджуватися на більш сучасних біомаркерах, як-от індексі здоров'я передміхурової залози (Prostate Health Index – PHI), 4Kscore, а також простатоспецифічному антигені РПЗ 3 (PCA3) та TMPRSS2:ERG, які можуть мати додаткову діагностичну цінність, порівняно з ПСА. Ці маркери показали обнадійливі результати в диференціації ХП від РПЗ, але їх клінічне застосування потребує подальшої валідації через масштабні дослідження.
Отже, взаємозв'язок між ХП, рівнем ПСА та РПЗ залишається складним і досі недостатньо вивченим. Подальші дослідження мають бути спрямовані на створення стандартизованих протоколів лікування при підвищенні ПСА у пацієнтів із ХП та ДГПЗ, уточнення ролі антибіотиків і вивчення інтеграції нових біомаркерів у рутинну клінічну практику. У цьому огляді наголошено на важливості індивідуалізованих діагностичних стратегій та інтеграції нових біомаркерів для оптимізації тактики ведення пацієнтів, зменшення кількості непотрібних біопсій і покращення клінічних результатів. Подальші добре сплановані дослідження повинні покращити наші знання та сприяти створенню доказових настанов для діагностики й лікування ХП і РПЗ.
Ключові слова: *хронічний простатит, простатоспецифічний антиген, рак передміхурової залози, біопсія передміхурової залози, доброякісна гіперплазія передміхурової залози.*

Prostate cancer (PCa) is one of the most common oncological diseases and a leading cause of death among men over 50 years old. In Europe, it is the most frequently diagnosed cancer in men and the third leading cause of cancer-related death in men [1]. Despite rapid advancements in diagnostic methods and the introduction of new biomarkers, prostate-specific antigen (PSA) measurement remains the most important tool for both the early detection of PCa and monitoring its treatment. One of the most debated topics in urology is PCa screening, where PSA and its various forms play a crucial role [1–3]. However, PSA is not a perfect marker for PCa due to numerous factors influencing its levels. Apart from malignancies, PSA levels can be affected by prostate size, patient age, inflammatory processes in the gland, and other conditions [4, 5]. These factors can lead to diagnostic errors, unnecessary biopsies, additional patient morbidity, and psychological stress.

The main prostatic disease that can influence PSA levels is a chronic prostatitis (CP). PSA elevation, especially during acute inflammatory flare-ups, has been well-documented in numerous studies [6–8]. The impact of CP on PC diagnostics can be divided into two main areas: the increase in PSA levels and the presence of cellular atypia in CP, both of which complicate the accurate diagnosis of PC. Current guidelines from both the European Association of Urology and the American Urological Association lack clear recommendations regarding the interpretation and management of patients with elevated PSA levels in the context of CP [1, 2]. Furthermore, substantial evidence highlights the impact of CP not only on PSA levels but also on the interpretation of prostate biopsy results.

Given this issue, we conducted a narrative review of the available literature over the past 20 years to assess the influence of CP on PCa diagnostics and outline potential treatment strategies in such cases. The collected publications were analyzed, and existing data were systematically reviewed.

There is general agreement that high PSA levels can indicate not only PCa but also result from benign conditions such as CP, complicating both diagnosis and management strategies [1, 2, 8]. The differentiation between malignancy and benign conditions remains a critical challenge, as highlighted in a systematic review by Ilic et al. (2018), which emphasizes the risk of over-diagnosis and unnecessary interventions resulting from PSA testing [5].

CP is a complex condition with a range of clinical symptoms linked to both inflammatory and non-inflammatory mechanisms. According to Khan et al. [9], CP includes various subtypes, each with distinct pathological processes contributing to high PSA levels. Patients with CP may experience persistent symptoms, including pelvic pain and urinary dysfunction, leading not only to a decrease in quality of life but also to additional stress [10]. Elevated PSA levels further complicate these cases, raising concerns of malignancy and often necessitating in-depth investigations, such as prostate biopsies, which carry risks of infection [11].

The pathogenesis of PSA elevation in CP is well-studied. It is primarily explained by prostate cell damage and the subsequent release of PSA. The primary mechanism for PSA elevation in patients with CP is inflammation in prostate tissue, which disrupts normal architecture and causes an increase in PSA in the bloodstream, so CP is one of the most important noncancerous cause of elevated PSA, along with prostate enlargement and physical causes [12, 13]. Inflammation, a hallmark of CP, can lead to significant increase in PSA [14] due to alterations in prostate tissue architecture and increased vascular permeability, facilitating the release of PSA into the bloodstream [12]. Additionally, tissue remodelling associated with chronic inflammation can alter normal secretory functions, further raising serum PSA levels. For example, studies have shown that chronic inflammation can significantly alter the histopathological characteristics of PCa, leading to erroneous diagnoses where benign prostatic tissue is misidentified as malignant, highlighting the importance of careful histological evaluation [15]. Therefore, CP serves as a complex interaction of inflammation, infection, and tissue alteration, culminating in a significant elevation of PSA.

