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Review Article

Testis–Gut-Reproduction Axis: The Key to Reproductive Health

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Reproductive health is an important issue for humanity. In the context of the increasing incidence rate of male infertility, it is essential to find the factors that affect male reproductive health. Gastrointestinal health is closely related to reproductive health. Gastrointestinal hormones (GIH) and gut microbiota (GM), as important material foundations for gastrointestinal function, can promote or inhibit testicular reproductive function, including spermatogenesis, sperm maturation, androgen synthesis, and even broader male diseases such as sexual function, prostate cancer, etc. On the contrary, the functional health of the testes is also of great significance for the stability of gastrointestinal function. This review mainly discusses the important regulatory effects of GIH and GM on male reproductive function.

1. Background

The intestine is the largest endocrine organ in the human body, capable of secreting numerous gastrointestinal hormones (GIH) [1]. GIH are a group of small molecule highly efficient bioactive substances secreted by endocrine cells in the gastrointestinal tract, which belong to the peptide class in chemical structure, so-called gastrointestinal peptides. GIH can not only locally regulate the activities of the gastrointestinal tract itself but also play a variety of roles, such as growth factors, neurotransmitters, fertility factors, sex hormones, etc. They extensively regulate systemic metabolic activities and are closely related to the occurrence and development of immune and inflammatory diseases, neoplasia, nervous and reproductive diseases [2].

GIH can physiologically affect the secretion of sex hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and affect the blood-testis barrier (BTB) to regulate spermatogenesis and can pathologically cause vascular inflammation, leading to erectile dysfunction (ED) [3, 4]. In addition, gut microbiota (GM) can also regulate the release and function of GIH, and there may be an interaction between them [3, 5, 6].

The number of genes of intestinal microorganisms is 150 times more than that of the human, and intestinal bacteria contribute 99.1% of them, which is considered the "second genome" and metabolic "organ" of the human, and some scholars predict that its metabolic capacity is even more critical than the host's own metabolism [7, 8]. The large number of GM plays an important role on the health. The GM is related to obesity, diabetes, mental disease, cardiovascular disease, intestinal disease, and other diseases [9–12].

In recent years, researchers have increasingly focused on how GM affects the occurrence and development of andrological diseases. Lundy et al. [13] found that there were certain compositional and functional differences in the gut, urine, and semen microbiota between infertile and healthy males, and the imbalance among the three promoted the occurrence of male infertility. Kang et al. [14] compared the composition of GM of patients with ED with that of healthy people; the results showed that there was a significant difference between the two groups, and they believed that *Actinomyces* may be a key pathogen. GM can affect male reproductive function through inflammation, metabolism, sex hormones, and other ways, which need further research [3].

