Chapter

Gut Microbiota–Penile Axis in Erectile Dysfunction: Mechanism, Clinical Challenges and Future Perspectives

R. C. Satish Kumar, B. R. Pradeepa, Anavarathan Vallipuram, Sathish Muthu and K. Sivabalaji

Abstract

Erectile dysfunction (ED) is a polyetiological condition, and its mechanisms have traditionally been considered vascular, neurogenic, hormonal, and psychogenic. Recent studies have shown that the gut microbiota is involved in male reproductive function. The gut–penile axis has been proposed to link altered intestinal microbiota and erectile dysfunction. This chapter reviews the most recent advances in the gut–penile axis with an emphasis on the physiological role, molecular mechanisms, experimental evidence, and therapeutic implications. Intestinal dysbiosis can influence sexual function through several mechanisms, including chronic inflammation, oxidative stress, endothelial dysfunction, nitric oxide dysfunction, gut–brain axis-mediated neuropsychological changes, and altered hormone metabolism. In preclinical models, there is compelling mechanistic evidence demonstrating the effects of the gut microbiome in the regulation of the hypothalamic–pituitary–gonadal axis, production of testosterone, and erectile physiology. The majority of human studies have been observational, but all have found an association between gut microbial changes and erectile dysfunction, and some recent Mendelian randomization studies have provided more robust evidence for a potential causal link between gut microbes and erectile dysfunction. The chapter also covers emerging therapies targeting the microbiome, including probiotics, prebiotics, synbiotics, postbiotics, dietary changes, and fecal microbiota transplantation (FMT), and their possible advantages and existing drawbacks. The chapter ends with a discussion of key clinical issues, methodological limitations, and future research directions needed to advance microbiome-based interventions into the clinical realm. The gut–penile axis provides an innovative new approach to the prevention, risk stratification, and individualized management of erectile dysfunction and is an emerging area of contemporary andrology.

Keywords: erectile dysfunction, gut microbiota, gut–penile axis, dysbiosis, endothelial dysfunction, probiotics, nitric oxide

1. Introduction

Erectile dysfunction (ED) is one of the most prevalent and life-limiting conditions in men's health, and its underlying biology is still unfolding. Andrology has divided ED into four main categories of causation: vascular, neurogenic, hormonal, and psychogenic. Although this framework continues to be clinically essential, it does not adequately account for the comorbidities that so often accompany ED, such as obesity, type 2 diabetes, depression, or metabolic syndrome, nor does it explain why lifestyle interventions frequently have a greater effect than would be predicted from vascular risk reduction alone.

Recently, the gut microbiome has become a potential connecting thread among these seemingly unrelated risk factors. The intestinal microbiota is known to influence systemic inflammation, vascular tone, metabolic homeostasis, and even circulating androgen levels – all of which are known to contribute to erectile physiology. This has led to the notion of a gut–penile axis focused on the mechanistically linked bidirectional interaction between intestinal dysbiosis and penile vascular–neurological function, which has recently emerged as a recognized concept in the literature [1, 2].

The present chapter summarizes the current knowledge on the gut–penile axis: the physiological basis underlying erectile function; molecular mechanisms proposed to connect dysbiosis to erectile impairment; preclinical and clinical evidence supporting this axis; and active therapeutic strategies. As is the purpose of this book, special emphasis is given to the clinical issues that currently block the application of this science to common andrological practice.

2. Epidemiology and burden of ED

The epidemiology of ED varies widely, from around 37% to 49% in different populations depending on the population studied, the definition of ED, and the age of the population samples [3]. The prevalence increases with advancing age; however, ED has been increasingly identified in younger men, especially in association with obesity, a sedentary lifestyle, psychological stress, and early cardiometabolic disease [4].

This condition is of personal and prognostic importance because ED is associated with a plethora of psychosocial impacts beyond sexual satisfaction, including reduced self-esteem, relationship problems, and depressive symptomatology, and is also a very early sentinel marker of systemic vascular disease, often occurring several years before the appearance of any overt coronary events.

