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ORIGINAL PAPER

The impact of inflammation on prostate tumor dynamics: A pathological perspective on prostate cancer and benign prostatic hyperplasia

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Summary *Introduction: Chronic inflammation is associated to the pathogenesis of prostate cancer (PCa) and benign prostatic hyperplasia (BPH).*
This study evaluated the correlation between inflammatory markers fibroblast growth factor-2 (FGF2), interleukin (IL)-8, and IL-6 in PCa and BPH tissues to understand their involvement in disease progression.
Methods: A cross-sectional investigation was carried out, examining prostate specimens from 62 male patients diagnosed with PCA or BPH. Specimens were taken via transurethral resection of the prostate (TURP) and stained with hematoxylin and eosin to look for inflammatory infiltrates and aggressiveness.
The levels of FGF2, IL-8, and IL-6 were evaluated using ELISA. Chi-square and logistic regression tests were used in the statistical analysis.
Results: High-grade inflammation was found in all BPH cases (100%), but not in PCa cases. In BPH tissues, elevated levels of IL-8 and IL-6 had a significant correlation with high-grade inflammation ($p < 0.05$). On the other hand, PCa tissues had considerably greater FGF2 levels than benign tissues ($p < 0.05$). Elevated FGF2 levels and the lack of high-grade inflammation in PCa tissues point to different pathogenic processes in PCa and BPH.
Conclusions: This study emphasizes the importance of chronic inflammation in BPH development, with IL-8 and IL-6 playing essential roles. The results imply that treating BPH by focusing on IL-8 and IL-6 may be beneficial. Increased levels of FGF2 in PCa tissues suggest that this protein may be used as a biomarker and therapeutic target for PCa. These findings highlight the importance of targeting both inflammatory and growth factor pathways for treating prostatic disorders.

KEY WORDS: *Prostatic inflammation; Prostate cancer; Inflammatory markers; Benign prostatic hyperplasia.*

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INTRODUCTION

Prostate cancer (PCa) and *benign prostatic hyperplasia* (BPH) are increasingly significant health issues, with their prevalence likely to rise due to an aging population (1, 2).
A deeper understanding of the natural history of prostate tumors is crucial for improving early detection and developing effective therapeutic strategies (3). The development of prostate tumors has been linked to a range of factors, including race, age, heredity, diet, and environment. Recent research suggests that prostatic inflammation may play a key role in both PCa and BPH (4-6), highlighting the need for further investigation into this connection (5, 6).
The hypothesis that inflammation can drive cancer cell proliferation has been explored for over 150 years. Recent preclinical research supports the idea that inflammation plays a role in the development and progression of PCa. The correlation between prostatic inflammation and BPH has been recognized since as early as 1937 (7). Despite these historical and preclinical insights, there remains a scarcity of comprehensive clinical data directly linking prostatic inflammation with tumor development and progression.
Understanding the immune pathways associated with prostate tumors could lead to novel therapeutic strategies (3,8). The inflammatory infiltrates found in prostate glands differ in type, intensity, and location, indicating the participation of various molecular processes (9). Pathological research is particularly valuable in this context, as it can provide more reliable insights into the association between inflammation and prostate tumors compared to epidemiological studies alone (5, 10).
Recent studies have identified inflammatory cytokines such as fibroblast growth factor-2 (FGF2) interleukin (IL)-8, and IL-6 as potential contributors to prostate tumor development (11, 12). FGF2 is known for its role as a potent growth factor, promoting abnormal prostate growth and the proliferation of basal epithelial cells, thus contributing to the pathogenesis of both PCa and BPH. IL-6 and IL-8 are also critical in stromal growth associated with BPH and cancer progression (11, 13). This study aims to explore the correlation between inflammation and prostate tumor development and progression by investigating these inflammatory markers and their roles in both PCa and BPH.

METHODS

Study population and tissue collection

A cross-sectional study was carried out to examine the

association between prostatic inflammation and the development of tumors. The study involved 62 prostate samples from patients with symptoms of obstruction who were diagnosed with either PCa and BPH. These samples were acquired during TURP procedures between April and September 2018. Participants were recruited from four major *Hospitals in Makassar: Universitas Hasanuddin Hospital, Ibnu Sina Hospital, Awal Bros Hospital, and Wahidin Sudirohusodo Hospital*. The investigation was granted authorization by the Institutional Review Board, and informed consent was gathered from all individuals prior to their participation in the study.

