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Review Article

Gut Microbiome: A Potential Controller of Androgen-Modulated Disease

Shuang Liu, Luna Liu, Dandan Luo, Yu Su and Qingbo Guan*

Department of Endocrinology, Shandong Clinical Medical Center of Endocrinology and Metabolism, Shandong University, China.

***Corresponding author:** Qingbo Guan, Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Shandong Clinical Medical Center of Endocrinology and Metabolism, 324, Jing 5 Rd, Jinan, Shandong, 250021, ter of Endocrinology and Metabolism, 324, Jing 5 Rd, Jinan, Shandong, 250021, China.

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Abstract

Hypoandrogenism in males and hyperandrogenism females are both androgen disorders, which can adversely impact a variety of physiological factors. Recent studies provide that one of the principal regulators of circulating androgen is the gut microbiota. In this review, we elaborate on how gut microbial imbalance (dysbiosis) may lead to dysfunction of androgen synthesis, thereby contributing to androgen-driven disease. Some of the most common metabolic diseases namely obesity, metabolic syndrome, polycystic ovary syndrome and hypogonadism have been discussed and delineated along with recent findings. Then, suggestions for future research concerning the study are put forward as well.

Keywords: Androgen; Obesity; Gut microbiota; Complications

Introduction

The co-evolution of human microbial communities with human hosts is critical to human health [1]. The human gut have the greatest numbers of microbiota in the body [2], indeed, there is growing evidence that the gut microbiota and its bacterial genome (the microbiome) affect energy harvesting, fat storage, controlling satiety, modification feeding behaviour and regulating inflammatory responses within the host [3]. Under normal circumstances, gut microbiota in adults is dominated by members of three bacterial divisions, the *Firmicutes* (Gram-positive), *Bacteroidetes* (Gram-negative) and Actinobacteria (Gram-positive) [4]. The imbalances of its composition are related to homeostasis and lead to several non-intestinal pathologies [4]. Actually, recently studies proposed that the gut microbial can affect androgen levels. As reported, transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, leading to elevated testosterone and metabolomic change [5]. In reality, it involves a variety of molecular mechanisms which can be divided to several aspects: directly infect androgen levels through specific bacterial communities [6], and bacterial products [7], or modulate the enterohepatic recirculation of androgens and participate in redox reaction [8,9]. It is widely accepted that androgen plays a significant role in many diseases, such as obesity and metabolic syndrome, type 2 diabetes mellitus,

polycystic ovary syndrome and hypogonadism. This review will introduce the influence of the gut microbiome has on androgen, discussed the role of gut microbiota in androgen-driven disease. Then, we proposed two related research prospects: developing gut microbiota-based intervention and diagnostic criteria for female androgen excess (AE) and male androgen deficiency (AD).

Changes in Gut Microbiota Influence Homeostasis

Gut microbes are constantly interacting with intestinal epithelial cells. Gut microbiota are physically separated from mucosal immune system by a single epithelial cell layer, mucosal immune system can avoid the development of chronic inflammation and the subsequent loss of the intestinal epithelium integrity [10]. Changes of bacterial composition influence intestinal homeostasis. In the case of gut microbial imbalance, the permeability of the intestinal barrier increases, which promotes bacterial products, especially LPS synthesis [11], and as we know, LPS is believed as a key factor to cause low-grade inflammation and related to reactive oxygen species(ROS)-induced oxidative stress which contributes to insulin resistance, endotoxemia and so on [12,13]. On the other hand, altered of gut microbiota can also affect short-chain fatty acids (SCFAs) synthesis [14], which can regulate immune function, induce ROS and prevent passage of macromolecules such as endotoxin between intestinal epithelial cells by enhance the production of epithelial tight junction proteins [15,16]. As reported, administered sodium butyrate to mice significantly alleviated high fat diet-induced obesity and restored plasma glucose, insulin and leptin to control levels [17]. Secondly, *Firmicutes*/*Bacteroidetes* (F/B) ratio also correlates with disease, for example, obese mice have more of *Firmicutes* and less of *Bacteroidetes* in their gut compared with lean mice, similar findings were observed with obese people [18]. At last, the gut microbiota can communicate with the brain through the microbiota-gut-brain axis, which is mainly composed of the nervous pathway, endocrine pathway, and immune pathway, so it is a crucial part of the gut-brain network [19]. Actually, gut microbiome also plays an important role in cognitive conditions such as anxiety, depression and memory impairment, which has been described extensively beyond the scope of this review, furthermore, the microbiota maintains central nervous system homeostasis by regulating immune function and blood brain barrier integrity [20]. In a word, imbalance of the gut microbiota not only leads to inflammatory response and detrimental to gut epithelial health, but also affect emotion and physiological stress. Therefore, gut microbiome diversity is important to gut homeostasis and health.