3. Physiology of penile erection

Normal erection is a neurovascular process driven by smooth muscle relaxation, endothelial function, and a parasympathetic process in the corpora cavernosa. Afferent stimulation releases acetylcholine from the terminals of the cavernous nerve, and it binds to endothelial muscarinic receptors to increase endothelial nitric oxide synthase (eNOS) activity, while at the same time, non-adrenergic, non-cholinergic cavernous nerve fibers release nitric oxide (NO) from the terminals of the cavernous nerve through neuronal nitric oxide synthase (nNOS) [5, 6]

Nitric oxide diffuses into adjacent smooth muscle cells and stimulates the enzyme soluble guanylyl cyclase, which transforms guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP) [5]. Cyclic guanosine monophosphate (cGMP) is hydrolyzed by phosphodiesterase type 5 (PDE5), the enzyme targeted by sildenafil and similar drugs, which have proven efficacy in humans; elevated levels of cGMP lead to the closure of calcium channels and a decrease in intracellular calcium, resulting in the relaxation of corpus cavernosum smooth muscle, increased arterial inflow, and sinusoidal engorgement [7].

This NO–cGMP axis is not a standalone pathway but is highly responsive to the vascular and metabolic environment surrounding it; endothelial health, oxidative balance, and systemic inflammatory state all influence its efficiency. Gut-derived signals are now known to intervene at this sensitive time in development.

4. Pathophysiology of ED

Classical ED pathophysiology can be broken down into four interrelated domains. Vascular ED is a result of atherosclerotic or endothelial damage to the inflow of the penile arteries, often with the same risk factors as coronary artery disease. Neurogenic ED is caused by damage to the central or peripheral nerves that control the erectile reflex, which can occur in diabetic neuropathy, spinal cord injury, or a surgical procedure in the pelvic area. Hormonal ED is when there is a disturbance in the production of hormones that changes libido or causes a cavernosal tissue response. Psychogenic ED is the result of performance anxiety, depression, or relationship problems that act as inhibitors of central pathways that override the peripheral erectile capacity [8].

Two mechanisms are common to almost all organic subtypes: oxidative stress and endothelial dysfunction. These convergent pathways are important to remember and come into play, and, as the following sections will describe, gut dysbiosis is not a separate disease mechanism but rather contributes to this axis of oxidative and endothelial damage [9, 10].

5. Gut microbiota and male reproductive health

The gut microbiota is increasingly recognized as an active endocrine-like organ, affecting distant tissues, including the male reproductive axis, and this is now known. Conventionally colonized mice have significantly higher intratesticular and serum levels of testosterone and follicle-stimulating hormone; gut bacteria are directly involved in androgen metabolism. The microbiome regulates intratesticular testosterone levels by regulating the expression of steroid-processing enzymes that are able to deconjugate glucuronidated steroids, and conventionally colonized mice show higher levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) than germ-free animals, showing that normal output of the hypothalamic–pituitary–gonadal (HPG) axis requires commensal microbes [11, 12].

The testobolome refers to the collective group of gut microbial enzymes and metabolic pathways that may affect the systemic hormone levels of androgens, such as testosterone, and their metabolic activity and regulation. In a mechanistic way, it modifies forms of testosterone and DHT in the intestinal lumen – an effect that has

been termed the "testobolome" effect [13] – and also regulates blood–testis barrier integrity and Sertoli cell function through short-chain fatty acid (SCFA) signaling; both of these functions lead to effects on spermatogenesis and steroidogenesis [14].

Together, these cross-sectional studies have identified some specific genera associated with male sex hormone concentrations in blood, including *Acinetobacter, Dorea, Ruminococcus, and Lactobacillus*; and Mendelian randomization approaches suggest a potential causal link between microbiota composition and sex hormone levels, with at least some of these associations confirmed as causal and pointing from the microbiota to the sex hormones, rather than the other way around [15].

6. The gut–penile axis: A conceptual framework

Intestinal dysbiosis may act on the NO–cGMP pathway or on central arousal circuits simultaneously via a series of overlapping inflammatory, metabolic, vascular, hormonal, and neuropsychological pathways, as described in the gut–penile axis concept; The NO–cGMP pathway and central arousal circuits are not mutually exclusive, but rather both are affected by dysbiosis, and each of these pathways independently connects to the NO–cGMP pathway or to central arousal circuits [1, 2].

This framework is clinically relevant because it integrates previously separate ED risk factors in obesity, metabolic syndrome, depression, and aging, as common upstream modulators. It is also a partial explanation of the multiple domains of ED risk in which interventions that reshape the microbiome have a different effect than does a PDE5 inhibitor.