Prostate processing and histological analysis

All collected prostate specimens were processed and subjected to histological analysis. Hematoxylin and eosin staining was performed on all samples. A qualified pathologist examined the specimens to assess the presence and extent of inflammatory infiltrations and their aggressiveness.

Degree of inflammation

Morphological description (typical inflammatory cell density, cells/mm^2) was classified as low grade (individual inflammatory cells, most of which separated by distinct intervening spaces [< 100]), moderate grade (confluent sheets of inflammatory cells with no tissue destruction or follicle formation/ lymphoid nodule [100-500]), and high grade (confluent sheets of inflammatory cells with tissue destruction or follicle/nodule formation [> 500]) (14).

Inflammatory aggressiveness

Inflammation was assessed using a 4-point scale: grade 0 indicates no interaction between glandular epithelium and inflammatory cells; grade 1 denotes contact between glandular epithelium and inflammatory cells, with minimal epithelial dissociation present; grade 2 involves interstitial inflammatory infiltration with limited glandular epithelium disruption (less than 25%); grade 3 reflects glandular epithelium disruption exceeding 25% of the examined material (15). In this study, grades 0 and 1 were classified as having no glandular disruption, and grades 2 and 3 were classified as glandular disruption groups.

Inflammatory location

Stromal inflammatory cells are located in the prostatic stroma, distant from prostatic glands. Periglandular inflammatory infiltrates are centered around glands and ducts, approaching glands and ducts closely. Glandular inflammatory infiltrates are found within the epithelium and/or lumens of glands and ducts (14).

Inflammatory markers evaluation

The inflammatory cytokines FGF2, IL-8, and IL-6 levels in prostate samples were quantified using ELISA kits from R&D Systems (*Minneapolis, MN)*. The procedure followed the manufacturer's instructions. In summary, 100 µL of each sample was added in duplicate to the wells and incubated at room temperature for 1.5 hours. Subsequently, 100 µL of biotinylated antibodies was added to each well and incubated for one hour at 37°C. After this step, streptavidin-horseradish peroxidase was applied for 45 minutes, followed by a 30-minute incubation with 3,3',5,5'-TMB. The reaction was terminated with sulfuric acid, and absorbance was recorded at 450 nm using a PHERAstar microplate reader (*BMG LABTECH, Durham, NC*). FGF2, IL-8, and IL-6 concentrations were quantified in ng/mL.

Prostate-specific antigen (PSA) examination

A 3 cc blood sample was taken from the vein, then centrifuged to take the blood serum. Then, the blood serum was examined by the Architech Plus device from Abbott (*Chicago, Illinois, USA*) using a Monoclonal antibody PSA reagent from Meridian Bioscience (*Memphis, TN, USA*) with catalog #M86806M. The PSA concentrations was quantified in ng/mL.

Statistical analysis

The data were evaluated to distinguish BPH from PCa based on their pathological characteristics. The chi-square test was utilized to evaluate the correlation between inflammatory infiltrates and the presence of prostate diseases. To examine the association between inflammatory infiltrates and prostate diseases aggressiveness, the Kruskal-Wallis test was conducted. Additionally, Spearman correlation test was performed to determine the correlation between PSA, inflammatory markers and age. A p-value of less than 0.05 was deemed statistically significant, with a confidence interval set at 95%. All statistical analyses were conducted using SPSS software.

RESULTS

Baseline characteristics of patients

The study included 62 prostate glands from male subjects (Table 1), with 51 glands (82.3%) diagnosed as BPH and 11 glands (17.7%) as prostate cancer. The average age of the patients was 69 ± 9 years, while the median volume of the glands measured 65 ± 35 cm^3. Inflammatory aggressiveness showed glandular disruption in 49 glands (79%) and no glandular disruption in 13 glands (21%). The mean PSA level for PCa was 92.16 ± 39.35.

Table 1.
Characteristics of participants.

Variables	n (%)
Age (years), mean (± SD)	69 (± 9)
Glands	
Benign prostate hyperplasia	51 (82.3)
Prostate carcinoma	11 (17.7)
Degree of inflammation	
Low grade	45 (72.6)
Moderate grade	0 (0)
High grade	17 (27.4)
Inflammatory aggressiveness	
No glandular disruption	13 (21)
With glandular disruption	49 (79)
PSA level (ng/mL), mean (± SD)	
PCa	92.16 (± 39.35)
BPH	20.54 (± 24.53)
Prostate volume (cc), mean (± SD)	65 (± 35)

PSA: Prostate specific antigen; PCa: Prostate cancer; BPH: benign prostatic hyperplasia.

