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FEMALE SEXUAL DYSFUNCTION AND DISORDERS (A PASTUSZAK AND N THIRUMAVALAVAN, SECTION EDITORS)

The Gut Microbiome and Men's Sexual Health

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Abstract

Purpose of Review Currently, there is no literature assessing for a potential relationship between the gut microbiome and men's sexual health. The purpose of this paper is to review the literature on the gut microbiome and its effect on human health, in healthy and diseased states. We also aim to review the literature on men's sexual health and then extrapolate a potential relationship between the gut microbiome and sexual health diseases.

Recent Findings Many studies have suggested a correlation between the gut microbiome and components of the metabolic syndrome, cardiovascular disease, and inflammation. Men's sexual health diseases, such as erectile dysfunction and hypogonadism, have also been associated with components of the metabolic syndrome and cardiovascular disease.

Summary Due to the bidirectional relationships seen between the gut microbiome and men's sexual health, with the metabolic syndrome, cardiovascular disease, and inflammation, it is highly likely that an association between men's sexual health and the gut microbiome exists also. Future studies should begin looking at this potential relationship with the aim of developing gut microbiome targeted diagnostic and therapeutic tools for the treatment of men's sexual health diseases.

Keywords Gut microbiome · Men's sexual health · Hypogonadism · Erectile dysfunction · Metabolic syndrome · Cardiovascular disease

Introduction

The gut microbiome (GM) is the flora of microbes that are found in the gastrointestinal tract of their host organisms [1–3, 4•]. This flora consists of trillions of microbes that collectively contribute to vital functions to its host organism such as metabolic, immune, and nutritional functions [1–3, 4•]. The alteration in the GM composition and function, labeled as GM dysbiosis, has been shown to be associated with the pathogenesis of numerous diseases such as obesity, hypertension, diabetes, and cardiovascular diseases [5–7]. Our knowledge in this field has expanded rapidly over the past years due to increased availability and reduced cost of gene sequencing [3, 4•].

Erectile dysfunction (ED) and hypogonadism (HG) are common conditions in men that can lead to drastic decrease in their quality of life [8, 9]. Prevalence increases greatly with age, with recent studies suggesting a 10% increased risk for ED for every decade of life [10, 11]. Obesity, hypertension, diabetes, and cardiovascular diseases have also all been shown to have an association with numerous men's sexual health diseases [12, 13]. As such, there is a likelihood that an association between the GM and men's sexual health exists, but a clear connection is yet to be established.

The aim of our literature review is to extrapolate a potential relationship between the GM and men's sexual health by looking at how the GM exerts its effect on the overall being and how it manifests in certain diseases in men.

Gut Microbiome

A host's GM is composed of trillions of bacteria, viruses, and eukaryotic microorganisms [1–3, 4•]. They represent about

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50% of the cells found in the human body and can weigh up to 0.2 kg in the average adult [14•]. Despite these stunning numbers, the microbial flora in the human gut is relatively stable at the phylum level, with almost all individuals conserving Bacteroidetes and Firmicutes. A lot of variety exists when comparing the relative proportions of these phyla in different individuals [15]. At the level of species, the variation in composition increases exponentially compared with what is observed at the phylum level [16]. In humans, the ideal GM consists of a widely diverse flora of bacteria, viruses, and eukaryotic microbes [1–3, 4•, 14•, 15, 16]. A diverse GM plays a role in numerous vital metabolic and signaling functions, extending from immunomodulation, to fiber fermentation and vitamin production, to inducing inflammatory cascades, to providing mucosal protection by competitively inhibiting pathogens and fortifying membranous barriers [1–3, 4•, 14•, 15, 16].

Immune System Functions

Symbiotic gut microbes are the first line of internal defense against pathogens in combination with the host immune system [17]. A healthy microbiome can prevent colonization by outcompeting pathogens for nutrients and attachment sites of the gut's lining through a phenomenon called the "barrier effect" [17]. The mucosal innate immune system develops through its early exposure to gut microbes which triggers the growth of its elements. In the literature, Björkstén et al. showed that a reduction in microbial exposure early in life can cause autoimmune and allergic disease [18].