7. Molecular mechanisms

Current mechanistic evidence suggests six inter-related processes through which gut dysbiosis is believed to negatively influence erectile function. These are summarized below in a general order from microbial signal to cavernosal endpoint, but they represent a complex network of events rather than a linear sequence. **Figure 1** shows Gut–penile axis: Mechanism linking gut dysbiosis to erectile dysfunction.

7.1 Inflammation

Dysbiosis leads to increased intestinal permeability, allowing bacterial lipopolysaccharide (LPS) from Gram-negative bacteria to enter the systemic circulation, a phenomenon known as "metabolic endotoxemia." LPS stimulates Toll-like receptor 4 on immune and endothelial cells, leading to the release of tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and other pro-inflammatory cytokines [1, 16], which act directly on Leydig cells and suppress androgen synthesis. Simultaneously, it causes the activation of NADPH oxidase in cavernosal endothelial cells, thus linking the gut inflammatory effects to the hormonal and vascular pathways that are essential for normal erectile function [17].

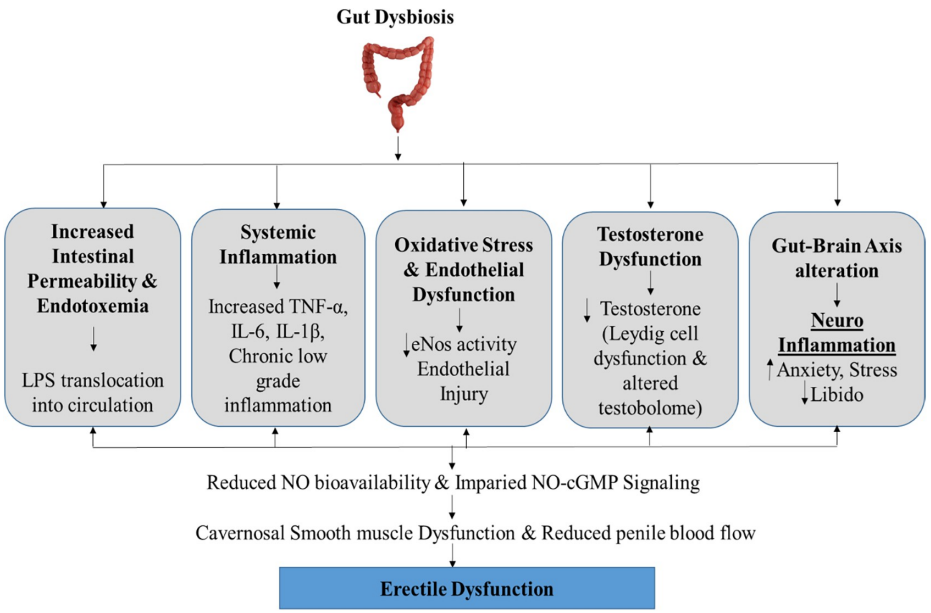


Figure 1.
Gut–penile axis: Mechanism linking gut dysbiosis to erectile dysfunction.

7.2 Oxidative stress

Chronic low-grade intestinal inflammation leads to the sustained generation of excessive reactive oxygen species via NADPH oxidase, xanthine oxidase, and mitochondrial dysfunction. Oxidative stress, a prevalent consequence of smoking, dysbiosis, and aging, as well as a characteristic of diabetes, functions as a unifying pathway through which microbiota-derived signals engage with existing vascular risks, thereby exacerbating them at a specific location, particularly in the relaxation of cavernosal smooth muscle [9, 10].

7.3 The NO pathway impairment

In addition to oxidative quenching of NO, dysbiosis can generate NO-suppressing metabolites that directly decrease the expression and function of NO synthase. The efficacy of PDE5 inhibitors operates downstream of NO production; thus, a significant reduction in the NO pool upstream of PDE5 may explain the subset of patients with ED who do not respond to standard treatments, prompting interest in microbiome-targeted adjuncts [5, 7].

7.4 Endothelial dysfunction

The vascular convergence point of the above three pathways is endothelial dysfunction. The diminished endothelial-dependent vasodilation, decreased cavernosal arterial compliance, and pro-thrombotic, pro-adhesive endothelial phenotype that contribute to chronic inflammation and oxidative stress lead to the onset of ED prior to the manifestation of clinical cardiovascular dysfunction, thereby

establishing ED as an early cardiovascular warning sign, now recognized as being partially modulated by the microbiota [8].

