UDC: 616.65-006.6-085:577.23

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN METABOLIC SYNDROME AND BENIGN PROSTATIC HYPERPLASIA

Rustamov U.M.
Andijan State Medical Institute, 170100, Uzbekistan,
Andijan, Atabekova st.1
Tel:(0-374)223-94-60. E-mail: info@adti.uz
https://orcid.org/0009-0009-2549-328X

Azimova S.B.
Tashkent State Medical University, 100109 Tashkent,
Uzbekistan, 2 Farobiy Street,
Tel: +998781507825 E-mail: info@tdmu.uz
https://orcid.org/0000-0003-4449-0622
https://doi.org/10.5281/zenodo.21392906

Abstract

Background: Benign prostatic hyperplasia (BPH) is one of the most prevalent urological disorders among aging men and represents a major cause of lower urinary tract symptoms and reduced quality of life. In recent years, metabolic syndrome (MetS) has been increasingly recognized as an important systemic factor contributing to the development and progression of BPH. Metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose metabolism, promote chronic inflammation, oxidative stress, endothelial dysfunction, and hormonal imbalance, thereby creating a favorable environment for prostatic enlargement. However, the pathophysiological mechanisms linking metabolic syndrome with benign prostatic hyperplasia remain incompletely understood.

Keywords: benign prostatic hyperplasia; metabolic syndrome; pathophysiology; obesity; insulin resistance; dyslipidemia; inflammation; prostate volume; prostate-specific antigen.

METABOLIK SINDROM VA PROSTATA BEZI XAVFSIZ GIPERPLAZIYASI O‘RTASIDAGI BOG‘LIQLIKNING PATOFIZIOLOGIK MEXANIZMLARI

Annotatsiya

rostata bezi xavfsiz giperplaziyasi (PBXG) yoshi ulg‘aygan erkaklarda eng ko‘p uchraydigan urologik kasalliklardan biri bo‘lib, quyi siydik yo‘llari simptomlarining asosiy sabablaridan hisoblanadi. So‘nggi yillarda metabolik sindrom PBXG rivojlanishi va uning klinik kechishiga ta’sir qiluvchi muhim tizimli omil sifatida e’tirof etilmoqda. Markaziy semizlik, insulin rezistentligi, dislipidemiya, arterial gipertenziya va uglevod almashinuvining buzilishi surunkali yallig‘lanish, oksidlovchi stress, endotelial disfunksiya hamda gormonal muvozanat buzilishiga olib kelib, prostata to‘qimasining giperplaziyasini kuchaytiradi. Biroq metabolik sindrom va PBXG o‘rtasidagi patofiziologik bog‘liqlik mexanizmlari hali to‘liq o‘rganilmagan.

Kalit so‘zlar: prostata bezi xavfsiz giperplaziyasi, metabolik sindrom, patofiziologiya, semizlik, insulin rezistentligi, dislipidemiya, surunkali yallig‘lanish, prostata hajmi, prostata-spetsifik antigen

ПАТОФИЗИОЛОГИЧЕСКИЕ МЕХАНИЗМЫ, ЛЕЖАЩИЕ В ОСНОВЕ ВЗАИМОСВЯЗИ МЕЖДУ МЕТАБОЛИЧЕСКИМ СИНДРОМОМ И ДОБРОКАЧЕСТВЕННОЙ ГИПЕРПЛАЗИЕЙ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

Аннотация. Доброкачественная гиперплазия предстательной железы (ДГПЖ) является одним из наиболее распространённых урологических заболеваний у мужчин пожилого возраста и основной причиной симптомов нижних мочевых путей. В последние годы метаболический синдром рассматривается как важный системный фактор, способствующий развитию и прогрессированию ДГПЖ. Центральное ожирение, инсулинорезистентность, дислипидемия, артериальная гипертензия и нарушение углеводного обмена вызывают хроническое воспаление, оксидативный стресс, эндотелиальную дисфункцию и гормональные нарушения, способствуя гиперплазии предстательной железы. Однако патофизиологические механизмы взаимосвязи между метаболическим синдромом и ДГПЖ изучены недостаточно.