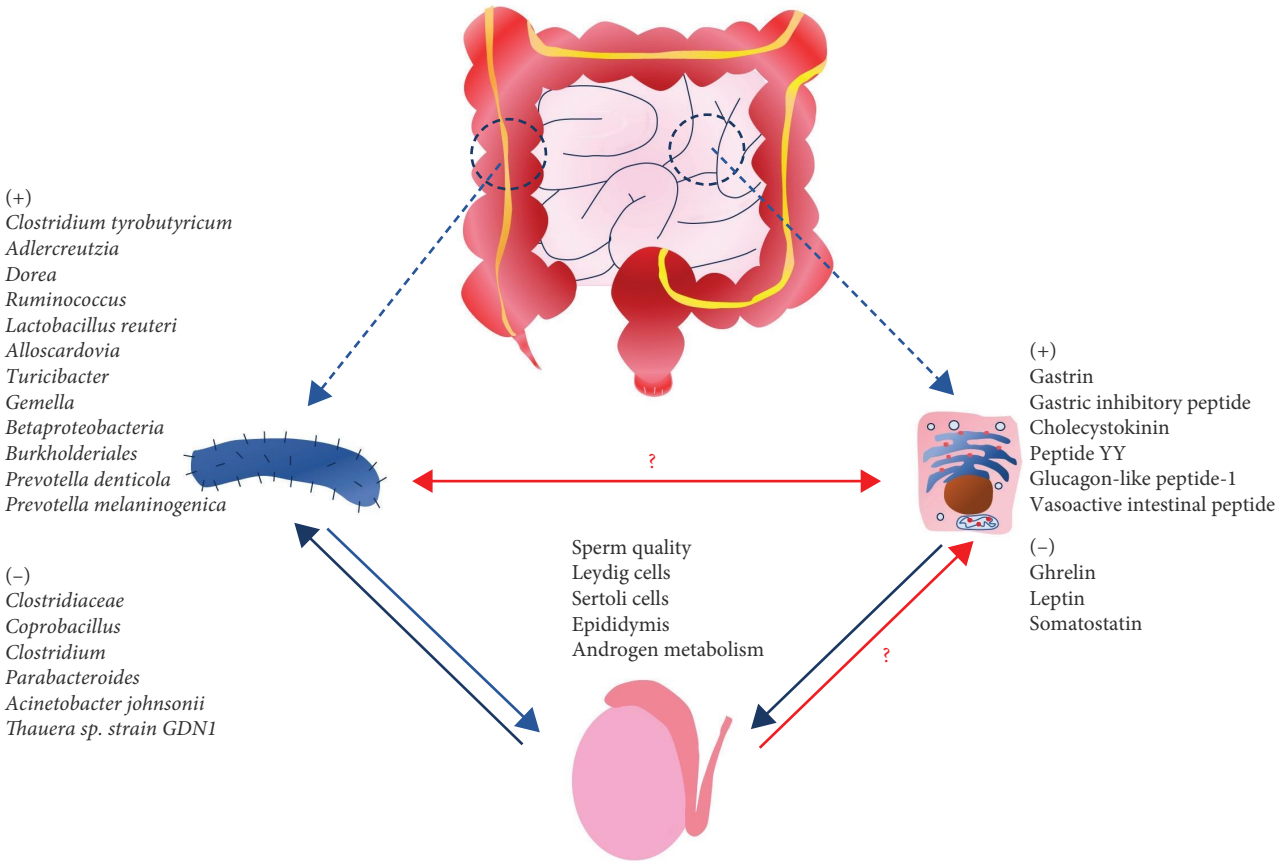

Figure 1: Testis–gut-reproduction axis. (1) GIH and gut microbiota regulate testicular reproductive function. (2) (+) represents a hormone with protective effects or a microbiota positively correlated with testosterone levels, while (−) represents the opposite. (3) Androgens can also affect the composition of gut microbiota. (4) In the future, further discussions will be conducted on the impact of androgens on GIH, as well as the interaction between gut microbiota and GIH. (5) Reproductive health and gastrointestinal health are closely related, and they interact with each other, which is of great significance in maintaining human health.

Androgen is the most important sex hormone in men, mainly including T secreted by testes and a few T precursors secreted by adrenal glands, such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). Its role runs through the whole life cycle of male growth, development, and aging and is closely related to the occurrence and development of male diseases. T can be converted into dihydrotestosterone (DHT) with stronger activity by 5α-reductase and exerts its role by binding to androgen receptor, or it is converted into estrogen by aromatase and then works with estrogen receptor [15]. Some studies have shown that GM can regulate androgen metabolism [16–18], affecting the permeability of BTB, testicular endocrine function, penile erectile function [3, 19], and other male reproductive health problems, but the mechanism of GM regulating androgen needs to be further studied and explained [20].

Based on this, we assume the existence of a testis–gut-reproduction (TGR) axis. Testis is the target of GM and GIH. Simultaneously, GIH and GM are two main factors that can directly affect the physiology and pathology of the reproductive system and can also regulate the level of androgen to affect reproductive health.

This article uses the Boolean logical operator "AND" to match vocabulary such as GIH, GM, androgens, testes, and male reproduction and uses these as search terms to search for relevant literature in databases such as MEDLINE and Web of Science. We review the effects of GIH and GM on reproductive health and then explain how GM affects androgens, which elucidate the connotation of the TGR axis (Figure 1).

2. The Effect of GIH on Male Reproductive Function

GIH are divided into two categories with protective and damaging effects. Some common GIH can protect the structure and function of the testis, such as gastrin (GAS), gastric inhibitory peptide (GIP), cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide-1 (GIP-1), vasoactive intestinal peptide (VIP), etc. Similarly, some GIH have a potential risk of damage to testicular structure and function, such as ghrelin, leptin, somatostatin (SST), etc. We start our narrative

Table 1: Gastrointestinal hormones with potential protective effects on male reproductive function.

Author	Research object	GIT hormone or related molecules	Expression site	Action
Schalling et al. [21]	Monkey, human	GAS, GAS mRNA	Human seminiferous tubules, sperm cells	Releasing during sperm acrosome reaction, promoting fertilization
Li et al. [22]	SD rats	GAS receptor	Testis	Associating with testicular injury
Killion et al. [23]	Mice	GIP receptor	Testis	Acting on the development of sperm fertilization potential
Shimizu et al. [24]	Mice	GIP receptor	Testis	Promoting sperm–egg fusion
Persson et al. [25]	Rat, mouse, guinea pig, pig, monkey	CCK, pro-CCK, CCK mRNA	Spermatogenic cells, sperm cells, epididymis	Promoting sperm–egg fusion
Persson et al. [26]	Rat, mouse	CCK, CCK mRNA	Seminiferous tubules	Acting on spermatogenesis
Zhou et al. [27]	Mice	CCK receptor	Acrosomal region of mature sperm	Acting on sperm capacitation
Fernandez–Fernandez et al. [28]	Rat	NPY receptor (Y_2, Y_5) mRNA	Hypothalamus, pituitary	Controlling LH and FSH secretion
Pinilla et al. [29]	Rat	NPY receptor (Y_2, Y_5) mRNA (but not related to function)	Hypothalamus, pituitary	Stimulating LH and FSH secretion
Izzi-Engbeaya et al. [30]	Human	PYY	—	Acute intravenous infusion of PYY not affecting the reproductive axis in healthy men
Caltabiano et al. [31]	Human, mice, rat	GLP-1 receptor, GLP-1 receptor mRNA	Leydig cells	Inhibiting Leydig cell tumors
Martins et al. [32]	Human	GLP-1 receptor	Sertoli cells	Regulating testicular energy homeostasis
Li et al. [33]	Rat	GLP-1	Leydig cells	Stimulating stem Leydig cell development
Yesil et al. [34]	Rat	GLP-1 analog	Stromal cells, endothelial cells of testis	Reducing iron accumulation, oxidative stress, and cell apoptosis
Abdel-Hakeem et al. [35]	Rat	GLP-1 analog	Testis	Inhibiting apoptosis, endoplasmic reticulum stress, activating autophagy of testis
Abdullah et al. [36]	Rat	GLP-1 analog, Kisspeptin	Testis	Improving testicular oxidative state, suppressing testicular inflammation and apoptosis
Degirmentepe et al. [37]	Rat	GLP-1 analog	Testis	Inhibiting testicular inflammation, oxidative stress, and apoptosis
Yuan et al. [38]	Rat	GLP-1 analog, GLP-1 receptor	Corpus cavernosum smooth muscle cells	Regulating smooth muscle dysfunction, oxidative stress, and autophagy
Agnese et al. [39]	Cartilaginous fish	VIP, VPAC2R (VIP receptor)	Leydig cells, Sertoli cells, prespermatogonia, spermatogonia	Acting on steroidogenesis and spermatogenesis
Rosati et al. [40]	Podarcis sicula, Rattus	VIP, VPAC1R, VPAC2R	Epididymis	Controlling sperm maturation and fertilization
Siow et al. [41]	Human	VIP	Sperm cells	Stimulating sperm motile activity
Gong et al. [42]	Human	VIP	Leydig cells, intratesticular arterioles	Regulating testicular function
Lissbrant et al. [43]	Rat	VIP	Testis	Increasing blood flow in the testis
Can et al. [44]	Rat	VIP	Testis	Inhibiting mast cell activity, increasing the heparin content, protecting testicular tissue from detorsion injury
Willis et al. [45]	Rabbit, human, monkey	VIP	Penis and other genitourinary tract	Upgrading penile intumescence and erection