7.5 Metabolism of testosterone

The depletion of commensals with enzymatic capabilities to metabolize steroids and facilitate their deconjugation and enterohepatic recycling results in a reduction of bioavailable testosterone, which contributes to hypogonadal manifestations that subsequently exacerbate ED through effects on libido and direct impacts on cavernosal tissue, as elaborated in Section 5. Certain microbial genera are associated with testosterone levels in males, and interventional animal studies have confirmed that supplementation with a strain of *Limosilactobacillus reuteri*, which promotes androgens, can restore testosterone levels [13, 18]

7.6 Gut–brain axis and psychogenic contributions

Gut dysbiosis affects central neurotransmission and hypothalamic–pituitary–adrenal (HPA) axis reactivity via vagal afferent signaling, microbial SCFA production, and cytokine-driven neuroinflammation. Animal studies of chronic stress have shown that dysbiosis and changes in SCFA levels precede and predict anxiety-like and depressive-type behaviors in stress-susceptible models. This pathway is supported by the bidirectional relationship between depression and anxiety, and psychogenic ED and may be an important mechanism whereby dysbiosis can lead to erectile impairment that is independent of vascular and hormonal changes, which are often neglected in purely urological accounts of ED [8]. **Table 1** shows Mechanism linking gut dysbiosis to erectile dysfunction.

8. Preclinical evidence

Animal studies offer the best evidence at present for the gut-penis axis, and much of the evidence in these models directly relies on the manipulation of their microbiome, which is not ethically or practically possible in humans. Testicular testosterone levels and HPG axis signaling are consistently decreased by the absence of a microbiome, as demonstrated in germ-free and gnotobiotic mouse models,

Mechanism	Gut-derived mediator	Effect on erectile physiology	Clinical consequence
Inflammation	LPS, TNF-α, IL-6	Chronic inflammation	Erectile dysfunction
Oxidative Stress	ROS	NO depletion	Reduced cavernosal relaxation
Endothelial dysfunction	Reduced eNOS activity	Impaired vasodilation	Decreased penile blood flow
Testosterone dysregulation	Altered testobolome	Reduced androgen production	Hypogonadism-associated ED
Gut-brain axis	SCFAs, vagal signaling	Anxiety, depression	Psychogenic ED

Table 1.
Mechanism linking gut dysbiosis to erectile dysfunction.

where fecal microbiota transplantation (FMT) from a hormonally intact donor can shift HPG axis signaling and cause changes in gonadotropin and testicular weight profiles in recipient animals [11, 12, 19].

Mechanistically consistent evidence for the gut–brain contribution of psychogenic ED, discussed in the context of the gut–brain axis and psychogenic contributions, is indirectly provided by the ability of butyrate-producing and *L. reuteri* strains to restore testosterone and improve testicular histology (including seminiferous tubule architecture) in stress-vulnerable rodent models, where gut dysbiosis leads to reduced SCFA levels [14, 20].

9. Clinical evidence

A rapidly growing body of human evidence has emerged on the gut–penile axis since 2020, and most of it has been observational. A community-based, cross-sectional study from Japan showed that the relative abundance of both Alistipes and Clostridium XVIII were independently correlated with erectile function scores, which was among the first human associations between specific taxa and ED [2, 21]

The characterization of ED dysbiosis further revealed distinct dysbiosis signatures in a Chinese pilot case-control study, showing that ED dysbiosis is associated with changes in taxa involved in branched-chain amino acid metabolism and inflammatory potential, thereby suggesting the potential of this axis as a diagnostic tool for ED status [21, 22]. A subsequent study proposed gut microbiota composition itself as a candidate indicator of ED status, further reinforcing the diagnostic potential of this axis [23].

The most methodologically important development to date is a study that used a two-sample Mendelian randomization analysis to test the causal relationship between specific gut microbial taxa and ED risk, rather than relying on correlation alone. In this analysis, both risk-conferring and protective taxa were identified, and genetic-epidemiological evidence supported a causal relationship rather than reverse causation or shared confounding [2].