Metabolic and Signaling Functions

The GM has numerous vital metabolic and signaling functions, of which many are not found in the human body alone. These functions include the synthesis of vitamins (B1–B12 and K), processing food, digestion of complex polysaccharides, synthesis of essential amino acids, biotransformation of bile, and production of short-chain fatty acid metabolites, such as butyrate and acetate that act as energy source for colonic bacteria and possess anti-inflammatory effects [19, 20]. Foods such as cereal grains, asparagus, artichokes, legumes, leeks, kale, and cabbage are known as prebiotics, they are only partially digestible and although the mechanism is still unclear, it is believed that they enrich specific beneficial microbial populations [20]. The microbiota can communicate with the central nervous system through multiple pathways by acting on the vagus nerve, producing neurotransmitters, modulating the hypothalamic–pituitary–adrenal axis, and producing hormones [21].

Bidirectional Communication Between the Gut Microbiome and the Host Organism

Communication between the microbiota and the host organism primarily occurs in a bidirectional manner and this can be accomplished in a variety of ways. Short-chain fatty acids (SCFAs) are one of many metabolites produced by gut microbes that play a key role in T cell differentiation [22]. Antimicrobial peptides (AMPs) are produced by both the host and gut microbes and are involved in the detection and degradation of pathogenic microbes in the gut [23].

T cell differentiation is one of the primary immunomodulatory influences that microbes have on the host's immune system. The exact mechanism in which microbes influence T cell differentiation is not clear; however, it is widely hypothesized that it occurs at least partly through the production of SCFAs [24]. SCFAs in combination with organic acids and alcohols are metabolic end-products that are produced in the lower GI tract by fiber fermentation [25]. These SCFAs can then bind to G-protein-coupled receptors (GPCRs) on intestinal epithelial cells and stimulate differentiation of T cells [26].

Symbiotic microbes present in the GM can help combat pathogenic microorganisms. This can be accomplished through AMPs which are produced by symbiote microbes and are released in high concentrations when invasive pathogens are detected in the intestinal ecosystem [23]. Similarly, defensins and cathelicidins are AMPs that are produced by host cells in response to changes in concentrations between symbiotic and pathogenic microbes. When the concentration of pathogenic microbes increases, AMPs operate by binding to pathogenic bacterial membranes, disrupting them, and ultimately resulting in cell death [27].

Men's Sexual Health

ED is defined as the inability to achieve or maintain an erection that is sufficient for satisfactory sexual performance [28]. ED is common with studies suggesting a 10% increased prevalence rate for every decade of a man's life [28]. HG in adult men is a clinical and biochemical syndrome associated with a low level of testosterone, which may adversely affect multiple organ functions and quality of life [29•]. The extent of the prevalence of HG in men is underappreciated and, as a result, a large number of hypogonadal men remain undiagnosed and untreated [29•]. Peyronie's disease (PD) is a superficial fibrosing condition of the penis characterized by the presence of fibrotic plaques often leading to penile deformity, with or without concomitant pain [30]. Most commonly, men with PD will present to a men's health specialist in their sixth decade of life, with a mean age of around 52–57 years old [30]. Once thought to be a rare condition, PD has shown to have a reported prevalence of around 9% in adult men [31].

Men's Sexual Health and Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, with ischemic heart disease accounting for the majority of deaths in males [32]. Prevalence of CVD increases with age and the risk of a cardiovascular event is higher in men, when compared with women, up until midlife [32]. Vascular health is affected by various risk factors including age and hormonal and metabolic parameters [32].