Table 2: Gastrointestinal hormones with potential adverse effects on male reproductive function.

Author	Research object	GIT hormone or related molecules	Expression site	Action
Gaytan et al. [46]	Human	Ghrelin, GHS-R1a	Sertoli cells, Leydig cells, spermatocytes	Regulating testicular function
Moretti et al. [47]	Human	Ghrelin	Sertoli cells, Leydig cells, rete testis, epididymis, vas deferens, seminal vesicles, ejaculated sperm	Involving in fertilization (unclear)
El-Eshmawy et al. [48]	Human	Ghrelin	—	Regulating adolescent growth and development
Ishikawa et al. [49]	Human	Ghrelin	Leydig cells, testis interstitium	Inversely correlating with the serum T concentration
Fang et al. [50]	Boar	Ghrelin mRNA, GHS-R1a mRNA	Testis	Inversely correlating with the serum T concentration
Ishikawa et al. [51]	Human	Leptin, leptin receptor	Spermatocytes, Leydig cells	Increasing spermatogenic disorders, inhibiting T production
Yuan et al. [52]	Mice	Leptin	Testis	Regulating T secretion, protecting testicular structure and function
Wang et al. [53]	Mice	Leptin	—	Impairing blood-testis barrier integrity, sperm parameters, suppressing testicular steroidogenesis
Ramos-Lobo et al. [54]	Mice	Leptin receptor	—	Inhibiting T production, regulating GnRH fiber density
Sasaki et al. [55]	Human	SST	Testis, epididymis, prostate, semen	Regulating reproductive function
Zhu et al. [56]	Rat	SST1-3 mRNA	Seminiferous tubules, germ cells, Leydig cells	Regulating germ cell development, testicular function
Goddard et al. [57]	Porcine	SST mRNA	Spermatogonia, Leydig cells	Inhibiting DNA synthesis in spermatogonia
Krantic et al. [58]	Porcine	SST2 receptor mRNA	Sertoli cells	Inhibiting Sertoli cell proliferation
Gerendai et al. [59]	Rat	SST	—	Regulating testicular steroidogenesis

from this classification. Tables 1 and 2 show the general information of this section.

2.1. The Protective Effect of GIH

2.1.1. GAS. GAS is secreted by G cells in the gastric antrum, duodenum, colon, and pancreas. It can promote gastric acid secretion, epithelial cell proliferation and differentiation, participate in maintaining iron homeostasis, and regulate gastric function [60]. However, GAS-like mRNA is also expressed in human testicular seminiferous tubules [21]. The seminiferous tubules are the places where sperm is produced. Schalling et al. [21] demonstrated that biologically active α-aminated GAS is expressed in ejaculated spermatozoa through immunocytochemical staining of human testicles. All GAS detected in human testis is in the form of precursor, and most of the ejaculated sperm cells are α-carboxylated GAS-17 or GAS-34. The expression level of GAS receptor protein significantly increased after the electrical injury of the rat testis, suggesting that it may have a potential protective mechanism in testicular injury [22]. This indicates that GAS may protect testicular spermatogenic function and promote fertilization.

