RELATIONSHIP BETWEEN BENIGN PROSTATIC HYPERPLASIA AND CORONARY ARTERY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: *The prevalence of Benign Prostate Hyperplasia (BPH) increased to 40% in men over 40 and then to about 80% in men over 70. Prior research has demonstrated a correlation between inflammatory processes in the development of Benign Prostatic Enlargement (BPE), Lower Urinary Tract Syndrome (LUTS), and coronary artery disease (CAD) and symptoms of atherosclerotic illness, such as dyslipidemia, hypertension, and non-insulin-dependent diabetic mellitus.* ***Objective:*** *In this study, we would like to review studies regarding the relationship between BPH and CAD.* ***Material &Methods:*** *This study was a combination of systematic review followed by a meta-regression analysis. Performed on PubMed and Google Scholar. Randomized controlled trials, prospective and retrospective cohort studies were included in the study. The search was performed in English and was limited to articles published between January 1st, 2000 until October 31st, 2023.* ***Results:*** *Database search yielded a total of 103 articles, which were systematically eliminated, leaving 7 relevant articles. Analyzed articles showed a significant relationship between BPH and CAD. CAD was proven to be significantly able to provide a higher risk on BPH by 2.99 times compared to control.* ***Conclusion:*** *Compared to individuals without BPH, there was a substantial correlation between CAD and BPH patients.*

Keywords:*Benign prostate hyperplasia, coronary artery disease, lower-urinary tract syndrome, systemic review.*

ABSTRAK

Pendahuluan:*Prevalensi hiperplasia prostat jinak (BPH) meningkat menjadi 40% pada pria di atas 40 tahun dan kemudian menjadi sekitar 80% pada pria di atas 70 tahun. Penelitian sebelumnya telah menunjukkan korelasi antara perkembangan pembesaran prostat, Lower-Urinary Tract Syndrome (LUTS), penyakit jantung koroner (PJK) dan gejala penyakit aterosklerotik, seperti dislipidemi, hipertensi, dan diabetes melitus yang tidak bergantung pada insulin.* ***Tujuan:*** *Dalam penelitian ini, kami ingin meninjau penelitian mengenai hubungan antara BPH dan PJK.****Bahan & Cara:*** *Penelitian ini merupakan kombinasi tinjauan sistematis yang diikuti dengan analisis meta-regresi. Artikel dicari pada PubMed dan Google Scholar. Studi yang dimasukkan dalam penelitian adalah randomized controlled trials (RCTs), studi kohort prospektif dan retrospektif. Pencarian dilakukan dalam bahasa Inggris, dan dibatasi pada artikel yang diterbitkan antara 1 Januari 2000 hingga 31 Oktober 2023.* ***Hasil:*** *Pencarian database menghasilkan total 103 artikel. 96 artikel tereliminasi secara sistematis dan menyisakan 7 artikel relevan. Artikel yang dianalisis menunjukkan hubungan yang signifikan antara BPH dan PJK. PJK terbukti secara signifikan mampu memberikan risiko lebih tinggi terhadap BPH sebesar 2.99 kali dibandingkan kontrol.* ***Simpulan:*** *Terdapat korelasi substansial antara pasien CAD dan pasien BPH, bila dibandingkan dengan individu tanpa BPH.*

Kata kunci: *Hiperplasia prostat jinak, penyakit jantung koroner, lower-urinary tract syndrome, sistematik review.*

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INTRODUCTION

Men often suffer from benign prostatic hyperplasia (BPH), a common genitourinary disorder. According to reports, the prevalence of BPH increased to 40% in men over 40 and then to about 80% in men over 70.[1] Although BPH is a histological process, men are commonly diagnosed with BPH in clinical settings if they exhibit persistent or bothersome lower urinary tract symptoms and an enlarged prostate on digital rectal examination.