These integrated studies are coherent and methodologically robust; however, they are limited by a small sample size, a cross-sectional design, and diverse taxonomic outcomes among various cohorts, likely attributable to differences in diet, geography, and sequencing techniques. Furthermore, longitudinal or interventional human trials focusing on ED as a primary and pre-specified outcome are essentially absent [24].

10. Emerging therapeutic strategies

Based on the above mechanistic and correlative evidence, modulation of the gut microbiome has become a promising adjunctive therapy for ED. In the literature, it is suggested that there are six approaches that overlap, from simple dietary ones to those still under experimentation in the microbiome transplantation field. **Figure 2** shows therapeutic targets along the gut-penile axis.

10.1 Probiotics

The inflammatory and oxidative mechanisms described above have been suggested to be mediated by beneficial bacteria, particularly Lactobacillus and

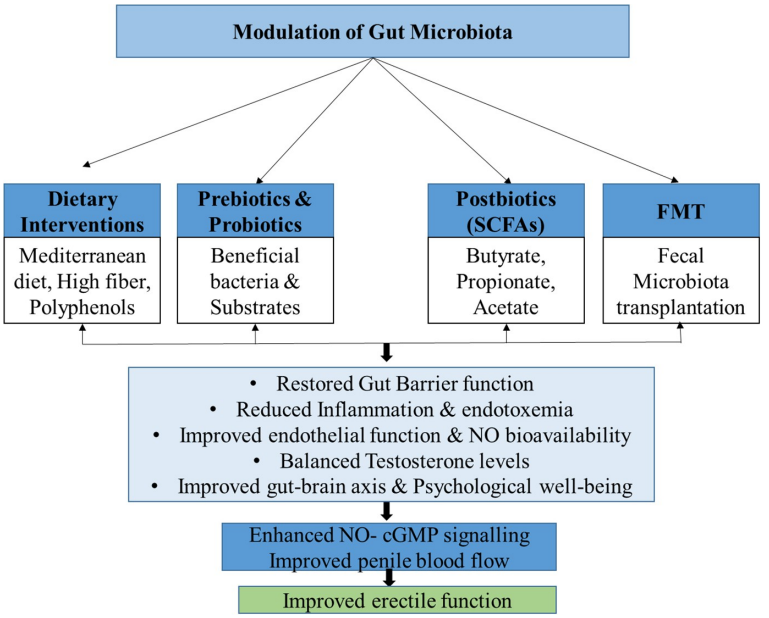


Figure 2.
Therapeutic targets along the gut-penile axis.

Bifidobacterium strains, as has been shown in an RCT of healthy aging men who had a measurable increase in testosterone after 12 weeks of probiotic supplementation, although the primary outcome of the study was the hormone system and not erectile function itself [25].

10.2 Prebiotics

Non-digestible fibers that selectively feed beneficial commensals have the potential to indirectly benefit erectile health by increasing production of SCFAs (esp. butyrate), enhancing glycemic and lipid metabolism, and decreasing systemic inflammation. To date, there are no direct data on the prebiotic effects on ED; however, this evidence is largely derived from the effects of prebiotics on obesity, insulin resistance, and cardiometabolic markers, which are known risk factors for ED.

10.3 Synbiotics

Combination probiotic–prebiotic products are believed to exert synergistic effects, such as promoting the survival and colonization of introduced strains and providing substrates, but there is little evidence for specific erectile or andrological effects. Comparing probiotics, prebiotics, synbiotics, and FMT in other gastrointestinal dysbiosis studies offers a valuable methodological framework and highlights the need for additional studies in ED [17].

10.4 Postbiotics

Postbiotics are microbial cells, cell fragments, or microbial metabolites (e.g., SCFAs, bacteriocins, and bacterial lysates) that are non-viable or non-colonizing and can be used as a therapeutic approach, which is particularly advantageous in antibiotic-treated or immunocompromised patients. The most extensively studied postbiotic in this context is butyrate, which has been shown to have anti-inflammatory, barrier-restoring, and androgen-supportive properties in preclinical models, making postbiotic supplementation a logical – albeit largely unproven in human ED patients – continuation of the probiotic concept [13, 20].