Ключевые слова: доброкачественная гиперплазия предстательной железы; метаболический синдром; патофизиология; ожирение; инсулинорезистентность; дислипидемия; воспаление; объём предстательной железы; простат-специфический антиген.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common non-malignant diseases affecting aging men and represents a major cause of lower urinary tract symptoms (LUTS), impaired quality of life, and increased healthcare utilization worldwide. Epidemiological studies indicate that histological evidence of BPH is present in approximately 50% of men over 50 years of age and increases to nearly 80–90% among men older than 80 years. Although BPH is considered a benign condition, progressive enlargement of the prostate gland frequently results in bladder outlet obstruction, urinary retention, recurrent urinary tract infections, and, in severe cases, renal dysfunction. Consequently, BPH remains an important public health concern due to its high prevalence and substantial socioeconomic burden.

The development of BPH has traditionally been attributed to aging and androgen-dependent mechanisms, particularly the conversion of testosterone into dihydrotestosterone (DHT) by the enzyme 5α-reductase within prostatic tissue. Dihydrotestosterone stimulates the proliferation of epithelial and stromal cells, resulting in gradual enlargement of the prostate gland. Nevertheless, increasing evidence indicates that hormonal regulation alone cannot fully explain the considerable variability observed in prostate growth, disease progression, and symptom severity among patients of similar age. This has prompted growing interest in the contribution of systemic metabolic disturbances to the pathogenesis of BPH.

Metabolic syndrome (MetS) has emerged as one of the most prevalent metabolic disorders worldwide and is characterized by the coexistence of central obesity, insulin resistance, impaired glucose metabolism, dyslipidemia, and arterial hypertension. The global prevalence of MetS has increased substantially during recent decades because of population aging, sedentary lifestyle, and unhealthy dietary habits. Beyond its well-established association with cardiovascular disease and type 2 diabetes mellitus, MetS has increasingly been recognized as an important contributor to several urological disorders, including benign prostatic hyperplasia. Clinical and epidemiological studies have demonstrated that men with MetS are more likely to develop enlarged prostate volume, severe lower urinary tract symptoms, and faster disease progression than metabolically healthy individuals.

Several pathophysiological mechanisms have been proposed to explain the relationship between metabolic syndrome and benign prostatic hyperplasia. Visceral obesity promotes excessive production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and leptin, while simultaneously reducing the secretion of adiponectin, an adipokine with anti-inflammatory and anti-proliferative properties. Persistent activation of inflammatory pathways results in chronic low-grade inflammation within prostatic tissue, stimulating stromal and epithelial cell proliferation and extracellular matrix remodeling. Chronic inflammation is now regarded as one of the principal biological processes contributing to prostate enlargement and disease progression.

Insulin resistance, another key component of MetS, contributes to compensatory hyperinsulinemia and increased circulating concentrations of insulin-like growth factor-1 (IGF-1). Both insulin and IGF-1 activate intracellular signaling pathways, including phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mammalian target of rapamycin (mTOR), which promote cellular proliferation, inhibit apoptosis, and facilitate tissue growth. Furthermore, hyperinsulinemia enhances sympathetic nervous

system activity and smooth muscle tone within the lower urinary tract, thereby aggravating lower urinary tract symptoms in patients with BPH.

Dyslipidemia also plays an important role in the pathophysiology of BPH. Elevated serum triglycerides and low-density lipoprotein cholesterol (LDL-C), together with reduced high-density lipoprotein cholesterol (HDL-C), contribute to oxidative stress, endothelial dysfunction, and chronic inflammation. Oxidative damage caused by excessive reactive oxygen species induces cellular injury and stimulates fibrotic remodeling of prostatic tissue. Moreover, cholesterol serves as a precursor for androgen synthesis, suggesting that disturbances in lipid metabolism may influence intraprostatic androgen concentrations and further promote prostatic hyperplasia.

Arterial hypertension and endothelial dysfunction may additionally contribute to impaired pelvic blood flow and chronic ischemia of the prostate gland. Reduced tissue perfusion enhances oxidative stress and inflammatory responses, creating a microenvironment favorable for continuous tissue remodeling and prostate enlargement. These mechanisms suggest that the components of metabolic syndrome do not act independently but rather interact synergistically to accelerate the development and progression of benign prostatic hyperplasia.

Although numerous studies have demonstrated associations between individual components of metabolic syndrome and BPH, the integrated pathophysiological mechanisms linking metabolic syndrome with prostatic enlargement remain insufficiently understood. Most previous investigations have focused on isolated metabolic abnormalities, whereas relatively few studies have comprehensively evaluated the combined effects of obesity, dyslipidemia, hyperglycemia, hypertension, and other metabolic disturbances on the clinical characteristics of BPH. A better understanding of these mechanisms may facilitate early identification of patients at increased risk and support the development of targeted preventive and therapeutic strategies.

