EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH
(EEJSAR) ISSN: 2992-4146
©EEJSAR Publications Volume 7 Issue 3 2025

Gut Microbiome and BPH: Unravelling the Role of Dysbiosis in Prostatic Enlargement

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a prevalent condition in aging males, characterized by non-malignant enlargement of the prostate gland, leading to lower urinary tract symptoms (LUTS). Emerging evidence suggests a critical role of gut microbiome dysbiosis in the pathophysiology of BPH. The gut microbiota influences systemic inflammation, hormonal metabolism, and immune responses, all of which have been implicated in prostate enlargement. Disruptions in microbial composition may lead to increased gut permeability, promoting the translocation of inflammatory mediators and metabolic endotoxins that exacerbate prostatic hyperplasia. Furthermore, alterations in the gut microbiome can affect androgen metabolism, particularly dihydrotestosterone (DHT), a key driver of prostate growth. This review explores the complex interplay between gut microbiome dysbiosis and BPH, highlighting potential mechanisms linking microbial imbalances to prostate enlargement. We also discuss emerging therapeutic strategies, including probiotics, prebiotics, and dietary interventions, aimed at restoring gut microbial balance and mitigating BPH progression. Understanding the gut-prostate axis could provide novel insights into the prevention and management of BPH, offering a microbiome-centered approach to male urological health.

Keywords: Gut microbiome; benign prostatic hyperplasia; dysbiosis, inflammation; dihydrotestosterone; metabolic endotoxins; microbiome-targeted therapy

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent condition among aging men, characterized by the non-malignant enlargement of the prostate gland[1, 2]. It affects approximately 50% of men in their 50s, with prevalence increasing to nearly 90% in men aged 80 and older. BPH is a leading cause of lower urinary tract symptoms (LUTS), such as urinary frequency, urgency, weak stream, and nocturia, which significantly impact the quality of life[3]. Traditional risk factors for BPH development include hormonal fluctuations, aging, and genetic predisposition. However, emerging evidence suggests that gut microbiome dysbiosis may play a significant role in BPH pathogenesis[4, 5]. The gut microbiome is a complex and dynamic ecosystem consisting of trillions of microorganisms, including bacteria, fungi, viruses, and archaea. These microbes play essential roles in immune modulation, metabolism, and endocrine signalling [6, 7]. Dysbiosis, an imbalance in microbial composition, has been implicated in various chronic diseases, including metabolic disorders, cardiovascular diseases, and inflammatory conditions. Disruptions in microbial homeostasis may lead to systemic inflammation, altered androgen metabolism, and immune dysfunction, all of which are implicated in prostate enlargement and BPH progression [8, 9]. BPH is a progressive condition characterized by an increase in the size of the prostate gland due to excessive proliferation of stromal and epithelial cells [10, 11]. The enlarged prostate compresses the urethra, leading to obstructive and irritative urinary symptoms. Primary risk factors for BPH include age, hormone imbalance, genetic factors, chronic inflammation, and metabolic syndrome. Recent insights into the gut-prostate axis suggest that gut microbiome alterations may influence prostate health, presenting an exciting avenue for further investigation[12]. Key functions of the gut microbiome include immune modulation, metabolism and nutrient absorption, and hormone regulation. Disruptions in microbial composition can lead to increased intestinal permeability, systemic inflammation, and metabolic dysfunction, all of which have been implicated in the pathophysiology of BPH [13]. Several mechanisms have been proposed to explain how gut dysbiosis may contribute to BPH development and progression: chronic systemic inflammation, altered androgen metabolism, oxidative stress and cell damage, metabolic dysregulation, and immune dysfunction and autoimmunity. Potential therapeutic interventions targeting gut dysbiosis include probiotics and prebiotics, dietary modifications, fetal microbiota transplantation (FMT), anti-inflammatory and antioxidant therapies, and metagenomics-based precision medicine[14]. The connection between gut dysbiosis and BPH represents an exciting area of research that may reshape our understanding of prostate health. While traditional risk factors such as aging, hormonal imbalances, and genetics remain critical, the influence of gut microbiota on systemic

inflammation, androgen metabolism, and immune function provide new insights into BPH pathogenesis[15, 16]. Future studies exploring the gut-prostate axis could lead to innovative microbiome-based interventions, offering potential alternatives or adjuncts to conventional BPH treatments. Addressing gut dysbiosis through dietary, probiotic, and anti-inflammatory strategies may hold promise in mitigating BPH progression and improving patient outcomes.