Such tissue changes can complicate the histological interpretation of biopsy samples. Additionally, diagnostic methodologies used in biopsy procedures may contribute to false positives. Techniques like sextant biopsy have inherent limitations affecting sensitivity and specificity and autopsy studies provide real important information toward the understanding of the prevalence of the disease [16, 17]. There is evidence suggesting that the

pathological interpretation of needle biopsy findings remains controversial, with interpretations subject to variability depending on the pathologist's experience and the criteria used for diagnosis. This can lead to inconsistent results, further complicating patient management [16, 18].

Although cellular changes in inflammation and tumorogenesis are generally distinct, they can appear strikingly similar in some cases. Cancerous transformations often involve nuclear atypia and increased mitotic activity, features not typically associated with CP. However, inflamed tissues can mimic these cancer characteristics, complicating both diagnostic and treatment strategies [19]. Understanding the morphological changes due to bacterial infections in CP is crucial for distinguishing between benign inflammatory processes and malignant transformations, ultimately impacting clinical management.

Another actively discussed issue is the impact of chronic inflammation in the prostate on carcinogenesis. Studies by Sfanos and Marzo (2012) suggest that inflammation can act as a driving force in prostatic carcinogenesis. Proliferative inflammatory atrophy is considered a precursor lesion for PCa, providing a plausible link between bacterial and viral infections in CP and subsequent cancer development [19]. Recognizing the overlap between chronic inflammatory conditions and neoplastic changes in prostate tissue is essential. Another crucial aspect of this interaction is the nature of the inflammatory environment in CP, which may foster conditions conducive to malignant transformation. This is echoed by Nickel et al. (2001), who classified chronic prostatic inflammation and correlated it with various risk factors for carcinogenesis [20].

At the same time, the degree of PSA elevation in different patients with CP can vary significantly and does not always correlate with changes in prostate tissue. Several factors can influence this process. Firstly, the severity of the inflammation – most authors agree that the activity of the inflammatory process is directly proportional to the increase in PSA levels. Several studies have tried to understand the implications of inflammation on PSA levels, revealing that even in the absence of malignancy, total serum PSA can still be correlated with prostate volume and inflammation in biopsies [14, 19]. It has been shown that the median percentage of tissue area with inflammation increased from 2% to 5% to 9.5% across PSA tertiles, and for every 5% increase in tissue area with inflammation, log PSA increased by 0.061 ng/mL [21].

Secondly, another well-described factor is the size of the prostate gland, which may depend on both hyperplastic processes in the gland itself (benign prostatic hyperplasia – BPH) and its swelling – direct anatomical manifestations of inflammation. Investigations indicate a remarkable relationship between PSA levels and prostate volume, suggesting that variations in prostate size significantly influence PSA readings. This impacts clinical decisions regarding prostate health, and serum PSA today serves as a predictor of prostate volume, indicating a direct association between the two variables [1]. This relationship is further emphasized by Fowke et al. (2006), who highlighted the correlation between body size, prostate volume, and PSA levels. Notably, larger prostate volumes commonly produce higher PSA levels, but PSA and free PSA (fPSA) levels decreased with increasing body mass index (PSA = 0.72, 0.69, 0.67, 0.59 ng/mL for BMI 18.5 to < 25, 25 to < 30, 30 to < 35, and ≥ 35, respectively), complicating the interpretation of these results in the clinical environment [22].

Another study on 223 patients with negative biopsies also demonstrated a positive correlation between PSA levels and prostate volume. To increase objectivity, the authors even proposed an inflammation grading system, but the degree of inflammation in the prostate did not show a significant correlation with PSA levels [23].

Besides these main factors affecting PSA levels during inflammation, other factors add uncertainty to PSA interpretation. For example, Henderson et al. (1997) identified racial differences in PSA levels among men without cancer, suggesting that demographic variables interact with prostate size to influence PSA readings [24].

A serious aspect of this issue is the difficulty of diagnosing both CP and its activity. The most common method involves detecting white blood cells, with CP typically diagnosed when there are more than 10 white blood cells per high-power field in expressed prostatic secretions. On digital rectal examination, these patients can have variable findings, including normal results, a boggy or firm prostate, and varying tenderness [7].