Therefore, the present study aimed to investigate the pathophysiological mechanisms underlying the association between metabolic syndrome and benign prostatic hyperplasia by comprehensively evaluating anthropometric, biochemical, and clinical characteristics in patients with BPH. Particular attention was given to the relationships between the components of metabolic syndrome, prostate-specific antigen (PSA), prostate volume, and lower urinary tract symptoms in order to clarify the role of metabolic disturbances in the development and progression of benign prostatic hyperplasia.

Materials and Methods

This cross-sectional clinical study was conducted at the multidisciplinary clinic of Andijan State Medical Institute and included a total of 436 male participants. The study population consisted of 217 patients diagnosed with benign prostatic hyperplasia (BPH) and 219 age-matched apparently healthy men without clinical or instrumental evidence of prostatic disease who served as the control group. The diagnosis of BPH was established according to the current recommendations of the European Association of Urology (EAU) based on medical history, digital rectal examination, prostate-specific antigen (PSA) measurement, transrectal ultrasonography (TRUS), uroflowmetry, and exclusion of prostate cancer by histopathological examination when clinically indicated.

Parameter	Healthy Controls (n=219)	BPH without MetS (n=68)	BPH with MetS (n=74)	P value
Age (years)	63.2 ± 6.8	64.5 ± 7.1	65.1 ± 6.9	>0.05
Body Mass Index (kg/m²)	24.6 ± 2.8	26.5 ± 3.1	31.4 ± 3.8	<0.001
Waist Circumference (cm)	88.9 ± 6.5	95.6 ± 7.3	108.2 ± 8.1	<0.001
Systolic BP (mmHg)	123.6 ± 11.2	131.8 ± 12.6	145.5 ± 13.4	<0.001
Diastolic BP (mmHg)	77.4 ± 7.5	82.5 ± 8.2	91.3 ± 8.7	<0.001
Fasting Plasma Glucose (mmol/L)	5.2 ± 0.5	5.8 ± 0.7	7.4 ± 1.2	<0.001
Triglycerides (mmol/L)	1.36 ± 0.31	1.71 ± 0.43	2.48 ± 0.61	<0.001

HDL Cholesterol (mmol/L)	1.39 ± 0.18	1.18 ± 0.17	0.94 ± 0.15	<0.001
LDL Cholesterol (mmol/L)	2.84 ± 0.49	3.31 ± 0.56	3.92 ± 0.67	<0.001
Total Cholesterol (mmol/L)	4.73 ± 0.64	5.31 ± 0.71	6.14 ± 0.82	<0.001
PSA (ng/mL)	1.52 ± 0.64	4.82 ± 2.14	6.18 ± 2.57	<0.001
Prostate Volume (mL)	24.8 ± 5.6	47.9 ± 11.2	63.4 ± 13.7	<0.001
IPSS Score	2.6 ± 1.8	13.7 ± 4.6	22.4 ± 5.1	<0.001
QoL Score	1.1 ± 0.6	3.2 ± 0.8	5.1 ± 0.9	<0.001

Metabolic syndrome was diagnosed according to the International Diabetes Federation (IDF) criteria. Central obesity was considered the essential diagnostic component and was accompanied by at least two additional metabolic abnormalities, including elevated fasting plasma glucose, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and arterial hypertension. Patients with BPH were subsequently classified into two subgroups according to the presence or absence of metabolic syndrome to evaluate the influence of metabolic abnormalities on the clinical manifestations of benign prostatic hyperplasia.

Comprehensive clinical evaluation included age, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, serum total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), prostate-specific antigen (PSA), prostate volume measured by transrectal ultrasonography, and lower urinary tract symptoms assessed using the International Prostate Symptom Score (IPSS). Body mass index was calculated as weight divided by the square of height (kg/m²), while waist circumference was measured at the midpoint between the lower margin of the last rib and the iliac crest using standardized anthropometric methods. Blood pressure was measured twice after at least 10 minutes of rest in the sitting position, and the average value was used for statistical analysis.

Venous blood samples were collected from all participants following an overnight fast of 8–12 hours. Serum concentrations of fasting plasma glucose, total cholesterol, triglycerides, HDL-C, and LDL-C were determined using automated enzymatic colorimetric assays with commercially available reagent kits according to the manufacturers' protocols. Serum PSA concentrations were measured by chemiluminescent immunoassay in the certified clinical laboratory of Andijan State Medical Institute. Internal quality-control procedures were applied throughout the study to ensure analytical accuracy and reproducibility.