The Gut Microbiome and Its Role in Systemic Health

The gut microbiome, an intricate ecosystem of bacteria, fungi, viruses, and archaea, is essential for human health, influencing various physiological functions such as metabolism, immune regulation, and hormonal balance[17]. This diverse microbial community interacts with the host in a symbiotic relationship, maintaining gut homeostasis through mechanisms that include nutrient metabolism, production of short-chain fatty acids (SCFAs), immune modulation, and preservation of the intestinal epithelial barrier. A well-balanced microbiome supports digestive processes, prevents pathogenic colonization, and contributes to the synthesis of essential bioactive compounds such as vitamins and neurotransmitters[18]. However, disruptions in this microbial equilibrium, known as dysbiosis, can lead to pathological conditions characterized by systemic inflammation, oxidative stress, and metabolic dysfunction[19]. Dysbiosis has been implicated in various chronic diseases, including obesity, diabetes, cardiovascular disorders, and even neurodegenerative conditions. Importantly, emerging evidence suggests that the gut microbiome may also play a crucial role in benign prostatic hyperplasia (BPH), a non-malignant enlargement of the prostate gland that affects aging men and contributes to lower urinary tract symptoms (LUTS)[20]. BPH development is closely linked to chronic inflammation and hormonal dysregulation, particularly the imbalance of androgens and estrogens [21]. The gut microbiota significantly influences both of these factors through its role in immune homeostasis and the metabolism of hormones such as testosterone and estrogen. Specific gut microbes participate in enterohepatic circulation by regulating enzymes such as β-glucuronidase, which affects the bioavailability and activity of sex hormones. Altered microbial composition may disrupt this balance, leading to increased estrogenic activity and inflammation, both of which have been associated with prostate tissue remodeling and hyperplasia[22]. Furthermore, gut-derived metabolites, such as lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO), can contribute to systemic inflammation by activating toll-like receptor 4 (TLR4)-mediated immune responses. Chronic low-grade inflammation, a hallmark of aging and metabolic syndrome, exacerbates prostatic tissue proliferation and fibrosis, creating a favorable environment for BPH progression. Additionally, dysbiosis-driven increases in oxidative stress can impair mitochondrial function, further promoting cellular senescence and fibrosis within the prostate[23]. Dietary and lifestyle factors significantly influence gut microbiota composition, suggesting that dietary interventions and probiotic supplementation may offer potential therapeutic avenues for BPH management[24]. Fiber-rich diets, rich in polyphenols and fermented foods, promote beneficial microbial populations that produce SCFAs, such as butyrate, which exhibit anti-inflammatory and immunomodulatory effects. Conversely, high-fat and processed food diets contribute to dysbiosis and inflammation, exacerbating metabolic and hormonal imbalances.[25] As research into the gut-prostate axis expands, understanding the mechanisms by which microbial alterations contribute to BPH may pave the way for novel microbiome-targeted therapies. Probiotics, prebiotics, and postbiotics could be explored as potential adjuncts to conventional BPH treatments, aiming to restore microbial balance and mitigate inflammation-driven prostate enlargement. Given the rising prevalence of BPH among aging men, integrating microbiome-centered strategies could offer a promising, non-invasive approach to disease prevention and management.

Dysbiosis and Prostatic Inflammation in BPH

Chronic inflammation has been increasingly recognized as a key driver of benign prostatic hyperplasia (BPH), with mounting evidence linking gut microbiome dysbiosis to systemic and localized prostatic inflammation. The gut-prostate axis plays a crucial role in modulating immune responses, metabolic pathways, and inflammatory processes that contribute to BPH development and progression. Several mechanisms underline this association[26–29]:

a. Increased Intestinal Permeability and Systemic Inflammation

Gut microbiome dysbiosis disrupts the integrity of the intestinal epithelial barrier, leading to increased permeability, commonly referred to as "leaky gut." This condition allows bacterial endotoxins, such as lipopolysaccharides (LPS), to translocate into systemic circulation. Elevated LPS levels stimulate Toll-like receptor 4 (TLR4) activation on immune cells, triggering nuclear factor-kappa B (NF-κB) signaling and the release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines contribute to chronic low-grade inflammation, a hallmark of BPH pathophysiology. Inflammatory mediators infiltrate the prostate, inducing stromal hyperplasia and epithelial proliferation, thereby exacerbating prostate enlargement.

b. Altered Short-Chain Fatty Acid (SCFA) Production and Immune Dysregulation

Short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, are metabolic byproducts of gut microbial fermentation of dietary fibers. SCFAs play a crucial role in maintaining gut homeostasis, regulating immune function, and exerting anti-inflammatory effects.

Butyrate: Enhances gut barrier function by promoting tight junction protein expression (e.g., zonula occludens-1) and suppresses inflammatory pathways by inhibiting histone deacetylases (HDACs). Reduced butyrate levels are linked to heightened systemic inflammation and increased risk of prostatic inflammation.