The exact origin of BPH is unknown, although it appears to be multifactorial as studies linking androgens and estrogens to the proliferation of stromal and epithelial cells in the prostate as well

as the activation of fibromuscular expansion.[2] It was discovered that diabetes patients have considerably lower perfusion rates in the prostate transition zone (TZ), where BPH originates, as compared to healthy controls.[3] An essential and perhaps androgen-dependent stage in the development of BPH and atherosclerosis is smooth muscle proliferation. Insulin-like growth factor (IGF-1) is also involved in the pathophysiology of coronary artery disease (CAD) and BPH.[4]

Prior research has demonstrated a correlation between inflammatory processes in the development of Benign Prostatic Enlargement (BPE), Lower Urinary Tract Syndrome (LUTS), and coronary artery disease (CAD) and symptoms of atherosclerotic illness, such as dyslipidemia, hypertension, and non-insulin-dependent diabetic mellitus.[5] Atherosclerotic plaque instability and rupture, which result in acute cardiovascular events, are mostly attributed to inflammation, both locally and systemically.[6] Earlier cross-sectional research have shown that compared to the general population, men with BPH or BPH-related LUTS have a higher prevalence of CAD.[7]

OBJECTIVE

In this study, we would like to review studies regarding the relationship between BPH and CAD.

MATERIAL &METHODS

This study was a combination of systematic review followed by a meta-regression analysis. Performed on the PubMed, Cochrane Database of Systematic Reviews, Google Scholar, and Directory of Open Access Journals (DOAJ) database, the search was conducted in English, using combination of keywords such as 'benign prostatic hyperplasia,' 'lower urinary tract symptoms,' 'acute coronary syndrome,' 'coronary artery disease,' and 'myocardial infarction.' The search was performed with a combination of some or all of these keywords, both in the title and abstract of the article. Search is limited to publications in the period January 1st, 2000 to October 31th, 2023.

Study designs included in this study were retrospective and prospective cohort studies, interrupted time series analysis, and cross-sectional studies. Literature review articles, case series, letters, notes, conference abstracts, and conference articles were excluded. Data were extracted using a standardized table that includes the name of the authors, year of publication, study design, study setting, number of subjects, the treatment used, and the key findings of each study. After searching and filtering articles based on search keywords, article analysis was carried out manually by considering the relevance of the title and abstract. Articles that meet the inclusion criteria and exclusion criteria are not clear will be analyzed further by reading the full text of the article and entering the relevant information in the data extraction table. The results obtained in the included studies will be compared with the results of other systematic reviews and other literature. Meta-regression analysis was performed to explore potential determinants of heterogeneity.

RESULTS

A systematic search was carried out and yielded 103 articles (Fig. 1). A total of 83 articles remained after rechecking and excluding duplicate articles. A total of 41 articles were eligible for this study. Then, after a comprehensive review of the full-text articles, the remaining 7 articles were included in this study. The results of the database search are described in Figure 1. The summary of each included study is described in Table 1.

Wang et al. BPH was linked to increased risks of heart disease, stroke, and CVD in Chinese adults, especially in males under 60. According to the study, BPH detection may be important for early CVD prevention and risk assessment.[1]

In a cross-sectional investigation including a cohort of patients with LUTS–BPH, Russo et al. found that males with moderate–severe LUTS had a greater than five-fold increase in their Framingham CVD risk score of ≥ 10%.[8]

In a large group of healthy, aging males, Meigs et al. discovered that CAD and free PSA levels independently increase risk for development of clinical BPH over a 9-year period, but cigarette smoking and increased physical activity appear to be protective factors.[9]

A major contributing factor to the pathophysiology of BPH may be an age-related impairment of blood supply to the lower urinary tract, as suggested by Berger et al.'s finding that patients with severe vascular disease had a significantly lower color pixel density and a higher resistive index in the transitional zone than healthy subjects. A potential contributing factor to the development of BPH is persistent ischaemia, which can be brought on by vascular injury.[2]

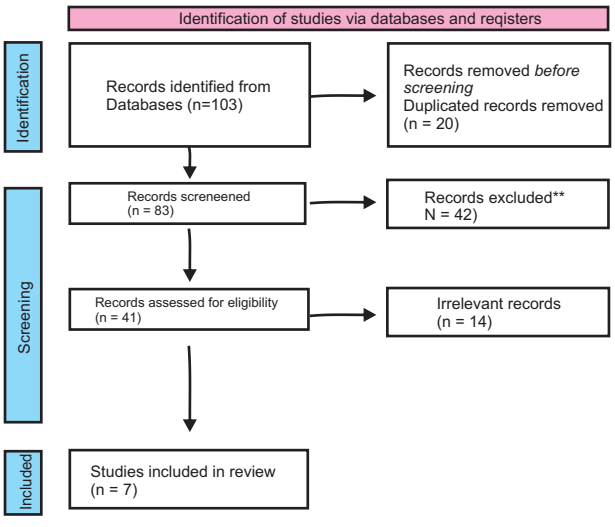

Figure 1. Study Flow Chart.