Table 2.
Pathological features of inflammation in 62 prostate glands.

Variables	BPH	PCa	P-value
Degree of inflammation			
Low grade	34 (75.6)	11 (24.4)	0.026
Moderate grade	0 (0)	0 (0)	
High grade	17 (100)	0 (0)	
Inflammatory location			
Stromal	9 (69.2)	4 (30.8)	0.22
Periglandular	0 (0)	0 (0)	
Glandular	42 (85.7)	7 (14.3)	

PCa: Prostate cancer; BPH: benign prostatic hyperplasia.

Table 3.
The comparison of clinical data and inflammatory marker between patients with low and high grade of inflammation.

Variable	Degree of inflammation		P-value
	Low grade	High grade	
Serum PSA levels (ng/mL), mean (± SD)	38 (42)	114 (334)	0.992
Age (years), mean (± SD)	70 (9)	66 (8.4)	0.145
Prostate volume (cc), mean (± SD)	67 (36)	57 (28)	0.394
IL-6 (ng/mL), mean (± SD)	382 (207)	638 (205)	0.000298
IL-8 (ng/mL), mean (± SD)	99 (43)	149 (41)	0.000149
FGF-2 (ng/mL), mean (± SD)	190 (43)	94 (67)	0.000074

PSA: Prostate specific antigen; IL-6: interleukin-6; IL-8: interleukin-8; FGF: fibroblast growth factor-2.

Pathological features of inflammation

Table 2 summarizes the pathological features of inflammation in the prostate glands as observed in patients with PCa and BPH. Out of the 62 patients, 45 exhibited low-grade inflammation (low-grade inflammation was present in 34 [75.6%] BPH glands and 11 [24.4%] PCa glands). In contrast, all 17 cases of high-grade inflammation were found in BPH glands, showing significant difference ($p < 0.05$). Regarding inflammation location and aggressiveness, 13 glands had stromal-only inflammation (9 in BPH and 4 in PCa), and 49 glands had glandular involvement (42 in BPH and 7 in PCa). The differences in inflammation locations were not statistically significant ($p > 0.05$).

Classification and degree of inflammation

Figure 1 illustrates the classification and degree of inflammation. Low-grade inflammation was the most prevalent pattern, characterized by a scattered infiltrate of inflammatory cells within the stroma. It was found in 34 (75.6%) BPH glands and 11 (24.4%) PCa glands. In contrast, high-grade inflammation, involving extensive areas of confluent infiltrate, was less common and observed in 17 (100%) BPH glands. A significant correlation was observed between the degree of inflammation and prostate diseases aggressiveness (rho = 0.786, $p < 0.05$). High-grade inflammation was linked to glandular disruption, whereas low-grade inflammation was associated with the absence of glandular disruption.

Comparison of clinical data and inflammatory markers

Table 3 compares clinical data and inflammatory markers between patients experiencing low-grade and high-grade inflammation. Patients with high-grade inflammation exhibited higher serum PSA levels than those with low-grade inflammation (114 vs. 38), this difference was statistically significant ($p < 0.05$).

Association between inflammatory markers (IL-6, IL-8, and FGF-2) and age with serum PSA levels

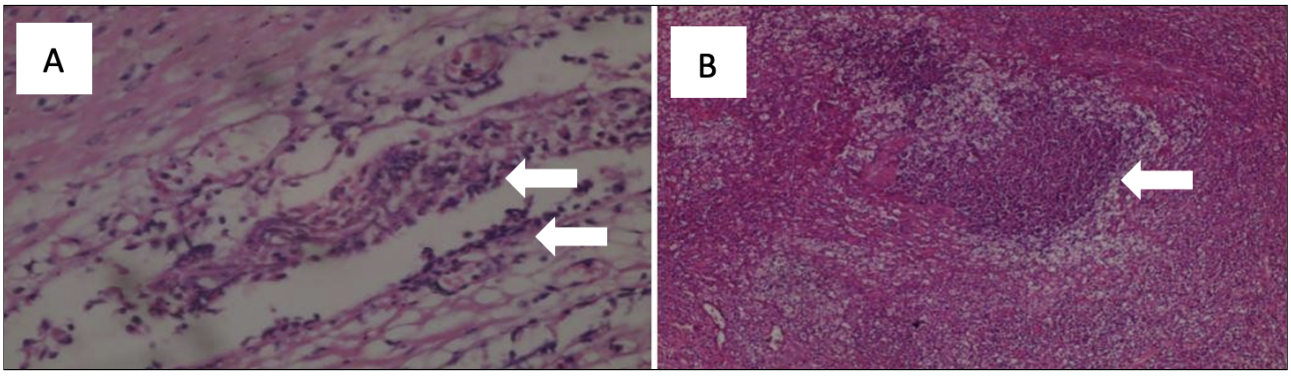
In table 4, no correlation was shown between the inflammatory markers (IL-6, IL-8, and FGF-2) and serum PSA