2.1.2. GIP. Fat, glucose, and amino acids can stimulate the secretion of GIP by small intestinal K cells and insulin by pancreas β cells, inhibit gastric glands from secreting gastric acid and pepsin, and slow down gastric peristalsis. It is proved that GIP and GIP receptor (GIPR) are expressed in the testicles of mice, affecting the reproductive ability of male mice [23, 61]. Killion et al. [23] suggest that the expression of GIPR in adipocytes and testes of GIPR gene knockout mice was significantly reduced. Although the number, morphology, and vitality of sperm were normal, the ability of fertilization in vitro was weakened. Shimizu et al. [24] also reported that GIPR was expressed in the seminiferous tubule of mice. Compared with the normal control group, the external fertilization rate of GIPR gene knockout mice decreased. The decrease in external fertilization ability of GIPR knockout mice is related to the decrease in the expression of pregnancy-specific glycoprotein 17 (Psg17). Psg17 is expressed in the acrosome of sperm, which may be a key factor in sperm–egg fusion, while GIP can regulate the expression of Psg17 in the testes, affecting fertilization ability [24, 62]. GIP can promote sperm fertilization ability.

2.1.3. CCK. CCK is secreted by type I cells in the duodenum and jejunum, which can inhibit gastric emptying and gastric acid secretion, stimulate gallbladder contraction, and secretion of the pancreatic digestive enzymes [63]. CCK and its receptor are expressed in pituitary cells, thyroid gland, pancreatic islet, adrenal gland, and testis [64]. CCK and its receptors, phosphorylate-related proteins tyrosine, and promote sperm capacitation. Persson et al. [25, 26] proved that CCK mRNA expression was detected in rat, mouse, and monkey testicular seminiferous tubule, and there was CCK in monkey testicular sperm acrosome granules, indicating that CCK may affect sperm fertilization through acrosome reaction [25, 26]. Zhou et al. [27] further indicated that CCK1 and CCK2 receptors are expressed in the acrosome region of mature sperm. Protein tyrosine phosphorylation is an important marker of sperm capacitation, and CCK1 and CCK2 receptor agonists can phosphorylate related protein tyrosine, promoting sperm capacitation [27]. CCK can act on the processes of sperm capacitation and replacement, thereby improving fertilization ability.

2.1.4. PYY. PYY is mainly produced in intestinal L cells and inhibits gastrointestinal peristalsis and dietary intake [65]. PYY can regulate the secretion of gonadotropin and affect the secretion of reproductive hormones in rats. The administration of PYY can directly stimulate the release of LH and FSH in the rat pituitary. High-dose PYY can elevate the level of LH and enhance the effect of Gonadotropin-releasing hormone on the secretion of LH and FSH [28, 29]. However, a study on the impact of PYY on human reproduction suggests that intravenous injection of biologically active PYY does not affect LH, FSH, and T levels [30]. This may be related to different administration methods and concentrations. PYY may regulate the function of the hypothalamic–pituitary–gonadal (HPG) axis, but further research is needed to determine.

2.1.5. GIP-1. GLP-1 is synthesized by L cells in the jejunum, ileum, and colon, which can promote insulin secretion, reduce appetite, and stimulate pancreatic islets β-cell regeneration and proliferation, improving pancreatic islet function, relaxing blood vessels, and protecting endothelial function [66–68]. The role of GLP-1 in reproduction has received attention, and the GLP-1 receptor (GLP-1R) is expressed in both human testicular Leydig cells and Sertoli cells, and Leydig cells may be a potential target for GLP-1 [31]. GLP-1 promotes the differentiation of rat Leydig cells, regulates metabolism and mitochondrial function of Sertoli cells [32, 33]. These two types of cells are crucial for maintaining normal spermatogenic function.

GLP-1R agonists (GLP1-RAs) can improve the damage of obesity and diabetes to testes and sperm, and enhance sperm vitality [69, 70]. The exenatide, somalutide, and liraglutide that can promote insulin secretion are all GLP1-RAs with potential anti-inflammatory and anti-atherosclerosis effects. Exenatide can inhibit the orchitis of mice caused by high-fat-induced obesity and reduce the expression of proinflammatory cytokines and the oxidative stress and apoptosis of testicular tissue [34, 35]. Somaglutide can regulate the GLP-1-mediated steroidogenesis signal pathway, and liraglutide can reduce the activities of apoptosis protease activating factor 1 (Apaf-1) and nitric oxide synthase (NOS). This improves the oxidative status of the testis, inhibits orchitis and cell apoptosis, and ameliorates ischemia/reperfusion-induced testicular dysfunction in rats [36, 37]. In addition, liraglutide can also regulate the function of corpus cavernosum smooth muscle, oxidative stress, and autophagy and ultimately upgrade ED in diabetes rats [38]. Therefore, GLP-1 analogs can protect testicular tissue and corpus cavernosum smooth muscle cells by exerting inhibitory effects on inflammatory response, oxidative stress, cell apoptosis, etc.

2.1.6. VIP. VIP is a gut peptide hormone that can regulate the function of nerve cells, epithelial cells, and endocrine cells, thereby affecting nutrient absorption, ion secretion, immune

regulation, and so on [71]. VIP and its receptor are expressed in the testis and epididymis, which may be involved in spermatogenesis [39, 40]. Siow et al. [41] also proved that VIP stimulates the activity of adenylyl cyclase, improves the level of cyclic 3′,5′-adenosine monophosphate (cAMP) in Leydig cells and activates protein kinase activity, stimulates sperm movement, and improves sperm vitality through cAMP-mediated axonal protein phosphorylation. Moreover, VIP protects the testicular vascular system. VIP and its receptors can be detected around and inside the vascular walls of adult healthy testes. VIP can dilate testicular blood vessels and regulate testicular blood flow and mean arterial pressure in rats [42, 43]. In addition, VIP can protect the testis from torsion injury by inhibiting the activity of mastocytes and increasing heparin content [44]. VIP may enhance sperm motility through direct or indirect means.