Gut Microbiota Can Affect Androgen Levels

As above, gut microbiota is essential for protecting from pathogens, maintaining of the physiology of immune homeostasis, and promoting of digestion and absorption of dietary nutrients for energy production [21]. Recently, studies shows that gut microbiota also closely related to androgens, which has different effects on metabolic diseases in men and women [22]. Compared to conventionally raised counterparts, Germ-free non-obese diabetic (NOD) male mice have lower systemic testosterone levels [5]. Additionally, transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, resulting in elevated testosterone and metabolomic changes [5]. This evidence proved the interactions between testosterone and the gut microbiome. In fact, gut microbiota can directly infect androgen levels through specific bacterial communities and bacterial products. We have known that products of 'estrobolome' are capable of metabolizing estrogens [23], specifically, hepatically conjugated estrogens excreted in the bile can be conjugated by bacterial species secretion of β-glucuronidase in the gut, leading to their reabsorption into the circulation [8,24,25]. Similarly, the bacteria -glucuronidase excises glucuronide from conjugated androgens and releases free androgens for reabsorption [8].

Gut microbiome also modulates androgens through reductive and oxidative reactions [9]. Androgens, such as androstenedione and testosterone, are C-19 steroids derived from C-27 cholesterol through reductive reactions. Further, as we know, gut microbiota can convert primary bile acids (BAs) into secondary BAs through deconjugation, dehydrogenation and hydroxylation. Sex steroid hormones and bile acids (BAs) has similar structure and they can both be recycled through enterohepatic circulation, enterohepatic circulation is partially regulated by the gut microbiome, so gut microbes determined whether they are excreted or recycled in a way [8]. It has known that a human gut microbe named *Clostridium scindens* can convert glucocorticoids into androgens by side-chain cleavage [8], which is associated with a cortisol-inducible operon (*desABCD*). Ridlon JM, et al. [6], proposed that *desABCD* could encode enzyme involved in anaerobic side-chain cleavage. The *desC* gene have found to encode 20α-hydroxysteroid dehydrogenase (HSDH), which is an enzyme that catalyzes a chemical intermediate in the biosynthesis of androgens 17α-hydroxyprogesterone (OHP) production. This operon also encodes *desAB* which may have steroid-17,20-desmolase/oxidase activity, and *desD*, a possible corticosteroid transporter. Additionally, there are some other special microbiomes (e.g. *SPF microbiota*, *segmented filamentous bacteria*, *Escherichia coli* or *Shigella–like*) is positively correlated with high blood testosterone levels in male mice [26]. Insenser M, et al. [27], proposed that women with PCOS has an increased abundance of the *Catenibacterium* and *Kandleria* genera which shows positive correlations with serum androstenedione concentrations. Another report shows that *Bacteroides vulgatus* was also elevated in the gut microbiota of individuals with PCOS, transplantation of fecal microbiota from women with PCOS or *B. vulgatus*-colonized recipient mice resulted in increased insulin resistance and infertility [28].

Gut Microbiota Dysbiosis Influence Androgen-Modulate Disease

Obesity and metabolic syndrome

The prevalence of obesity is increasing worldwide [29], the growing incidence of obesity and obesity-associated complications, including diabetes, cardiovascular disease, and stroke is rapidly becoming a major public health problem [30]. As we kown, Male androgen deficiency raises the risk of abdominal obesity and cause metabolic syndrome [31]. Generally, androgens can directly stimulate the androgen receptor (AR) or indirectly aromatizate androgens into estrogens and, thereafter, stimulate the estrogen receptors to regulate the adipose tissue metabolism in men [32]. After androgen deprivation therapies, such as either castration or a luteinizing hormone-releasing hormone analog for prostate cancer patients, also promote the development of obesity [33]. Aromatization of testosterone into 17β-estradiol (E2) is also critical to energy homeostasis in males [34]. In fact, hypogonadism after castration caused abdominal obesity in high-fat diet (HFD)-fed, but this phenotype was not induced in mice treated with antibiotics that disrupt the gut microflora [33]. As described above, a crucial reason that androgen deficiency lead to obesity is altered by the gut microbiome. In fact, androgen deficiency also can alter the gut microbiome and induce abdominal obesity in a diet-dependent manner [33], it has been found that the *Firmicutes*/*Bacteroidetes* ratio and *Lactobacillus* species increased in the feces of HFD-fed castrated mice [33]. At present, modulation of the gut microbiota through probiotics has been shown to ameliorate obesity and associated metabolic disorders both in animals and in humans. The two most commonly used probiotic which can enhance gut health are *bifidobacterium* and *lactobacillus* [35]. *Bifidobacteria* and *A. muciniphila* have been shown to improve high-fat diet-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance [36-38]. Treating PCOS rats with *Lactobacillus* and fecal microbiota transplantation (FMT) from healthy rats can decrease androgen biosynthesis [39].