Inci et al. demonstrated that prostate volume (PV), IPSS, and postmictional residual urine volume (PMR) are larger in individuals with coronary artery ectasis (CAE) as compared to controls with normal coronary angiograms. According to this study, endothelial dysfunction and vascular disease may be shared by BPH, LUTS, and CAE, but they may also be distinct conditions. According to this study, BPE and LUTS were at least as common in CAE as they were in CAD. LUTS and BPE should therefore be considered during follow-ups with CAE patients.10 Compared to patients with BPH, those without BPH experienced CAD less frequently. An essential and perhaps androgen-dependent stage in the development of BPH and atherosclerosis is smooth muscle proliferation.[11]

Even after eliminating participants with risk factors, participants with BPH had a considerably

Table 1. Summary of reviewed studies.

Author	Year	Design	Population (n)	Origin	Key finding
Wang et al.[1]	2022	cohort	5242	China	BPH was linked to increased risks of heart disease, stroke, and CVD in Chinese males, especially in those under 60
Russo et al.[8]	2015	Cross sectional	336	Italy	Men with moderate-to-severe LUTS had a five-fold higher chance of having a Framingham CVD risk score of ≥10%..
Meigs et al.[9]	2001	Cohort	1709	US	In a large cohort of healthy, aging men, free PSA levels and cigarette smoking independently enhance the risk of developing clinical BPH over a 9-year period. Increasing physical activity and quitting smoking appear to be preventive against this risk.
Berger et al.[2]	2006	Cohort	139	Austria	The development of BPH is mostly attributed to age-related deterioration of the prostate's blood flow.
Inci et al.[10]	2015	Cohort	558	Turkey	In addition to endothelial dysfunction and a shared vascular pathology, BPE, LUTS, and CAE may be distinct illnesses.
Weisman et al.[11]	2000	Retrospective	700	US	An essential and perhaps androgen-dependent stage in the development of BPH and atherosclerosis is smooth muscle proliferation.
Khandelwal et al.[12]	2017	Cross sectional	150	India	Those with BPH were shown to have a considerably greater incidence of CAD.

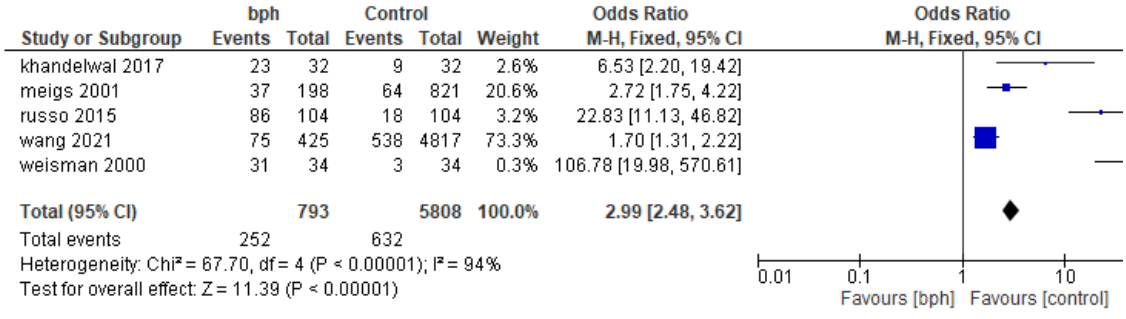

Figure 2. Forest Plot for Relationship between BPH and CAD.

increased incidence of CAD. Mean serum PSA and mean prostatic volume were also considerably greater in CAD individuals, as did the incidence of BPH. As a result, there may be a strong link between CAD and BPH.[12]

Figure 2 shows that results of the meta-analysis using a random effect approach showed that the overall odds ratio was 2.99 (95% CI 2.48-3.62), meaning that CAD was proven to be significantly able to provide a higher risk on BPH by 2.99 times compared to control. Statistical analysis showed very significant results ($p<0.00001$) and heterogeneity (I2) of 94% showed heterogeneous data distribution (random effect model)

The analysis in Figure 3 shows that there is a possibility of publication bias with an asymmetric axis shown by the distribution of 2 funnel plot on the left and 3 funnel plots on the right. The standard error of the left funnel plot is 0.15-0.25 and the standard error of the right funnel plot is 0.3–0.825..