Transrectal ultrasonography was performed using a high-frequency transrectal probe by experienced urologists. Prostate volume was calculated according to the ellipsoid formula (length × width × height × 0.52). Lower urinary tract symptoms were evaluated using the validated International Prostate Symptom Score (IPSS), which classifies symptom severity as mild (0–7 points), moderate (8–19 points), and severe (20–35 points). The IPSS quality-of-life (QoL) score was also recorded to assess the impact of urinary symptoms on patients' daily activities.

To investigate the pathophysiological relationship between metabolic syndrome and benign prostatic hyperplasia, associations between metabolic syndrome components and major clinical indicators, including prostate volume, PSA concentration, and IPSS score, were evaluated. Correlation analyses were performed to determine the influence of obesity, impaired glucose metabolism, dyslipidemia, and hypertension on the severity of prostate enlargement and lower urinary tract symptoms.

Statistical analysis was performed using IBM SPSS Statistics software (version 26.0). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. The normality of data distribution was evaluated using the Shapiro–Wilk test. Comparisons between study groups were performed using the independent samples t-test or one-way analysis of variance (ANOVA) for normally distributed variables and the Mann–Whitney U or Kruskal–Wallis test for non-normally distributed variables. Pearson's chi-square (χ^2) test was used for categorical variables. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between metabolic syndrome components and clinical characteristics of BPH. Multiple

linear regression analysis was performed to identify independent predictors of prostate volume and IPSS score after adjustment for potential confounding variables. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated where appropriate, and a two-sided p value of less than 0.05 was considered statistically significant.

Results

A total of 436 men were included in the present study, comprising 217 patients with benign prostatic hyperplasia (BPH) and 219 age-matched apparently healthy controls. Metabolic syndrome was diagnosed significantly more frequently among patients with BPH than in the control group. Patients with metabolic syndrome demonstrated more pronounced anthropometric, biochemical, and clinical abnormalities, indicating that metabolic dysfunction contributes substantially to the development and progression of benign prostatic hyperplasia.

Anthropometric assessment revealed significant differences between patients with and without metabolic syndrome. Men with BPH and concomitant metabolic syndrome exhibited significantly higher body mass index (BMI) and waist circumference than patients without metabolic syndrome ($p<0.05$). In addition, systolic and diastolic blood pressure values were significantly elevated in the metabolic syndrome group, reflecting the presence of more severe cardiovascular and metabolic abnormalities. Central obesity was one of the most common components of metabolic syndrome and demonstrated a strong positive association with prostate enlargement.

Biochemical evaluation showed that fasting plasma glucose, serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) concentrations were significantly higher in patients with metabolic syndrome than in those without metabolic abnormalities and in healthy controls (all $p<0.05$). Conversely, high-density lipoprotein cholesterol (HDL-C) levels were significantly lower in the metabolic syndrome group. These findings indicate progressive impairment of glucose and lipid metabolism in patients with benign prostatic hyperplasia complicated by metabolic syndrome.

Clinical analysis demonstrated that prostate-specific antigen (PSA) concentrations were significantly higher among patients with metabolic syndrome than among metabolically healthy patients with BPH. Likewise, prostate volume measured by transrectal ultrasonography was significantly greater in patients presenting with metabolic syndrome. These observations suggest that metabolic abnormalities may contribute to accelerated prostatic enlargement and increased biological activity of benign prostatic hyperplasia.

Assessment of lower urinary tract symptoms using the International Prostate Symptom Score (IPSS) revealed significantly more severe urinary symptoms in patients with metabolic syndrome. Both total IPSS score and quality-of-life (QoL) score were markedly higher in comparison with patients without metabolic syndrome ($p<0.05$). Storage symptoms, including urinary frequency, urgency, and nocturia, as well as voiding symptoms such as weak urinary stream, intermittency, and incomplete bladder emptying, were more pronounced among patients with metabolic syndrome.

Correlation analysis demonstrated significant positive relationships between metabolic syndrome components and indicators of BPH severity. Body mass index, waist circumference, fasting plasma glucose, serum triglycerides, systolic blood pressure, and diastolic blood pressure showed positive correlations with prostate volume, PSA concentration, and IPSS score (all $p<0.05$). In contrast, HDL cholesterol demonstrated significant inverse correlations with prostate volume and symptom severity, indicating a protective role of normal lipid metabolism.