Type 2 diabetes mellitus

Obesity and insulin resistance are major predisposing factors to type 2 diabetes, actually, androgen is also a main driver to it [40]. For example, androgen receptor knockout mice developed significant insulin resistance rapidly [41]. A polish study of gonadotropin-induced hypogonadism (HH) in type 2 diabetes mellitus (T2DM) males showed a negative association between *HbA1c* and *cfT* [42]. A meta-analysis showed a significant decrease in testosterone levels in men with type 2 diabetes mellitus [43]. Similarity, for female, AE has been suggested as risk factor for T2DM [43]. However, it has already described in the above that androgen levels are not solely mediated through their level of endogenous secretion, it is also related with gut microbiome [44]. Patients suffering from T2DM have significantly lower gut microbiota diversity compared to healthy controls [45]. Evidence of an increase in testosterone levels due to gut microbiome transfer coupled with direct evidence of testosterone synthesis from bacteria highlight the interaction between microbiome composition and testosterone levels. These testosterone-associate microbiotas may influence sex hormone driven disease states such as T2DM. In addition, inhibition of testosterone through SCFA and blockade of androgen receptor for female in late gestational can alter AE condition and reverse glucose dysregulation [24]. All of this result demonstrates that not only testosterone is important in the development of T2DM, the appropriate gut microbiota composition associate with androgen also plays a crucial role.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of androgen excess in women, affecting 5-10% of women of reproductive age [46], characterized by hyperandrogenism, hyperandrogenism, anovulation, and ovarian cysts [47], which contributes to infertility and metabolic problems. The pathogenesis of PCOS remain unclear, some researchers shows that it is related with dysbiosis of gut microbiota. As above, gut microbiota influences the level of testosterone. Patients suffering from PCOS tend to have less diverse gut bacteria than women who do not have the condition [48,49]. In germ-free mice, fecal microbial transplant from letrozole (a nonsteroidal aromatase inhibitor) induced PCOS model indicated that gut microbiota has a close relationship with its host's sex hormone levels and estrus cycles [50]. According to another mouse model experiment, female recipients of male cecal microbiota displayed increased testosterone levels, compared with unmanipulated females and female recipients of female cecal micriobiota [51]. Many of the conditions such as metabolic syndrome, infertility, polycystic ovary syndrome (PCOS) and cancer have been shown to be alleviated via bariatric surgery [52]. Besides, alteration of the gut microbiota through bariatric surgery has been shown to alter many of the negative metabolic signatures indicative of metabolic syndrome [52]. However, alleviate the symptom of PCOS not only through weight loss but also modulate hormone levels which may through changes of gut microbiota condition. Fecal transplantation from healthy rats to a rat PCOS model as well as lactobacilli transplantation has been shown to improve estrous cycles and decrease androgen biosynthesis [53]. PCOS has also been shown to be resolved through administration of metformin [54], which can regulate compose of gut microbiota [55] and used in treatment of type II diabetes.

Male hypogonadism

Late-onset hypogonadism is characterized by low serum testosterone levels and associated symptoms of poor morning erection, low sexual desire, erectile dysfunction, inability to perform vigorous activity, depression, and fatigue [56].These symptoms can

have a major impact on men's quality of life, especially when they affect relatively young men [57]. The two-prevailing theory of low testosterone levels in hypogonadism is due to a combination of reduced pituitary LH drive and a direct impairment of testicular function [58]. Currently, there are some researches indicated that gut microbiota may reduces leptin sensitivity and lead to leptin resistance. For example, a study of gut microbiota and leptin sensitivity showed that leptin treatment significantly reduced the body weight of germ-free mice compared to conventionally fed mice [59], at the same time, the hypothalamic expression of leptin resistance-associated suppressor of cytokine signaling 3 (Socs-3) was increased in conventionally fed mice more than germ-free mice [60]. Generally, leptin directly stimulate the anterior pituitary [61], and increasing hypothalamic GnRH pulsatility [62], to increases LH and FSH release. At a state of leptin resistance, leptin action impaired and hypothalamic pituitary axis function declined, which lead to low serum testosterone.