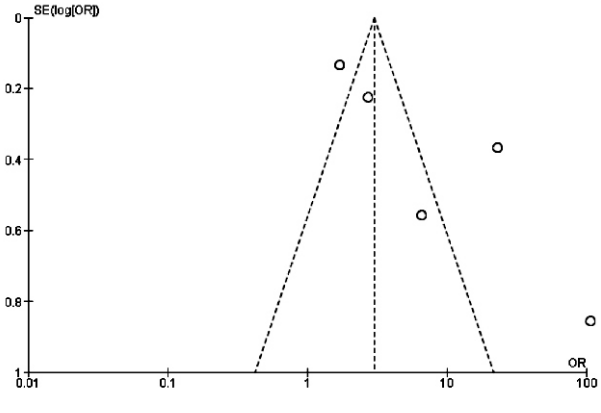

Figure 3. Funnel Plot for Relationship between BPH and CAD.

DISCUSSION

Men with BPH or BPH-related LUTS had a higher prevalence of CVD risk factors or CVD than men without these disorders, according to certain previous cross-sectional studies. The most significant increases in systolic blood pressure were observed to be connected with BPH-related LUTS, such as urgency, nocturia, and increased frequency of urination (all $P<0.001$).[7]

The results of the Russo et al.[8] investigation supported the theory that there was a direct correlation between the 10-year CVD risk score and the severity of LUTS. Despite prior findings regarding these interactions, the underlying theories are still up for debate. Although the pathophysiology of LUTS is thought to be complex, age-related changes in the structure and function of the bladder appear to be a major component.[13]

According to Meigs et al.,[9] men with CAD had a two-fold increased risk for clinical BPH, but men who were more physically active had a lower risk. Other studies have indicated a preventive effect of exercise on the development of BPH.[14] As the age-adjusted odds ratio for CAD predicting clinical BPH did not significantly reduce after controlling for connections with smoking or decreased physical activity, these characteristics were not shown to be responsible for the effect of CAD. Furthermore, there was no correlation found between clinical BPH and total calorie and dietary fat intake, sexual activity, usage of various drugs that affect smooth muscle or sympathetic nervous system function, or race.

Recent research has found that males with LUTS who are diabetic had significantly faster annual prostatic growth rates than men who are not diabetic.[15] Moreover, following age adjustment,

diabetes is linked to more severe BPH symptoms.[16] It has been demonstrated time and time again that peripheral occlusive disease and long-term diabetes mellitus are markers of atherosclerotic disease and an independent predictor of substantial atherosclerosis.[17] Consequently, a reduction in NO levels and the development of insulin resistance and diseases linked to glucose and lipid metabolism result in modifications to the endothelium-mediated vasodilatation processes. Specifically in arterioles and capillaries, this disturbance of normal endothelial vascular function affects insulin's metabolic actions, creating a negative feedback cycle.[18]

According to a study by Ozden et al., people with metabolic syndrome had considerably greater median annual growth rates for both the transition zone and the total prostate when compared to those without the condition. Traditional risk factors for coronary artery disease (CAD) include obesity, hypertension, dyslipidemia, smoking, and diabetes. These factors influence the development of CAD.[19]

Hypoxia in the prostate tissue can happen to patients who have either localized or widespread vascular injury. Hypoxia stimulates the release of angiogenic growth factors, including VEGF, fibroblast growth factors 2 and 7, transforming growth factor b, and interleukin 8 (IL-8), in addition to hypoxia-inducible factor 1. This shows that hypoxia may be a trigger for prostatic growth.[20] An additional risk factor for atherosclerotic disease is male gender. Numerous studies examined how androgens affected serum lipid levels.[21]

The function of chronic inflammation may be the basis for one of the possible processes explaining the link between BPH and CAD risk. It is commonly recognized that growth factors and androgens can promote the growth of prostatic nodules and prostatic cell proliferation, which can worsen BPH and cause chronic prostatic inflammation. Consequently, pro-inflammatory factors can release pro-inflammatory cytokines (like tumor necrosis factor, or TNF-α) and growth factors (like insulin-like growth factor, or IGF-1) when there is an inflammatory insult.[22]

CONCLUSION

Compared to individuals without BPH, there was a substantial correlation between CAD and BPH patients. More study should be conducted to analyze the relationship between BPH and the components of metabolic syndrome. There also should be more study using quantitative prostate parameter such as PSA and prostate volume.

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