10.5 Dietary interventions

The diet is the most clinically actionable and well-supported lever within this axis, primarily through the Mediterranean dietary pattern. A two-year randomized study demonstrated that adherence to the Mediterranean diet significantly improved ED, endothelial function, and systemic inflammatory markers, including C-reactive protein (CRP), in men with metabolic syndrome and ED. These improvements were likely mediated indirectly by diet-induced alterations in microbial composition and SCFA production, alongside direct antioxidant and anti-inflammatory effects. Dietary modification alone improves erectile function scores, which correlate with the extent of weight and waist circumference reduction, supporting the notion that microbiome-mediated and classical metabolic pathways may operate synergistically rather than as competing explanations for the impact of diet on erectile function scores [26].

10.6 Fecal microbiota transplantation

Stool-derived microbial communities, transferred from a healthy donor (FMT), are the most direct way to alter a patient's microbiome and have progressed from a niche Clostridioides difficile treatment to an expanding area of interest. In animal models, FMT from intact donors to antibiotic-free or germ-free recipients has been observed to restore gonadotropin signaling and testicular function. A recent clinical perspectives article highlights the rationale, safety concerns, and knowledge gaps pertaining to FMT and male sexual dysfunction specifically [27].

Despite this promise, FMT for ED remains investigational because no randomized controlled trial (RCT) has been published that includes an adequate number of patients or designates ED as a primary outcome endpoint. Furthermore, practical challenges such as donor screening, standardization of microbial dosages, microbial engraftment, and FDA classification remain unresolved for clinical implementation [27]. **Table 2** shows summary of experimental evidence and therapeutic strategies.

11. Clinical challenges and research gaps

Nonetheless, there exist significant challenges in applying the gut-penis axis research to andrological practice, which are highlighted here due to their critical relevance, particularly within the framework of a book focused on clinical issues.

Aspect	Key findings	Clinical Implications
Animal studies	Germ-free mice show reduced testosterone; probiotic colonization restores hormonal function	Strong mechanistic evidence
Human studies	Dysbiosis is associated with ED; Mendelian randomization suggests causality	Clinical association established
Probiotics	Improve testosterone and reduce inflammation	Promising adjunct therapy
Prebiotics/ synbiotics	Enhance SCFA production and microbial balance	Potential supportive therapy
Mediterranean diet	It improves endothelial and erectile function	Recommended lifestyle intervention
FMT	Restores gut microbiota in experimental studies	Investigational approach

Table 2.
Summary of experimental evidence and therapeutic strategies.

- The predominant human evidence is observational: most clinical investigations are either cross-sectional or small case-control studies, with Mendelian randomization research being a rare exception that offers causal inference conclusions [2, 21, 22].

- Taxonomic diversity among cohorts: Numerous investigations encompass diverse bacterial genera, likely influenced more by diet, geographic location, ethnicity, and sequencing/bioinformatics techniques than by a consistent ED-associated signature.

- Observational studies are complicated by confounding factors, such as obesity, diabetes, and metabolic syndrome, which independently influence both the gut microbiome and erectile function, thereby complicating the establishment of a definitive causal relationship between the microbiome and erectile function.

- The evidence for probiotics, prebiotics, synbiotics, postbiotics, and FMT regarding this axis primarily relies on related outcomes (testosterone, metabolic indicators, and other dysbiosis-associated conditions) rather than erectile function as a designated primary endpoint [17, 25].

- Methodological heterogeneity – variations in sequencing platforms, the taxonomic level employed for classification, and the outcome instruments, such as IIEF, used across studies – complicates the synthesis and meta-analysis of findings. Donor screening, dose standardization, and long-term safety data for sexual health purposes are inadequately developed with regard to regulatory and safety issues of FMT [27].

None of these factors undermines the biological plausibility of the gut–penile axis; instead, they delineate the kind of data necessary to substantiate the therapeutic application of microbiome-directed therapy in the management guidelines for ED.

12. Future perspectives

Multiple avenues are poised to shape the future trajectory of research. The integration of metagenomic sequencing, serum metabolomics, and standardized andrological phenotyping (IIEF-5, penile Doppler indices, hormonal panels) would enable a more precise identification of the microbial signals that affect cavernosal tissue, rather than relying solely on an assumed mechanism. Future longitudinal studies involving a cohort of patients with repeated microbiome sampling prior to and following standard ED therapies (PDE5 inhibitors, testosterone replacement, lifestyle intervention) may elucidate whether dysbiosis is a causative factor, a consequence, or a mere bystander marker of the underlying metabolic decline. The most essential contribution lacking in the field is robustly powered randomized studies with erectile function designated as a pre-specified primary endpoint, rather than as a secondary or exploratory outcome.