There is also other abundant evidence linking gut microbiota with a direct impairment of testicular function leads to low testosterone. Absence of the normal microbiota influences the formation and the integrity of the blood-testis barrier (BTB) as well as the intra-testicular levels of testosterone [63]. Leptin also can reduced tight junction-associated proteins in Sertoli cells to impair blood test is barrier integrity [64]. In addition, the lysis of gram-negative gut microbiome leads to the continuous production of lipopolysaccharide (LPS) [65]. There are some studies indicated that oxidative stress due to LPS-induced inflammation related to apoptosis of Leyding cells [66-69]. Through recognizing LPS, Toll-like receptor 4 (TLR4) activates innate immunity and promotes the secretion of proinflammatory cytokines [70]. The cytokines such as TNF-α, IL-1β, and IL-6 directly inhibiting testicular function, for instance, inhibit the Leydig cell function by regulate steroidogenic acute regulatory protein and regulate function of Sertoli cell to impair testosterone production [71,72]. Probiotics have a positive role in improving testicular function. For example, *bifidobacteria* positively correlated with leptin levels in mice [73]. Fed the purified *L. reuteri* to mice presented significantly larger testicles and dominant male behavior compare with common controls [74]. Indeed, rats fed a high-fat diet fed probiotic mixture containing *lactobacillus* and other probiotic bacteria also can prevent sperm oxidative stress and associated sperm quality decline [75].

Future Areas of Study

Given the mounting evidence of the effects of the gut microbiome on androgen-related disease, these results provide important implications for two research directions in future: gut microbiota-based intervention and gut microbiota-based diagnostic criteria for AD or AE. Firstly, elucidating the mechanisms underlying the associations between AD (or AE) and gut microbiota will be instrumental in the development of this target to combat it. The molecular mechanisms are expected to be multiple. For instance, as discussed above, gut microbiota dysbiosis could affect SCFA metabolism which is associated with gonadotropin levels, blood-testis barrier and phosphorylation of CREB. In addition, gut microbiota can regulate androgens through secretion of β-glucuronidase, an enzyme that can cleaves off glucuronide from androgen conjugates. Future research may be targeted to finding efficient ways of promoting a healthy microbiota. Although the role of modulate gut microbiota to regulate androgen levels has been gradually confirmed, randomized control studies are needed to better define the therapeutic efficacy of treatment of androgen-modulated disease. Characterization of the microbiota and metabolome composition before and after bariatric surgery, take probiotics or FMT may help elucidate microbial and metabolic components of healthy and disease states which could have further therapeutic and diagnostic applications [76-79].

Earlier diagnosis is effective in the treatment of androgen-related diseases. Identification and validation of specific bacterial taxonomic groups sensitively altered in AD (or AE) patients can be developed as gut microbiota associated biomarkers may help predict or detect AD (or AE) and improve detection accuracy. Certainly, the idea that gut microbiota serves as a biomarker of these diseases is premature with the currently available data, and comprehensive comparison of changes in bacterial species in patients with other diseases should be performed first to examine their specificity. Therefore, a lot of work needs to be done to verify the feasibility of this strategy, and then large-scale trials need to be conducted to develop diagnostic criteria based on gut microbiota and validate its accuracy, before it can be adopted in clinical practice.

Conclusion

In decade years, infertility caused by AE in female and AD in male is increasing and it has become an increasing public health problem. There is growing evidence shows that modulate the gut microbiota can affect androgen levels, which offers exciting future therapeutic applications. Modulation of the gut microbiome through bariatric surgery, fecal microbiome transfer, probiotics and pharmaceutical (metformin) methods also shows promise for combating the metabolic aspects of disease states, which subsequently contribute to resolving related disease. Beyond to that, gut microbiota could also be used to diagnostically in unison with serum and urinary to identify risk factors for these diseases or as a biomarker. However, the impact of specific microbiota composition on the metabolic profile is an emerging area of research. With the development of technology, the relationship between microflora and androgen-related diseases will be more and more discovered. Regulate gut microbiota may provide an attractive diagnostic and therapeutic target for future research to improve the associate infertility.

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Conflict of Interest

Authors declare no conflict interest.

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