Table 4.
Correlation between PSA, inflammatory markers and age.

Variable	Variables	Statistics	
PSA	IL-6	Correlation coefficient	0.157
		p-value	0.322
	IL-8	Correlation coefficient	0.113
		p-value	0.475
	FGF-2	Correlation coefficient	-0.077
		p-value	0.630
	Age	Correlation coefficient	-0.52
		p-value	0.742

Spearman correlation test.

Figure 1.
Degree of inflammation based on histopathological examination: A. Low-grade inflammation [presence of scattered inflammatory cells (arrow)] (HE staining, magnification 10x); B. High-grade inflammation [extensive areas of inflammation with the formation of lymphoid nodules (arrow)] (HE staining, magnification 4x).



levels (rho = 0.157, p = 0.322; rho = 0.113, p = 0.475; and rho = -0.077, p = 0. 630, respectively). Additionally, serum PSA levels did not show a correlation with the patients' age (rho = 0.069, p = 0.626).

Increased inflammatory marker concentration in prostate diseases tissue

The levels of FGF2, IL-8, and IL-6 were measured in prostate diseases samples. Patients with high-grade inflammation had significantly higher concentrations of IL-6 compared to those with low-grade inflammation (638 *vs.* 382, $p < 0.05$). The mean IL-6 concentration in benign tissues was recorded at 493 pg/ml, whereas in cancerous tissues, it was 264 pg/ml, indicating a significant difference ($p < 0.05$; Figure 2).

Likewise, IL-8 levels were found to be greater in high-grade inflammation cases compared to low-grade inflammation (149 *vs.* 99, $p < 0.05$). The mean IL-8 concentration was 120 pg/ml in benign tissues and 83 pg/ml in cancer tissues ($p < 0.05$; Figure 3).

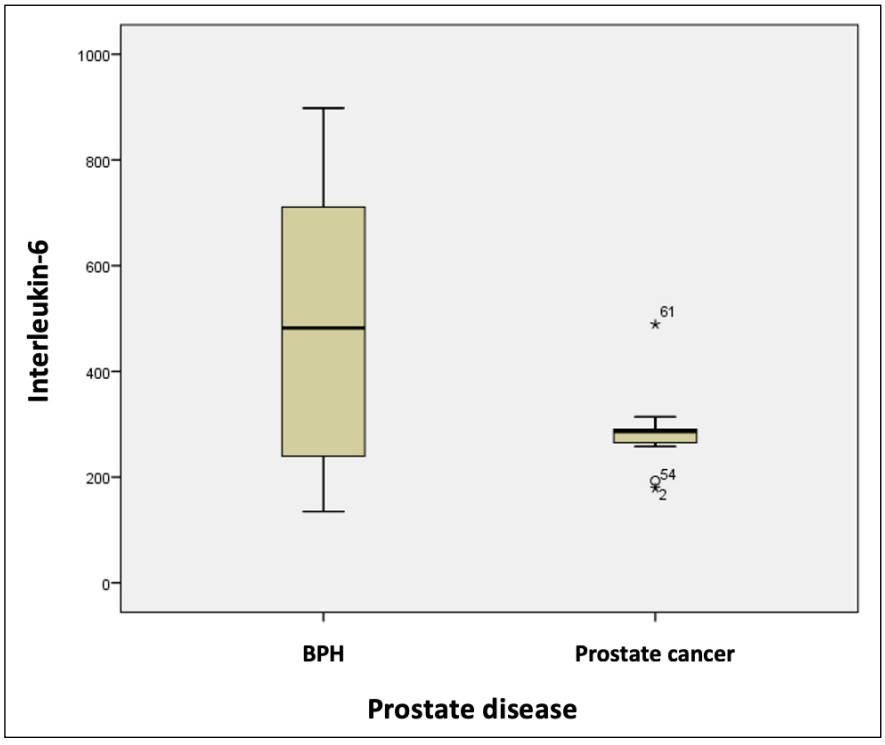


Figure 2.
The comparison of IL-6 tissue levels between prostate diseases (p-value < 0.05).