In addition, VIP, as an inhibitory neurotransmitter, participates in the neural regulation of erection. VIP combined with phentolamine has a synergistic effect, causing venous occlusion, and is used to treat moderate and severe ED [45, 72]. In patients with neurogenic impotence, VIP expression in the penile corpus cavernosum is weakened [73]. And injecting VIP cDNA into the corpus cavernosum of rats can increase the expression of VIP mRNA in the corpus cavernosum, increase the average amplitude of intracavernosal pressure, improving erectile function [74]. Hence, VIP can also act on the penis, enhancing penile erection function.

2.2. The Damaging Effects of GIH

2.2.1. Ghrelin. Ghrelin is a growth-hormone secretagogue (GHS) released by the stomach, regulating energy metabolism and cellular homeostasis [75, 76]. Ghrelin and the functional type 1a receptor GHS-R1a are found in the testis of humans and rats, which suggests the reproductive regulatory effects [46, 47]. It can regulate the development of spermatogenic cells and the proliferation of Leydig cells [46, 47]. Ghrelin is negatively correlated with serum T levels [48, 49]. Ghrelin may reduce T synthesis by inhibiting steroid synthase in Leydig cells [49, 50]. This suggests that Ghrelin may inhibit spermatogenic cell function by reducing T synthesis in Leydig cells.

2.2.2. Leptin. Leptin in mammals is almost released from adipose tissue, but it is also partially expressed in nonadipose tissue [77]. It is reported that leptin and leptin receptor (LEPR) are expressed in testicular tissue [51]. High levels of leptin can directly damage the structure and function of the testis through the suppressor of cytokine signaling 3 (SOCS3)/phosphorylated signal transducer and activator of transcription 3 (pSTAT3) pathway, which is manifested by the reduction of testicular volume and weight, the diameter of the seminiferous tubule, the number of spermatocytes and spermatozoa, and testosterone synthesis [52]. The outcome is probably also related to leptin injuring the BTB composed of tight junctions of Sertoli cells [53]. Meanwhile, leptin can also affect the HPG axis to inhibit the synthesis of testosterone by Leydig cells [78]. It can be seen that spermatogenic cells, Sertoli cells, and Leydig cells all receive restrain from leptin. However, the role of leptin to reproductive function is controversial. This may be related to the developmental stage. Ramos–Lobo et al. [54] believe that in the early stages of life, leptin deficiency can damage the reproductive system and brain development, and even if the leptin signal is restored later, this lesion is difficult to reverse.

2.2.3. SST. SST is distributed in endocrine cells and nerve cells in the gastrointestinal tract, participating in inhibiting intestinal peristalsis and regulating gastrointestinal blood flow status [79]. SST is distributed in various forms in the testes, epididymis, and prostate of rats. SST14 plays a dominant role in the epididymis, prostate, and hypothalamus, and SST14 and SST28 can be detected in the testes [55]. Besides, the mRNA of the SST receptor was found to exist in the seminiferous tubules of the testes [56]. This indicates that SST can influence testicular function. It is indicated that SST can inhibit DNA synthesis in spermatogonia and Sertoli cells [57, 58]. Additionally, SST reduces serum T levels in intact adult rats and in vitro T secretion but not in immature rats, and in hemicastrated rats, this result is overturned [59]. This indicates that age and testicular status can also affect the role of SST.

3. The Effect of GM on Male Reproductive Function

Besides GIH, GM is another prominent gastrointestinal factor that affects male reproduction. The relationship between GM and reproductive health is receiving increasing attention [80]. It seems to be a causal relationship between GM and male infertility [3, 81]. Imbalance of GM may lead to spermatogenic disorders and inhibit hormone synthesis, and fecal microbiota transplantation (FMT) can improve semen quality and spermatogenesis [82, 83]. Androgens are crucial for maintaining normal male reproductive development and spermatogenic function, such as the number of spermatogonia, BTB, spermatogenesis, etc. [84]. As mentioned above, the GM can regulate the metabolism of androgens, affecting the occurrence and development of related diseases. For example, Al-Asmakh et al. [19] showed that compared with specific pathogen-free (SPF) mice, the testosterone content in the testes of germ-free (GF) mice was significantly reduced. After implanting *Clostridium tyrobutyricum* in GF mice, the testosterone content in the testes significantly increased. Therefore, we will now review the relationship between GM and androgen, as well as how GM regulates androgen metabolism.

3.1. GM Affects Androgen Levels. GM can affect androgen levels during two important periods in men: adolescence and old age. The interaction between androgens and organs such as the genitalia and brain propel changes in male development during adolescence [85]. A longitudinal comparison between nonadolescent and adolescent subjects showed that nonadolescent subjects were significantly more abundant in the order *Clostridiales*, family *Clostridiaceae*, genus *Coprobacillus*, while adolescent subjects had a significant increase in the abundance of class *Betaproteobacteria*, order *Burkholderiales*. However, there is no difference in the diversity of GM between adolescent and nonadolescent subjects in α and β diversity [86].