Ultimately, the gut microbiome may serve as a tool for risk stratification or as a biomarker to identify men at risk of ED, distinguishing those with a significant metabolic-inflammatory component from those with a primarily structural or neurogenic component, thus facilitating personalized andrological care instead of relying on the gut–penile axis as a universal model.

13. Conclusion

The gut-penile axis represents a biologically plausible and increasingly well-supported extension of the traditional understanding of ED, in which intestinal dysbiosis induces cavernosal disease via mechanisms of inflammation, oxidative stress, compromised NO signaling, endothelial dysfunction, disruption of androgen metabolism, and gut-brain-mediated psychogenic factors. While human studies, which are primarily observational, are gaining traction and converging in a consistent direction as Mendelian randomization analysis strengthens the case for causality rather than association, preclinical research in animals offers truly causal data.

The gut-penile axis is an emerging area of translational research with considerable clinical potential. Nonetheless, the aforementioned strategies lack sufficient evidence from procedures, and no ED-specific randomized controlled studies have been completed for any of them. Therefore, these methodologies should primarily be considered as potential solutions for risk assessment, prevention, lifestyle enhancement, and future therapeutic advancement rather than as established clinical interventions. Addressing these knowledge gaps through meticulously designed mechanistic investigations and well-powered clinical trials becomes a crucial translational priority in modern andrology.

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Conflict of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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References

[1] Kaltsas A, Giannakodimos I, Markou E, Adamos K, Stavropoulos M, Kratiras Z, et al. The role of gut microbiota dysbiosis in erectile dysfunction: From pathophysiology to treatment strategies. Microorganisms. 2025;**13**(2):250. DOI: 10.3390/MICROORGANISMS13020250

[2] Zhang Y, Chen Y, Mei Y, Xu R, Zhang H, Feng X. Causal effects of gut microbiota on erectile dysfunction: A two-sample Mendelian randomization study. Frontiers in Microbiology. 2023;**14**:1257114. DOI: 10.3389/FMICB.2023.1257114/TEXT

[3] Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al. Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. European Urology. 2010;**57**:804–814

[4] Goldstein I, Goren A, Li VW, Tang WY, Hassan TA. Epidemiology update of erectile dysfunction in eight countries with high burden. Sexual Medicine Reviews. 2020;**8**:48–58. DOI: 10.1016/J.SXMR.2019.06.008

[5] Burnett AL. The role of nitric oxide in erectile dysfunction: Implications for medical therapy. The Journal of Clinical Hypertension. 2006;**8**:53–62. DOI: 10.1111/J.1524-6175.2006.06026.X

[6] Melis MR, Argiolas A. Erectile function and sexual behavior: A review of the role of nitric oxide in the central nervous system. Biomolecules. 2021;**11**:1866. DOI: 10.3390/BIOM11121866

[7] Ghalayini IF. Nitric oxide-cyclic GMP pathway with some emphasis on cavernosal contractility. International Journal of Impotence Research. 2004;**16**:459–469. DOI: 10.1038/SJ.IJIR.3901256

[8] Crocetto F, Amicuzi U, Musone M, Imbimbo C, Tammaro S, Napolitano L, et al. Erectile dysfunction: A comprehensive review of pathophysiology. Diagnosis and Contemporary Management Medicine. 2026;**62**:854. DOI: 10.3390/MEDICINA62050854

[9] Zhu D, Pham QM, Wang C, Colonnello E, Yannas D, Nguyen BH, et al. Erectile dysfunction and oxidative stress: A narrative review. International Journal of Molecular Sciences. 2025;**26**(7):3073. DOI: 10.3390/IJMS26073073

[10] Kaltsas A, Zikopoulos A, Dimitriadis F, Sheshi D, Politis M, Moustakli E, et al. Oxidative stress and erectile dysfunction: Pathophysiology, impacts, and potential treatments. Current Issues in Molecular Biology. 2024;**46**:8807–8834

[11] Al-asmakh M, Stukenborg JB, Reda A, Anuar F, Strand ML, Hedin L, et al. The gut microbiota and developmental programming of the testis in mice. PLoS One. 2014;**9**:e103809

[12] Lv S, Huang J, Luo Y, Wen Y, Chen B, Qiu H, et al. Gut microbiota is involved in male reproductive function: A review. Frontiers in Microbiology. 2024;**15**:1371667

[13] Veerus L, Subrahmanian A, Blaser MJ. The testobolome in microbial testosterone metabolism and human health. Npj Biofilms and Microbiomes.