In a study of 9457 patients with a 7-year follow-up, patients who had a diagnosis of ED during follow-up showed a significantly increased risk of a cardiovascular event when compared with individuals without ED [33]. In a 2017 study by Lane-Cordova et al, data on 1136 men with CVD was collected and it was found that men with more severe CVD were at an increased risk of ED [34]. Banks et al. studied 95,038 men and found that patients with ED had a significant increased risk of experiencing a cardiac event then when compared with patients without ED [35]. The results were upheld when comparing patients with a history of CVD; those who presented with severe ED had approximately a 2-fold higher chance of experiencing a cardiovascular event compared with those without complaints of ED [35]. A few studies have shown there is no evidence suggesting a relationship [36, 37].

Endothelial dysfunction has also been demonstrated in cases of male HG. A 2011 study by Mäkinen et al. that involved 83 men with andropausal symptoms found that endothelium-dependent brachial artery flow-mediated dilatation (FMD) was inversely correlated with serum testosterone, suggesting that testosterone may have an adverse effect on endothelial function [38]. More commonly, however, studies have shown a correlation in the opposite direction with results suggesting that low total and free testosterone levels were associated with endothelial dysfunction after controlling for age, traditional cardiovascular risk factors, diabetes mellitus, liver/renal disease, and hypertension or intake of antihypertensive medication [39–41]. Studies on the association between testosterone and artery calcification in healthy men are also inconsistent. A 2016 study of 3164 male subjects suggests that there is a negative association between free testosterone levels and the risk of a positive coronary artery calcium score [42]. Similarly, another study of 211 male patients who were diagnosed with stable coronary artery disease showed that higher levels of testosterone were negatively predictive of the extent of coronary artery calcification [43]. On the other hand, a study of 978 relatively healthy men found no association between abdominal aortic calcification and levels of testosterone [44]. Multiple studies suggest that higher levels of testosterone are protective of arterial elasticity or that decreasing levels of testosterone may lead to arterial stiffness [42, 45–51].

There have been no prospective studies that have attempted to establish an association between PD and CVD. There have however been a few retrospective studies that have suggested associations between PD and hypertension, systemic vascular disease, and serum lipid abnormalities; all of which are risk factors for CVD [52, 53]. Other studies have shown no significant associations [54, 55].

Men's Sexual Health and Metabolic Syndrome

The metabolic syndrome (MetS) is a cluster of conditions that occur simultaneously which can increase the risk of heart disease, stroke, and type 2 diabetes. These components include abdominal obesity as measured by waist circumference, elevated triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose levels [56]. Further information on these components of MetS can be found in Table 1. The prevalence of MetS is continuously increasing over time and is now reaching epidemic proportions. In many Western countries, the prevalence of MetS is estimated to be at least one-fifth of the adult population and increases with age [56].

Numerous studies suggest that there is a bidirectional relationship between HG in males and MetS. A study by Antonio et al. which included 1651 men showed that lower baseline total testosterone levels are associated with an increased risk of developing MetS ($p < 0.001$). After controlling for sex hormone-binding globulin, insulin resistance, and BMI, the association was upheld [57]. Another large study performed by Laaksonen et al. showed that lower levels of testosterone are linked to a higher risk of developing MetS and diabetes [58]. This association upheld after adjusting for age, CVD, smoking, alcohol intake, and socioeconomic status. In a follow-up study, Laaksonen et al. reported that men with MetS at baseline had a 2.6-fold increased risk of developing HG [59]. This growing body of evidence suggests that it is reasonable to conclude that male HG and MetS are associated in a bidirectional manner.

Similarly, numerous studies have suggested a bidirectional relationship between ED and MetS [60, 61]. In a 2015 study by Park et al. of 1910 middle-aged men, MetS was found to be independently predictive of erectile dysfunction [62]. In a 2012 case-control study of 65 patients of which 37 were diagnosed with ED, criteria for MetS were met by 64.9% of the patients with ED versus 9.5% in the control cohort ($p < 0.001$). Abdominal circumference, mean systolic and diastolic arterial blood pressure, median glucose levels, and median glycated hemoglobin were all significantly greater in the ED group. On multivariate analyses controlling for age, body mass index (BMI), international index of erectile function (IIEF), tobacco use, sedentary lifestyle, and alcohol consumption, MetS remained strongly associated with ED [63]. These studies suggest that it is reasonable to conclude that ED is an independent predictor of MetS and that the same is true in regards to the reverse, suggesting a bidirectional relationship.