Comparison within the adolescent subject group showed a positive correlation between the abundance of genera *Adlercreutzia*, *Dorea*, *Ruminococcus*, and T levels, while the abundance of genera *Clostridium* and *Parabacteroides* was negatively correlated with T levels [87]. This implies a dynamic correlation between specific GM categories and androgen levels during adolescence. Nevertheless, whether changes in the GM during adolescence drive changes in androgen levels or whether elevated androgen levels alter the structure of the GM remains unclear and requires further research [85–87].

The GM affects the androgen levels in the elderly. Androgens can promote hair growth and enhance hair gloss, which symbolizes vigorous vitality. It is shown that the elderly mice fed probiotic yogurt or *Lactobacillus reuteri* have significantly higher levels of androgens and faster and denser hair growth compared to these fed a regular diet, indicating that the GM can restore androgen levels to younger levels [88]. A clinical study obtained similar results, showing that elderly male subjects with higher T levels showed a significant increase in nine bacterial groups and a significant decrease in six. Among them, except for the genus *Alloscardovia* belonging to the Actinobacteria phylum, most of the increased bacteria belonged to the phylum *Firmicutes*, such as *Clostridiales*, *Turicibacter*, and *Gemella* [89]. Meanwhile, researchers believe that GM can regulate T metabolism in elderly men and suggest that bacterial preparations may be used in the future to prevent and treat T-related diseases [89].

3.2. GM Affects the Progression of Androgen-Related Diseases and Body State. It is widely believed that androgens have a protective effect [90]. In line with this, the androgen level in female mice receiving the GM of male mice increased, inhibited, and reduced pancreatic islet inflammation and production of antibodies, significantly delayed the onset time and cumulative incidence rate of type 1 diabetes (T1D), while the onset time and cumulative incidence rate of T1D in female mice receiving the GM from the same sex were similar to those in untreated female mice [16]. This strongly demonstrated the potential of GM to regulate androgen to affect disease occurrence. Exercise can increase the cross-sectional area and strength of skeletal muscles in mice, accompanied by an increase in serum T levels and changes in GM structure. After using antibiotics to remove the intestinal microbiota in mice, exercise no longer increased androgen levels, resulting in a corresponding decrease in skeletal muscle performance. Subsequently, FMT was carried out to increase the serum androgen levels of antibiotic-treated mice and improve muscle performance [91]. The above studies certificated that increasing the diversity and abundance of bacterial communities, as well as supplementing probiotics, such as *C. tyrobutyricum* [19] and *L. reuteri* [88] can increase the level of androgens in the body, improve the state of the body, and the occurrence and development of diseases. On the contrary, the imbalance of GM, an increase in opportunistic pathogenic bacteria, and a decrease in androgen levels are more closely related [92].

In some cases, an increase in T levels can promote disease progression. Unlike T1D and skeletal muscle manifestations, androgen deprivation therapy (ADT) is a necessary treatment for prostate cancer patients, as androgen promotes the cancer progression. The contradiction lies in the compensatory synthesis of T and DHT by the GM of patients receiving ADT treatment and castrated mice. After T absorption into the bloodstream, it can inhibit the effect of ADT and promote cancer development, while antibiotics or probiotics and prebiotics can delay the occurrence of androgen resistance and prostate cancer progression [93–95]. Cao et al. [17] analyzed the characteristics of GM in patients with nonobstructive azoospermia (NOA), and the results showed that seven bacteria, including *Prevotella denticola* and *Prevotella melaninogenica*, were positively correlated with serum T levels. *Acinetobacter johnsonii* and genus *Parabactoides* were negatively correlated with serum T levels. They believe that changes in GM structure, to some extent, explain the pathogenesis of NOA. The GM may serve as a biomarker for prostate cancer and NOA in the future, assisting clinical screening, diagnosis, and treatment.

3.3. The Mechanism of GM Regulating Androgen Metabolism

3.3.1. GM Metabolizes Androgens in the Intestine. GM expresses steroid metabolic enzymes that can synthesize, transform, and decompose androgens. First, the GM can metabolize androgens in the intestine through processes such as de glucuronization, lysis, and reduction. T undergoes reduction and glucuronization in the liver to produce glucuronized T (T-G) and glucuronized DHT (DHT-G), which are excreted into the intestine with bile. The GM can convert T-G and DHT-G to free form by deglucuronization. It is shown that the levels of free DHT in the cecum and colon of normal mice and healthy adult males are much higher than those in the small intestine, and the levels of T-G and DHT-G in the small intestine are significantly higher than those in the distal intestine. In contrast, the levels of T-G and DHT-G in the cecum of GF mice are significantly higher than those in the free type, comparable to the levels of androgens in the small intestine of normal mice, indicating that the GM has β glucosidase activity, which can participate in androgen metabolism [96]. However, the results showed that the serum T levels of GF mice were similar to those of ordinary mice, which was inconsistent with these research results [16, 88, 91, 97]. It may be related to the detection method, mouse strain, and age. Second, both androgens and glucocorticoids are synthesized from cholesterol [98]. The GM has steroid-processing enzymes that can directly participate in the metabolism of androgens and glucocorticoids. Glucocorticoids are synthesized from cholesterol through the adrenal cortex, and about 4%–8% can enter the intestine with bile acids synthesized by the liver. *Clostridium scidens* and other bacterial communities can express steroid-17,20-deaminase, which cleaves the glucocorticoid side chain and converts it into 11 β-hydroxyandrostenedione, further reduced to substances with biological activity comparable to DHT, such as 11-oxoandrogen, 11-ketotestosterone, and 11-ketodihydrotestosterone [99–101]. Thus, it can be considered that the GM participates in the synthesis of androgens in the intestine.