Propionate and Acetate: Modulate immune responses by influencing regulatory T cells (Tregs), which help maintain immune tolerance and reduce excessive inflammation. Dysbiosis-associated SCFA depletion impairs Treg function, fostering a pro-inflammatory microenvironment that accelerates BPH pathogenesis.

c. **Imbalance in Pro- and Anti-Inflammatory Cytokines**

The gut microbiome plays a pivotal role in shaping immune homeostasis through its interaction with gut-associated lymphoid tissue (GALT). A balanced microbiome promotes the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which help suppress excessive immune activation. However, dysbiosis disrupts this balance, leading to excessive activation of pro-inflammatory cytokines, including:

Interleukin-6 (IL-6): Promotes prostate epithelial cell proliferation and fibrosis, contributing to prostate enlargement. Elevated IL-6 levels are correlated with increased BPH severity.

Tumor Necrosis Factor-alpha (TNF-α): Stimulates NF-κB activation and oxidative stress, further driving chronic inflammation within the prostate.

Interleukin-17 (IL-17): Associated with Th17 cell activation, which has been implicated in autoimmune-like inflammation contributing to prostate tissue remodeling and hyperplasia.

d. **Microbial Metabolites and Hormonal Regulation**

Beyond inflammation, gut microbiota influence androgen metabolism, a key driver of BPH. Certain bacterial species possess β-glucuronidase activity, which facilitates the enterohepatic recirculation of androgens such as dihydrotestosterone (DHT). Increased DHT levels in prostatic tissue promote stromal cell proliferation and fibrosis, worsening BPH progression. Additionally, gut microbial-derived metabolites, such as trimethylamine-N-oxide (TMAO), have been linked to oxidative stress and vascular dysfunction, potentially exacerbating BPH-related lower urinary tract symptoms (LUTS). The interplay between gut microbiome dysbiosis and BPH highlights the importance of microbial homeostasis in prostate health. Targeting the gut microbiota through probiotics, prebiotics, and dietary interventions aimed at restoring SCFA levels and reducing systemic inflammation could offer a novel therapeutic approach for mitigating BPH progression. Further research is needed to elucidate specific microbial signatures associated with BPH and their potential as diagnostic or therapeutic targets.

Gut Microbiome and Androgen Metabolism

Testosterone and its more potent derivative, dihydrotestosterone (DHT), are crucial regulators of prostate growth. The gut microbiome influences androgen metabolism by[30, 31]:

Modulating Enzyme Activity: Certain gut bacteria express enzymes such as β-glucuronidase, which can alter androgen metabolism and influence DHT levels.

Impacting Estrogen Balance: Dysbiosis can lead to increased conversion of androgens into estrogenic compounds, which may contribute to prostate tissue proliferation.

Interfering with Bile Acid Metabolism: Bile acids regulate steroid hormone synthesis, and alterations in microbial composition may disrupt this balance, influencing androgenic signaling in the prostate.

Potential Microbiome-Targeted Therapies for BPH

Given the emerging evidence linking gut dysbiosis to BPH, microbiome-modulating therapies may offer novel treatment approaches:

Probiotics and Prebiotics: Supplementation with beneficial bacteria (e.g., *Lactobacillus* and *Bifidobacterium*) and prebiotic fibers can help restore microbial balance and reduce inflammation.

Dietary Interventions: A diet rich in fiber, polyphenols, and omega-3 fatty acids supports a healthy gut microbiome, potentially mitigating BPH progression.

Fecal Microbiota Transplantation (FMT): Although still in experimental stages, FMT has shown promise in modulating systemic inflammation and metabolic disorders, which may have implications for BPH management.

Pharmacological Modulation: Emerging drugs targeting microbial pathways, such as antibiotics or microbiome-based therapies, may help regulate inflammation and hormone metabolism.

Future Directions and Research Perspectives

Despite growing interest in the gut-prostate axis, further research is needed to:

i. Establish a causal relationship between gut dysbiosis and BPH progression.
ii. Identify specific microbial signatures associated with BPH risk.
iii. Investigate the efficacy of microbiome-targeted therapies in clinical settings.
iv. Explore personalized medicine approaches based on gut microbiome profiling.

CONCLUSION

The gut microbiome plays a crucial role in maintaining systemic homeostasis, and its dysregulation may contribute to BPH pathogenesis through inflammatory, metabolic, and hormonal pathways. Understanding the

intricate relationship between gut dysbiosis and prostatic enlargement opens new avenues for BPH management. Targeting the microbiome through dietary modifications, probiotics, and other therapeutic interventions holds promise for improving prostate health and reducing the burden of BPH in aging men.

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CITE AS: Odile Patrick Thalia (2025). Gut Microbiome and BPH: Unravelling the Role of Dysbiosis in Prostatic Enlargement. EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH, 7(3):1-5