In addition, the diagnostic challenges associated with CP span both clinical and laboratory levels. For example, distinguishing between acute and chronic inflammatory processes can be problematic, affecting treatment decisions and leading to potential misinterpretations. The lack of standardized diagnostic criteria for CP further complicates the issue, as established guidelines may not fully address all nuances in histopathological assessments [9, 10].

Another diagnostic method for CP is detecting changes during transrectal ultrasound prostate examination. In the study by M. Okuja, which examined 277 men over the age of 30, it was shown that the average prostate volume was 26 mL, progressively increasing with age (from 22 to 38 mL), as did PSA levels (from 0.9 to 7 ng/mL) in patients aged 30–39 and 60–69 years, respectively [25]. Notably, 47% of patients had nodules in the prostate, and their PSA levels were significantly higher than in patients without nodules (2.0 vs 1.1 ng/mL).

There is no unanimous consensus on the treatment strategy for elevated PSA in patients with BPH and CP. Most authors agree on the need for prolonged antibiotic therapy, often combined with nonsteroidal anti-inflammatory drugs and alpha-blockers, which may normalize PSA levels. The duration of antibiotic use ranges from 4 to 12 weeks [6–8].

Bozeman et al. (2002) demonstrated that effective treatment for CP significantly reduces serum PSA levels, suggesting that addressing inflammatory processes can mitigate PSA elevation. The mean PSA decreased by 36.4%, from 8.48 ng/mL before treatment to 5.39 ng/mL after treatment ($p < 0.001$). In 44 patients (46.3%), serum PSA fell below 4 ng/mL. Of the 51 patients whose PSA remained above 4 ng/mL, biopsy revealed PCa in 13 cases (25.5%), chronic inflammation in 37 cases (72.5%), and benign prostatic hypertrophy in 1 case (1.05%). The authors concluded that patients responding positively to treatment may not require biopsy, thus increasing its accuracy from 13.7% to 25.5% [7].

Other studies found that after treating CP, PSA decreased by 33.8%, from 8.12 to 5.37 ng/mL. Even with PSA levels below 2.5 ng/mL, PCa was detected in 13% of cases, compared to 27% when PSA exceeded 4.0 ng/mL [23]. Similar findings by other researchers also reported significant PSA reductions following prostatitis treatment, with PCa diagnosed in 12% of cases with PSA < 2.5 ng/mL and in 30% of cases with PSA > 4.0 ng/mL [26].

A systematic review by D. E. Taha, including 31 studies, showed antibiotic therapy durations ranging from 2 to 8 weeks, with ofloxacin and ciprofloxacin being the most prescribed drugs [27]. The studies focused on PSA levels from ≥ 4 to ≤ 10 ng/mL. Antibiotic therapy normalized PSA levels by varying percentages (16–59%), with PSA decreases ranging from 17% to 80%. Among patients with stable or reduced PSA, carcinoma was found in 40–52% and 7.7–20.3%, respectively, with no cancer detected when PSA dropped below 4 ng/mL [27].

Conversely, some studies highlight that while PSA decreases after antibiotics, cancer detection rates remain unaffected. An analysis of 206 patients with elevated PSA who underwent antibiotics followed by biopsy showed PSA reductions in 56.3% of cases and no change or increase in 43.7%, with cancer detection rates of 34.5% vs 38.9%, respectively. The overall PSA change was significant (6.38 vs 5.95 ng/mL) [6]. A meta-analysis involving 2,035 patients showed that after antibiotics the volume of PSA decreased more in symptomatic patients without PCa than symptomatic patients with PCa, but this statistical difference was not found in asymptomatic patients of antibiotics group and all patients of control group [28]. The authors concluded that antibiotics treatment cannot decrease elevated PSA of asymptomatic patients and reduce unnecessary biopsy.

However, the duration of treatment, choice of antibiotics, and criteria for effectiveness vary significantly. Since CP can be caused by diverse microbes, including atypical ones, a particular antibiotic may not always be effective so for bacterial CP pharmacological treatments show differing efficacy [29]. For chronic abacterial prostatitis, which accounts for many cases, treatment often focuses on symptom relief using analgesics, anti-inflammatory drugs, and alpha-blockers [13, 30].

The selection and duration of antibiotic therapy in CP can significantly impact clinical outcomes [31]. Prolonged antibiotic courses (4–12 weeks) show promise in reducing PSA and alleviating symptoms [13, 30]. Bjerklund Johansen et al. (1998) advised tailoring treatment duration to individual response and severity [29]. On the other hand, the unnecessary extension of antibacterial treatment can lead to adverse effects, including gastrointestinal disorders and the risk of resistance to antibiotics [28, 31]. This highlights the importance of weighing effectiveness against potential side effects.