Table 1 Components of the metabolic syndrome

Component	Criteria
Elevated waist circumference	Dependent on the population/country studied
Elevated triglycerides	≥ 150 mg/dL
Reduced HDL-C	< 40 mg/dL in males; < 50 mg/dL in females
Elevated blood pressure	Systolic ≥ 130 and/or diastolic ≥ 85 mmHg
Elevated fasting blood glucose levels	≥ 100 mg/dL

*Having 3 out of 5 of these components is indicated for a diagnosis of metabolic syndrome

***HDL-C*, high-density lipoprotein cholesterol

To date, there have been no prospective studies that have attempted to establish an association between PD and MetS. However, there have been a multitude of retrospective studies that have shown associations between PD and components of MetS [52, 53, 64–67]. On the contrary, other studies have suggested that there is no association between PD and components of MetS [54, 55].

Men's Sexual Health and Inflammation

Inflammation of tissue can be indicative of certain diseases and there are a number of inflammatory markers that can be measured that suggest inflammatory responses [68]. These inflammatory markers include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and plasma viscosity (PV), among others, and can be measured through blood tests [68]. The pathophysiologies of ED, HG, and PD have all been shown to have some sort of inflammatory pathway [69–84].

ED has been shown to be associated with a number of inflammatory markers in the literature [69–74]. Vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and fibrinogen, all three of which are inflammatory markers, have been shown to have increased blood serum levels in men with ED [69, 70]. A 2003 study of men with ED showed an association between penile arterial disease severity and blood serum CRP levels [71]. Another study showed significantly higher CRP blood serum levels in patients with ED when compared with those without ED [72]. Tumor necrosis factor-alpha (TNF-α) has also been linked to ED with numerous studies showing increased TNF-α levels in men complaining of ED [73, 74].

There is a vast amount of literature showing a correlation between HG and inflammation [75–80]. CRP, IL-6, fibrinogen, white blood cell count, and TNF-α have all been shown to be strongly negatively associated with testosterone levels [75–78]. Randomized trials have shown that testosterone replacement therapy in hypogonadal men was successful in reducing levels of adipokines [79, 80]. These studies suggest that testosterone is protective against inflammation, however, to establish a strong correlation, a larger number of inflammatory markers need to be evaluated.

The exact mechanism of the pathophysiology of PD remains unknown; however, it is widely suggested that an inflammatory cascade may be implicated. PD is characterized by tunical fibrosis and plaque formation that result in bending of the penis [30]. The pathophysiology is thought to begin with macro- or micro-trauma of the erect penis and the subsequent initiation of abnormal wound healing and inflammation [81]. Further details on the proposed pathophysiology of PD can be seen in Fig. 1. Studies on animal models and cadaveric specimens with PD have shown the abnormal collagen deposition, elastin fibers, and fibrin of the tunica albuginea [81–83]. Myofibroblasts play a role in normal wound healing and studies using PD rat models have shown abnormal high levels of myofibroblast, which may be the cause of the abnormal accumulation of collagen and subsequent fibrosis [84].

Gut Microbiome Dysbiosis

GM dysbiosis is defined as the deviation from a normal healthy flora of gut microbes to a composition that is associated with numerous pathologies and diseased states [1–3, 4•]. CVD, the components of MetS, inflammatory bowel disease, hypertension, Parkinson's disease, and numerous other diseases have all been shown to be associated with GM dysbiosis [5, 21, 85–87].