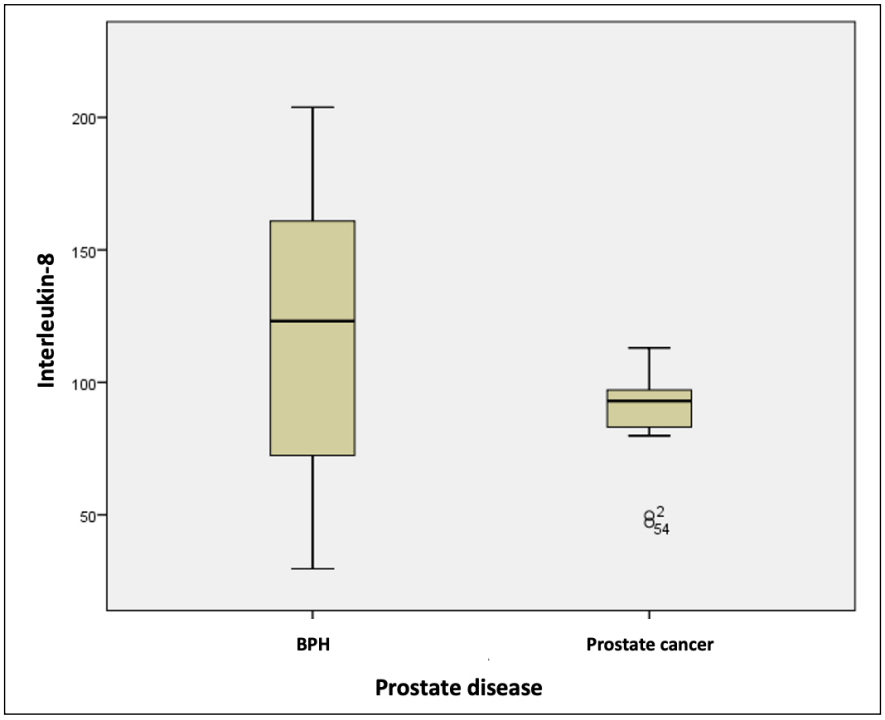


Figure 3.
The comparison of IL-8 tissue levels between prostate diseases (p-value < 0.05).

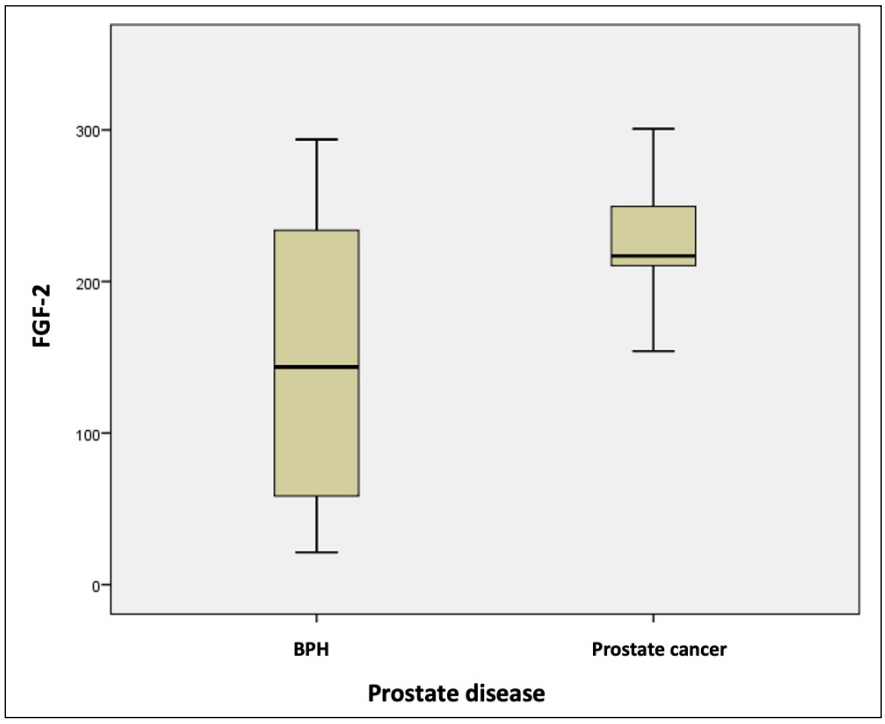


Figure 4.
The comparison of FGF-2 tissue levels between prostate diseases (p-value < 0.05).