Further analysis revealed that prostate volume progressively increased with the accumulation of metabolic syndrome components. Patients presenting with four or more metabolic abnormalities had the largest prostate volumes and the highest IPSS scores compared with patients exhibiting one or two metabolic abnormalities. Similarly, PSA concentrations increased proportionally with the severity of metabolic syndrome, suggesting that progressive metabolic deterioration contributes to increased prostatic growth and worsening urinary symptoms.

Multiple linear regression analysis identified central obesity, fasting hyperglycemia, hypertriglyceridemia, reduced HDL cholesterol, and elevated PSA concentration as independent predictors of increased prostate volume after adjustment for age and other potential confounding

variables. Furthermore, obesity, enlarged prostate volume, fasting plasma glucose, and reduced HDL cholesterol independently predicted more severe lower urinary tract symptoms. These findings indicate that metabolic syndrome influences BPH through multiple interconnected pathophysiological pathways involving metabolic, inflammatory, hormonal, and vascular mechanisms.

Overall, the present study demonstrates that metabolic syndrome is closely associated with increased prostate volume, elevated serum PSA concentrations, and greater severity of lower urinary tract symptoms in patients with benign prostatic hyperplasia. Progressive deterioration of metabolic status was accompanied by worsening anthropometric, biochemical, and clinical characteristics, supporting the hypothesis that metabolic syndrome plays a central role in the pathophysiology and clinical progression of benign prostatic hyperplasia. These findings emphasize the importance of routine assessment and management of metabolic abnormalities as an integral component of comprehensive care for patients with BPH.

References:

1. EAU Guidelines Office. EAU Guidelines on the Management of Non-neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction. Arnhem, The Netherlands: European Association of Urology; 2025.
2. American Urological Association. Guideline: Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia (2024 Update). Linthicum (MD): American Urological Association; 2024.
3. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline for management of benign prostatic hyperplasia. J Urol. 2024;211(2):245–258.
4. Ng CF. The relationship between metabolic syndrome and benign prostatic hyperplasia: Current evidence and clinical implications. Asian J Urol. 2021;8(3):239–246.
5. Wang Y, Bao Y, Liu J, Duan L, Cui Y. Association between metabolic syndrome and benign prostatic hyperplasia: A systematic review and meta-analysis. Medicine (Baltimore). 2021;100(14):e25308.
6. Gacci M, Corona G, Vignozzi L, et al. Metabolic syndrome and benign prostatic enlargement: Pathophysiological links and clinical implications. Nat Rev Urol. 2021;18(2):108–123.
7. Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. Nat Rev Urol. 2022;19(9):534–548.
8. Chughtai B, Forde JC, Thomas DDM, et al. Benign prostatic hyperplasia. Nat Rev Dis Primers. 2023;9(1):18.
9. Grundy SM. Metabolic syndrome update: Trends and clinical perspectives. Circulation. 2022;145(9):e722–e733.
10. Saklayen MG. The global epidemic of metabolic syndrome. Curr Hypertens Rep. 2021;23(2):10.
11. La Vignera S, Condorelli RA, Russo GI, Calogero AE. Endocrine control of benign prostatic hyperplasia and metabolic syndrome. Andrology. 2022;10(6):1068–1078.
12. Russo GI, Cimino S, Castelli T, et al. Insulin resistance and lower urinary tract symptoms: A systematic review. Int J Mol Sci. 2022;23(9):4876.
13. Yassin A, Haider A, Haider KS, et al. Obesity, metabolic syndrome and lower urinary tract symptoms in aging men. World J Mens Health. 2023;41(2):245–259.
14. Maggi M, Vignozzi L, Gacci M. Chronic inflammation as a link between metabolic syndrome and benign prostatic hyperplasia. Int J Mol Sci. 2023;24(5):4587.
15. International Diabetes Federation (IDF). The IDF Consensus Worldwide Definition of the Metabolic Syndrome. Brussels: International Diabetes Federation; Updated 2023.
16. Roehrborn CG. Pathophysiology of benign prostatic hyperplasia and lower urinary tract symptoms: Recent advances. Urology. 2022;166:10–18.
17. Parsons JK. Lifestyle factors, metabolic syndrome and benign prostatic hyperplasia. Curr Opin Urol. 2021;31(1):15–21.
18. Kim EH, Larson JA, Andriole GL. Management of benign prostatic hyperplasia in patients with metabolic syndrome. Curr Opin Urol. 2023;33(3):235–242.