Apart from its synthetic effects, it is revealed that *Thauera sp. strain GDN1* can decompose androgens in the intestinal

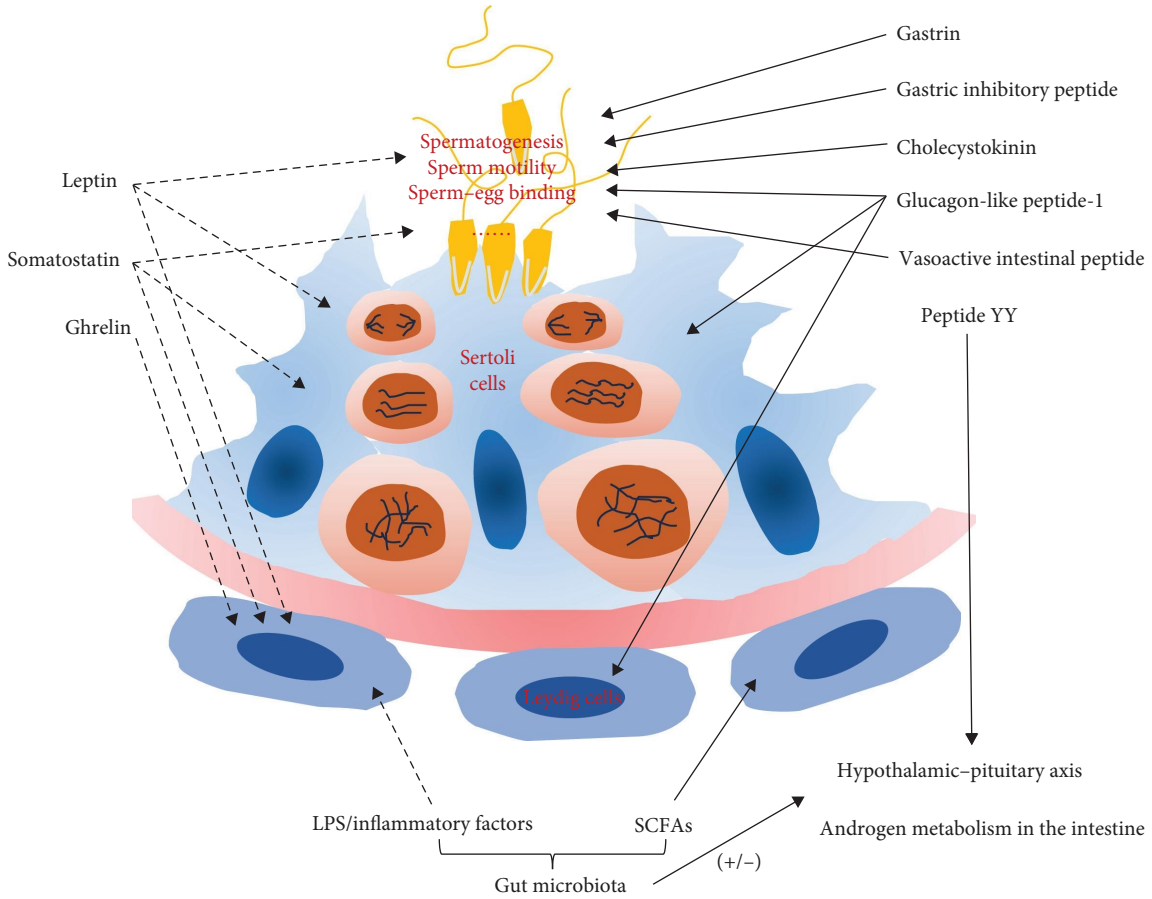

Figure 2: The action of GIH and GM on testicular tissue. (1) The position pointed by the arrow represents the site or physiological process of action of GIH and GM. (2) The solid line represents a promoting effect, the dashed line represents an inhibitory effect, and (+/−) indicates a possible bidirectional regulation.

tract of mice, hinder the hepatic intestinal circulation of androgens, and lower serum androgen levels [102]. However, as a steroid metabolite similar to bile acids, the existence of hepatointestinal circulation in androgens requires intensive study [103].

3.3.2. GM Regulates Androgen Synthesis in Leydig Cells. The GM can affect Leydig cells and regulate androgen metabolism. Metabolites of GM and their own components can both affect testicular secretion function [8, 17]. *C. tyrobutyricum* can secrete short-chain fatty acids (SCFAs) such as butyric acid, enhance the expression of specific genes in Leydig cells and mRNA encoding enzymes involved in T production (such as Insl3, Hsd3b1, Hsd17b11, cyp1a1, and cyp19a), and promote T synthesis in mouse testes [19]. There is a negative correlation between androgen levels and various inflammatory factors such as C-reactive protein, monocyte chemotactic protein 1, and tumor necrosis factor-α [104, 105]. The damage to the intestinal mucosal barrier causes lipopolysaccharides (LPS) in the cell wall of gram-negative bacteria to enter the human circulation, promoting the production of immune responses, oxidative stress, and inflammatory factors, harming Leydig cells and inhibiting T synthesis [7, 17]. Probiotics can produce SCFAs, protect intestinal barrier function, promote the production of anti-inflammatory factors such as interleukin 10 (IL-10), and inhibit the chronic low-grade inflammatory state [20, 106]. Poutahidis et al. [107] demonstrated that elderly mice fed with *L. reuteri* showed an increase in testicular interstitial area and a number of interstitial cells, an increase in nuclear volume, and an increase in serum T levels compared with the control group, indicating that probiotics restored Leydig cell function. At the same time, the study showed that this effect was achieved by inhibiting pro-inflammatory factor interleukin 17 (IL-17) and upregulating anti-inflammatory factor IL-10 [107]. Substances such as SCFAs and LPS derived from GM can directly act on the testes or affect the inflammatory state, thereby impacting the synthesis of androgens in the testes.