Interestingly, FGF2 concentration was higher in low-grade inflammation compared to high-grade inflammation (190 *vs.* 94, $p < 0.05$). The mean FGF2 concentration was higher in cancer tissues compared to benign tissues (238 *vs.* 148, $p < 0.05$; Figure 4).

Discussion

Chronic inflammation is associated to the development of various prostatic conditions, but the precise roles and mechanisms of inflammatory markers like FGF2, IL-8, and IL-6 are still not well understood. In this study, prostate samples from patients with PCa and BPH were examined, with a focus on inflammation presence and severity, and the concentrations of FGF2, IL-8, and IL-6. High-grade inflammation was found in all BPH cases, but not in PCa cases. Elevated IL-8 and IL-6 levels were detected in BPH tissues with high-grade inflammation, while FGF2 concentrations were significantly higher in cancerous tissues compared to benign tissues. The presence of high-grade inflammation in all BPH cases and its absence in PCa cases suggest a strong link between inflammation and BPH pathogenesis. Chronic inflammation appears to be a critical driver of hyperplastic growth in the prostate, as indicated by the elevated levels of IL-8 and IL-6 in inflamed tissues. This finding implies that targeting inflammatory pathways could be a potential therapeutic strategy for BPH.

One potential reason for the lack of significant inflammation in PCa tissues is that inflammation's role in PCa may be intricate and influenced by the context. In the initial phases of PCa, inflammation may be a key factor in fostering carcinogenesis. However, as the cancer advances, elements like genetic mutations and epigenetic alterations may take precedence in facilitating tumor growth. According to De *Marzo et al.*, inflammation may trigger the onset of cancer, but further oncogenic developments are necessary for the progression to full malignancy (16).

IL-6 and IL-8 levels

The elevated levels of IL-8 and IL-6 in BPH tissues highlight their significant role in promoting an inflammatory microenvironment. IL-6 is known for its multifunctional role in immune response and cell proliferation, while IL-8 is involved in the recruitment of inflammatory cells and angiogenesis. These findings indicate that IL-8 and IL-6 are key mediators in the inflammatory processes contributing to BPH development.

The heterogeneity of inflammatory responses might also influence the overall impact of inflammation on prostate disease progression (17). As the inflammatory infiltrates in prostate tissues are heterogeneous in nature, severity, and location hence it is a possible explanation to why the elevated IL-6 and IL-8 are significant in BPH but not uniformly present in PCa tissues (17, 18).

FGF2 levels

The markedly elevated levels of FGF2 found in PCa tissues compared to benign tissues suggest that growth factors could be more critical in the advanced stages of cancer development. FGF2 contributes to cell growth, differentiation, and angiogenesis, all of which are vital processes for tumor progression and metastasis (19). This finding suggests that FGF2 could be a potential biomarker for PCa and a target for therapeutic interventions. The elevated levels of FGF2 in PCa tissues support the idea that as PCa progresses, growth factors like FGF2 become more critical in sustaining tumor growth and promoting metastasis (20-22).

Inflammation's Role in BPH vs PCa: *Where are we now*?

In their study, *Inamura and Terada* highlighted the roles of IL-8 and IL-6 in benign prostatic hyperplasia (BPH), explaining how these cytokines facilitate tissue remodelling and smooth muscle contraction, which can affect the progression of the disease. This finding aligns with our results, which demonstrate elevated levels of IL-8 and IL-6 in BPH tissues with marked inflammation (23). Based on our observations, it seems likely that these cytokines are key players in the inflammatory process, acting as the molecular pathways through which chronic inflammation influences prostatic diseases.

Other research has also pointed to this, linking it to the pro-inflammatory environment created by increased levels of IL-8 and IL-6 (10, 24).