Gut Microbiome and Cardiovascular Disease

Numerous studies have suggested that the alteration of the GM composition may be associated with an increased risk of the development of CVD. In a 2017 metagenome-wide association study on stools of 218 individuals with atherosclerotic CVD and 187 healthy controls, a significant increase in abundance of *Enterobacteriaceae* and *Streptococcus* species was seen [88]. Further evidence for the involvement of the GM in the pathology of CVD comes from trimethylamine-N-oxide (TMAO). TMAO is a GM-dependent plasma metabolite that has been associated with increased CVD risk, as shown in numerous human and animal studies [89, 90]. TMAO is known to modulate cholesterol metabolism in arterial walls, and when present in systemic circulation increases

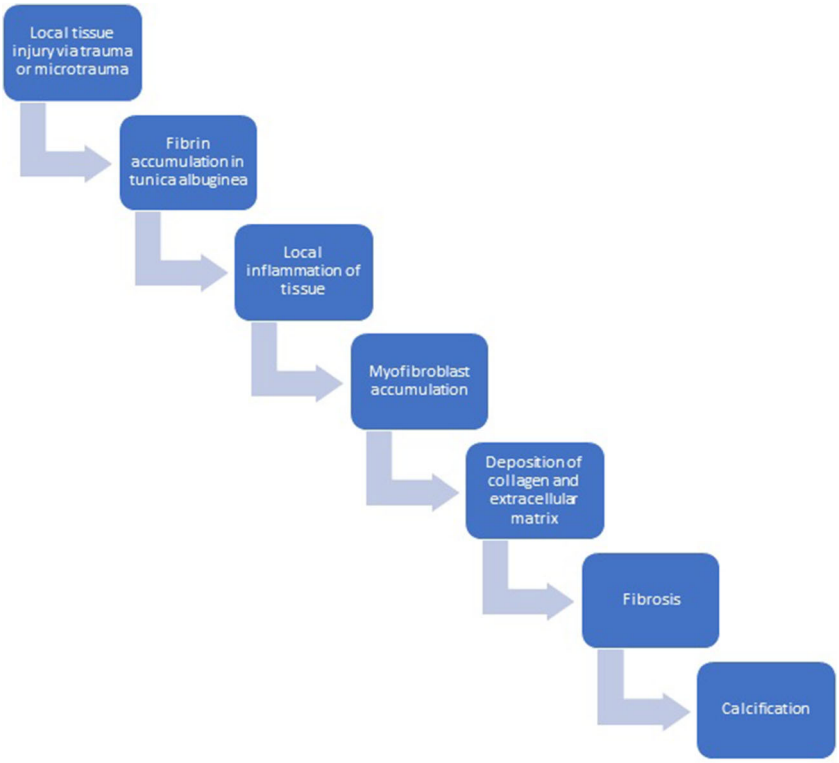

Fig. 1 Proposed pathogenesis of Peyronie's disease

deposits and decreases removal of cholesterol from peripheral endothelial cells lining arterial walls [91]. High plasma concentrations of TMAO trigger pro-inflammatory responses, inducing vascular inflammation [92]. In a 2013 study of 4007 patients, participants in the highest quartile of plasma TMAO levels had a 2.5-fold increased risk of a major adverse cardiovascular events compared with those in the lowest quartile. In the same study, plasma levels of TMAO were markedly suppressed after the administration of antibiotics and then reappeared after discontinuing antibiotics, suggesting that the GM plays a role in the anabolism of TMAO [93]. In an animal model presented by Wang et al., atherosclerotic plaque formation was prevented in mice when plasma TMAO levels were reduced [94]. In a 2015 study by Gregory et al., atherosclerotic activity was transmitted through the transplantation of gut microbiota from a diseased group of mice to a healthy control group. The study suggests that fecal transplants may be a novel therapeutic technique applied in the setting of atherosclerosis [95].