3.3.3. GM Regulates Hypothalamic–Pituitary Function. The hypothalamic–pituitary axis may be one of the pathways through which GM affects T synthesis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which promotes the synthesis and secretion of LH in the anterior pituitary gland and stimulates the synthesis of T by Leydig cells. LPS can restrain hypothalamic–pituitary function and reduce serum LH levels through mediators such as Kisspeptin, inflammatory factors, and hypothalamic–pituitary–adrenal axis [107, 108]. However, Shen et al. [109] suggest that intraperitoneal injection of LPS into adult male mice can lead to acute systemic inflammation, eventuating excessive

activation of GnRH neurons in the medial preoptic area of the hypothalamus, ultimately increasing serum LH levels. Moreover, they consider that this may be related to LPS impairing the T synthesis ability of Leydig cells, causing a decline in negative feedback inhibition. There are contradictions in LH, which may be due to different species and age stages. There is controversy over whether the GM works through the hypothalamic–pituitary axis and what kind of action it produces [17, 19], which needs to be explicated.

In the bargain, androgens can also affect the GM [110, 111]. The two interact to jointly maintain physical health [90]. The relationship between GM and androgens is a scientific direction worth exploring. Herein, we only focus on discussing how the former affects the latter.

4. Conclusions

This article mainly reviews the protective and damaging effects of GIH on testicular function, as well as the regulatory effects of GM on androgens. GIH can affect the function of testicular Leydig cells and Sertoli cells, as well as the process of spermatogenesis and sperm quality. The GM may affect the occurrence and development of male diseases by regulating androgen metabolism. Figure 2 briefly shows the effects of GIH and GM on testicular tissues and cells. This is a meaningful aspect of TGR Axis. But there are still some noteworthy contents needing to be further explored. For example, the first is how the GM interacts with GIH. Secondly, at a macro level, how androgens or male reproduction affect GIH and GM, thereby influencing gastrointestinal health and even overall health.

Overall, the TGR axis establishes the viewpoint that includes two aspects: GIH and GM from the gastrointestinal tract regulate male reproductive system function, and testicles and other male reproductive system tissues and organs also affect GIH secretion and GM structure. GIH and GM are closely related to obesity, diabetes, neuropsychiatric diseases, and other diseases [112–115]. Therefore, the TGR axis may provide valuable guidance for the diagnosis and treatment of male reproductive-related diseases and the maintenance of physical health.

Abbreviations

LH: Luteinizing hormone
FSH: Follicle-stimulating hormone
T: Testosterone
BTB: Blood-testis barrier
ED: Erectile dysfunction
GM: Gut microbiota
DHEA: Dehydroepiandrosterone
DHEAS: Dehydroepiandrosterone sulfate
DHT: Dihydrotestosterone
T-G: Glucuronized T
DHT-G: Glucuronized DHT
TGR: Testis–gut-reproduction
GAS: Gastrin
GIP: Gastric inhibitory peptide
GIPR: GIP receptor
GLP-1: Glucagon-like peptide-1
GLP-1R: GLP-1 receptor
GLP1-RAs: GLP-1 receptor agonists
CCK: Cholecystokinin
PYY: Peptide YY
VIP: Vasoactive intestinal peptide
SST: Somatostatin
Psg17: Pregnancy-specific glycoprotein 17
Apaf-1: Apoptosis protease activating factor 1
NOS: Nitric oxide synthase
cAMP: Cyclic 3',5'-adenosine monophosphate
GHS: Growth-hormone secretagogue
LEPR: Leptin and leptin receptor
SOCS3: Suppressor of cytokine signaling 3
pSTAT3: Phosphorylated signal transducer and activator of transcription 3
FMT: Fecal microbiota transplantation
SPF: Specific pathogen-free
GF: Germ-free
T1D: Type 1 diabetes
ADT: Androgen deprivation therapy
NOA: Nonobstructive azoospermia
SCFAs: Short-chain fatty acids
LPS: Lipopolysaccharides
IL-10: Interleukin 10
IL-17: Interleukin 17
GnRH: Gonadotropin-releasing hormone.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Zhao Jiayou contributed to the topic selection and academic guidance of the review. Zou Hede, Chen Wenkang, and Hu Baofeng contributed to the writing of the article. Zou Hede contributed to the production of the image. Chen Wenkang contributed to the production of tables. Hu Baofeng provided some academic guidance. Liu Hanfei contributed to the proofreading of the review. Zou Hede, Chen Wenkang, and Hu Baofeng have made equal contributions.

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