We also found in our observation that high-grade inflammation is found predominantly in BPH cases, as proposed by *Kramer et al.* who stated BPH might be an immune inflammatory disease, validating the association between inflammation and prostatic diseases. They found that inflammatory infiltrates are common in BPH tissues and are associated with disease severity (24, 25).

Robert et al. also found that inflammatory infiltrates are common in BPH tissues and are associated with disease severity (26). Further reinforcing the idea that inflammation plays a crucial role in the severity and progression of BPH.

De Marzo et al. discussed how chronic inflammation in the onset and progression of prostate cancer. They emphasized that chronic inflammation could foster a microenvironment conducive to cancer development, which aligns with our findings of increased FGF2 levels in prostate cancer tissues (16).

Their study suggested that inflammation could drive genetic and epigenetic changes that promote malignancy, aligning with our findings regarding the role of inflammatory markers.

Bridging the current gap

Our findings further reinforce the theory that chronic inflammation is a key factor in the development of BPH. The significant association between high-grade inflammation and BPH also supports the idea that targeting specific inflammatory pathways could be a potential therapeutic strategy. Increased levels of IL-8 and IL-6 suggest these cytokines are critical mediators of the inflammatory processes driving BPH, providing a deeper explanation of the disease's pathogenesis. The inflammation-driven model of disease was also proposed by as *Kramer et al.* who suggested that BPH might be fundamentally an immune inflammatory disease (25). Moreover, the absence of high-grade inflammation in PCa tissues, contrasted with the higher levels of FGF2, indicating that different mechanisms may be at play in PCa and BPH. This supports the hypothesis that while inflammation initiates BPH, other factors such as growth factors like FGF2 become more critical in later stages of PCa (5, 16, 27).

The differential expression of FGF2, IL-8, and IL-6 in PCa and BPH and tissues has significant clinical implications. Anti-inflammatory treatments targeting IL-6 and IL-8 may offer therapeutic benefits for patients with BPH by mitigating the inflammatory processes that drive hyperplasia. For instance, agents that block IL-6 signalling, such as tocilizumab, have shown efficacy in treating inflammatory diseases and might be repurposed for BPH treatment (28, 29). Furthermore, the elevated FGF2 levels in PCa suggest that therapies aimed at inhibiting FGF2 could be more relevant for managing PCa. Anti-FGF2 therapies, such as the use of FGFR inhibitors, are being explored in various cancers and could potentially be adapted for PCa (30). These targeted approaches could lead to more effective treatments tailored to the underlying pathophysiology of each condition (31). Overall, our findings suggest that a dual approach targeting both inflammation and growth factors might be necessary to effectively manage prostatic diseases, aligning with the multiple approaches for the treatment strategies proposed by recent clinical (31, 32).

A limitation of this study is that it included only 62 prostate glands, with 51 diagnosed with BPH and 11 with PCa. This relatively small sample size may limit the generalizability of the findings to a broader population. The study found no high-grade inflammation in PCa tissues, which raises questions about the role of inflammation in the later stages of cancer. This absence may indicate that other factors, such as genetic mutations, play a more significant role in PCa progression, but the study does not explore these factors in depth.

Conclusions

This study deepens our understanding of the distinct roles of FGF2, IL-8, and IL-6 in PCa and BPH. A significant correlation was observed between high-grade inflammation and BPH, characterized by increased levels of IL-8 and IL-6, while such inflammation was not present in PCa tissues. Conversely, FGF2 levels were found to be notably elevated in PCa tissues. These findings suggest different pathogenic mechanisms in BPH and PCa, with growth factors like FGF2 becoming more prominent in cancer progression. Future studies should focus on longitudinal designs to clarify the causal correlation between inflammation and prostate disease progression.

Investigating the molecular mechanisms underlying the differential expression while exploring other inflammatory cytokines. Conducting multicenter studies could be highly beneficial for several reasons: multicenter studies can recruit participants from various geographical locations and demographics, leading to a more diverse patient population. This diversity can help ensure that the findings are generalizable across different groups, which is crucial for understanding the broader implications of inflammation in prostate diseases. Researchers can significantly increase the sample size by pooling data from multiple centers. A larger sample size enhances the study's statistical power, allowing for more robust conclusions regarding the associations between inflammatory markers and prostate conditions.

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Declarations

Ethical approval: *This protocol was approved by the Institutional Review Board at our institution (no. UH18010030). All procedures involving human participants were performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.*

Availability of data and material: *The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.*

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