2026;**12**:9. DOI: 10.1038/S41522-025-00861-0

[14] Chen W, Zou H, Xu H, Cao R, Zhang H, Zhang Y, et al. The potential influence and intervention measures of gut microbiota on sperm: It is time to focus on testis-gut microbiota axis. Frontiers in Microbiology. 2024;**15**:1478082. DOI: 10.3389/FMICB.2024.1478082

[15] Santos-Marcos JA, Mora-Ortiz M, Tena-Sempere M, Lopez-Miranda J, Camargo A. Interaction between gut microbiota and sex hormones and their relation to sexual dimorphism in metabolic diseases. Biology of Sex Differences. 2023;**14**(1):4. DOI: 10.1186/S13293-023-00490-2

[16] Tremellen K. Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING)-a novel theory for the development of late onset hypogonadism in obese men. Basic and Clinical Andrology. 2016;**26**(1):7. DOI: 10.1186/S12610-016-0034-7

[17] Wu Y, Li Y, Zheng Q, Li L. The efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation in irritable bowel syndrome: A systematic review and network meta-analysis. Nutrients. 2024;**16**(13):2114. DOI: 10.3390/NU16132114

[18] Pakpahan C, Laurus G, Hartanto MC, Singh R, Saharan A, Darmadi D, et al. Potential relationship of the gut microbiome with testosterone level in men: A systematic review. PeerJ. 2025;**13**:e19289

[19] Organski AC, Rajwa B, Reddivari A, Jorgensen JS, Cross TWL. Gut microbiome-driven regulation of sex hormone homeostasis: A potential neuroendocrine connection. Gut Microbes. 2025;**17**(1):2476562. DOI: 10.1080/19490976.2025.2476562

[20] Tang L, Yang X, Zhou M, Feng L, Ji C, Liang J, et al. Inhibition of inosine metabolism of the gut microbiota decreases testosterone secretion in the testis. MSystems. 2024;**9**(4):e00138-24. DOI: 10.1128/MSYSTEMS.00138-24

[21] Kang J, Wang Q, Wang S, Pan Y, Niu S, Li X. Characteristics of gut microbiota in patients with erectile dysfunction: A Chinese pilot study. The World Journal of Men's Health. 2024;**42**(2):363–372. DOI: 10.5534/WJMH.220278

[22] Su Q, Wang K, Luo Y, Tang Q. Altered gut microbiota in erectile dysfunction patients: A pilot study. Frontiers in Microbiology. 2025;**16**:1530014. DOI: 10.3389/FMICB.2025.1530014/TEXT

[23] Qiao Y, Chen J, Jiang Y, Zhang Z, Wang H, Liu T, et al. Gut microbiota composition may be an indicator of erectile dysfunction. Microbial Biotechnology. 2024;**17**(1):e14403. DOI: 10.1111/1751-7915.14403

[24] Su Q, Tang Q, Ma C, Wang K. Advances in the study of the relationship between gut microbiota and erectile dysfunction. Sexual Medicine Reviews. 2024;**12**:664–669. DOI: 10.1093/SXMREV/QEAE049

[25] Ljunggren L, Butler E, Axelsson J, Åström M, Ohlsson L. Effects of probiotic supplementation on testosterone levels in healthy ageing men: A 12-week double-blind, placebo-controlled randomized clinical trial. Contemporary Clinical Trials Communications. 2024;**39**:101300. DOI: 10.1016/J.CONCTC.2024.101300

[26] Oteri V, Galeano F, Panebianco S, Piticchio T, Le Moli R, Frittitta L, et al. Influence of mediterranean diet on sexual function in people with metabolic syndrome: A narrative review. Nutrients. 2024;**16**(19):3397. DOI: 10.3390/NU16193397

[27] Chen J, Bu C, Li X, Wu L, He X. Therapeutic potential of fecal microbiota transplantation for male sexual dysfunction: Evidence and clinical perspectives. Microbiota Medicine Research. 2026;**1**:12–24. DOI: 10.1002/MMR3.70003