As an alternative to antibiotics, plant-based bio-preparations have been proposed to treat prostate inflammation without the side effects typical of antibiotics. One study used cernitin pollen extract for 30 days in patients undergoing biopsy [32]. Significant PSA reductions were observed, with differences between groups with positive and negative biopsies. The mean change in PSA was −0.6 ± 1.4 ng/mL and −7.6 ± 16.1% in the negative biopsy group – significantly different from baseline values. The study suggested that cernitin pollen extract could help avoid unnecessary prostate biopsies in patients with elevated PSA due to inflammation [32].

In summary, while evidence supports a 4–12 week treatment interval for bacterial CP, therapy must be individualized based on clinical evaluation and patient response to minimize side effects and optimize outcomes [23, 26].

After completing antibacterial therapy, follow-up examinations assess treatment outcomes. Though PSA levels often decline, there is no consensus on how to interpret these changes or decide on further treatment strategies. The role of other factors, such as prostate calculi, cannot be neglected as they can influence antimicrobial effectiveness, as indicated by Zhao et al. [33].

It is crucial to recognize that CP, especially when PCa is suspected, affects patients' quality of life and should be considered in treatment planning. Psychological support and patient education are vital, as CP often impacts mental health [34]. Educational programs that explain CP, PSA elevations, and the importance of treatment adherence help reduce anxiety and stigma, empowering patients to manage their condition [35]. Patients with CP and elevated PSA frequently experience psychological distress due to fear of cancer. One benefit of biopsy is the potential to rule out PCa, a major concern given its associated morbidity and mortality [36]. Understanding the cause of high PSA guides appropriate treatment strategies and improves patient outcomes.

At the same time, the decision to perform prostate biopsy should be thoroughly discussed with the patient, and the challenges of biopsies in this context cannot be neglected. Biopsies carry risks of complications such as infections and bleeding, especially in prostatitis patients [34, 36]. Research shows biopsy complications may have increased following changes in screening guidelines and patient selection criteria. False-positive results can heighten anxiety and delay treatment for patients ultimately diagnosed with benign conditions (American Society of Therapeutic Radiology and Oncology Consensus Panel, 1999) [37].

To reduce the number of biopsies in cases of BPH with CP, various methods have been proposed. One study involved 106 men with total PSA levels < 10 ng/mL who underwent biopsy negative for PCa and had no clinical prostatitis. The authors examined total PSA, fPSA, and the free-to-total PSA ratio (f/tPSA) in men with varying levels of inflammatory activity and showed that fPSA and f/tPSA correlated with active prostatitis, but not total PSA [38]. Another authors came to similar conclusion [39].

Among modern biomarkers, the use of PCA3 (PCa Antigen 3) is being explored in this context. For example, De Luca demonstrated in a study of 432 men that PCA3 levels significantly differed between groups with positive and negative biopsies, but among those with negative biopsies, there was no difference in PCA3 levels between patients with CP and others. CP was detected in 37.5% of those with negative biopsies [40]. A study of 267 patients with PSA levels of 4–10 ng/mL who underwent prostate biopsy

found CP in 27.3% of cases. It showed that %p2PSA and the Prostate Health Index (Beckman Coulter, USA) were much more sensitive in identifying CP than tPSA, fPSA, and %fPSA [39]. At the same time, other researchers found only marginal benefits in using the Prostate Health Index and PCA3 for differentiating CP and PCa [41].

Another study assessed the efficacy, specificity, and predictive value of a newly discovered biomarker, Zinc finger-like 1 protein (referred to as neuroendocrine marker – NEM), for the detection of PCa. The banked plasma samples from 508 men, with a median age of 67 years, were retrospectively analyzed to compare the performance of NEM and PSA in predicting subsequent histologic PCa. The authors concluded that NEM was more accurate than PSA in differentiating cancer from benign conditions, such as BPH or prostatitis, and can reduce the number of diagnostic biopsies and associated painful procedures and quality-of-life losses [42].

In summary, the interaction of chronic inflammation, histological changes, and diagnostic methodology contributes to the challenge of obtaining precise biopsy results in patients with CP. The treatment of patients with CP and elevated levels of PSA presents a clinical dilemma, combining the benefits and challenges related to prostate biopsy [43]. The relationship between elevated PSA levels and CP is supported by complex mechanisms that require careful diagnostic and therapeutic approaches [44]. Further research may pave the way for improving management strategies and developing clearer clinical guidelines. Overall, ongoing scientific studies must continue to deepen our understanding of these interrelations to enhance clinical outcomes for patients with prostate-related conditions.

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