Gut Microbiome and Metabolic Syndrome

GM dysbiosis has been shown to have correlations with several components of the MetS, including elevated blood pressure, obesity, and diabetes. Obese and lean phenotypes in mice have been shown to be transferrable through fecal microbiota transfer (FMT) [96, 97]. A lower ratio of *Bacteroidetes* to *Firmicutes* has been associated with both obesity and elevated blood pressure [98, 99]. Obesity-induced gut microbiome dysbiosis has been seen in mice. Obesity in these mice impacted cellular turnover of the intestine in the form of increased cell death and cell proliferation gene expression [100]. This study suggests a potential bidirectional relationship with the GM and obesity. In a study, insulin sensitivity was improved in patients with MetS through a FMT from a lean donor, suggesting that MetS can be treated through targeting the GM [101]. The metabolic syndrome in men (METSIM) study was published in 2017 and studied 10,197 Finnish men, revealing several associations between the GM and MetS [102]. *Methanobrevibacter* and *Peptococcaceae* were found to be correlated with reduced triglyceride levels; *Tenericutes* and *Christensenellaceae* were shown to be strongly associated with lower BMI and triglyceride levels and higher HDL levels; and TMAO was directly associated with the abundance of *Peptococcaceae* and *Prevotella* and negatively associated with the abundance of *Faecalibacterium prausnitzii* [102].

Gut Microbiome and Inflammation

Lipopolysaccharide (LPS) is a bacterial endotoxin shown to be involved in the inflammatory cascade of the host immune response in the gut [103]. LPS has been linked to the development of the inflammatory markers associated with components of the MetS and inflammatory conditions such as osteoarthritis [104]. Dietary intervention is a method of studying

the effect of the GM on inflammatory diseases. The effect of prebiotics on obese children was studied and found that children in the prebiotics group had a significant increase of *Bifidobacterium* and a significant decrease in blood plasma IL-6 levels [105]. A similar study found the same effect of prebiotics on *Bifidobacterium* but with a significant decrease in blood plasma CRP levels [106]. In a randomized, double-blind, placebo-controlled trial with 103 Crohn's disease patients, the study group was given 15 g of fructo-oligosaccharides per day, after 4 weeks, a significant reduction in IL-6 levels was seen [107]. Crohn's disease is a common chronic inflammatory condition of the gastrointestinal tract and is associated with GM dysbiosis.

Gut Microbiome and Men's Sexual Health

The GM composition in elderly men differs than that of younger men, *Bacteroidetes are* more dominant in the elderly and *Firmicutes* are more prominent in young adults [108]. Elderly men also have significant decreases in *Bifidobacteria*, *Bacteroides*, and *Clostridium* cluster IV [109]. Naturally then, all men will eventually have altered GM composition as they age and with this alteration comes the plethora of diseases described throughout this paper. Men's sexual health diseases, such as HG, ED, and PD, also increase in prevalence as men age, and although there have been no studies published to date associating them with the GM, it is highly likely that there is a link to be found. This link is likely due to the bidirectional relationships seen between the GM and diseases that also share bidirectional relationships with men's sexual health diseases.

Our group is currently working on multiple studies to attempt to find a link between the GM and men's sexual health. We are currently comparing the GM of men with ED and/or PD with relatively healthy matched controls. Their GM will be compared through metatranscriptome sequencing and we will be controlling for a variety of potential confounders. We aim to find a potential link between the GM and ED/PD in hopes that we can develop a mechanism to better diagnose and treat them by targeting the GM.

Conclusions

The GM is the flora of microbes that are found in the gastrointestinal tract of their host, and when altered, it can be associated with the pathogenesis of numerous diseases such as obesity, hypertension, diabetes, and cardiovascular diseases. These same pathologies are associated with men's sexual health diseases such as ED, male HG, and PD. With our expanding knowledge about the GM over the past years, we are ready more than ever to begin exploring its correlation with men's sexual health. Men's sexual health diseases are highly associated with significantly decreased quality of life in both the patients and their partners, making them important to treat. The presence of bidirectional relationships between the GM and a group of diseases and between men's sexual health and the same group of diseases is highly suggestive of an association between the GM and men's sexual health. However, until a study is published analyzing the two, a conclusion cannot be made.

Compliance with Ethical Standards

Conflict of Interest Dr. Yafi reports associations with Endo Pharmaceuticals as consultant and speaker; Antares Pharma as consultant and speaker; Coloplast as speaker and advisory board; and Viome: Clinical as trial primary investigator. All other authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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