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GUT MICROBIOTA AS A MODULATOR OF ENDOCRINE GLAND FUNCTION: A REVIEW OF THE GUT-ENDOCRINE AXIS BEYOND THE GUT-BRAIN CONNECTION.

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ABSTRACT:
The gut microbiota, the dynamic community of bacteria, viruses, fungi, and archaea present in the gastrointestinal tract, has been studied under the perspective of the gut-brain axis. Recent studies, however, report that microbial interactions with host physiology are much more than neurological—microbial modulation of endocrine gland function is now well established. A summary of recent knowledge of the gut-endocrine axis, focusing on the role of metabolites of the gut microbiome, such as short-chain fatty acids, secondary bile acids, indole derivatives and lipopolysaccharide, in communicating to distant organs and immune pathways by vagal and humoral pathways. We discuss microbiota regulation of endocrine system tone and dynamics, including the hypothalamic-pituitary-adrenal axis, thyroid hormone synthesis, thyroid autoimmunity, pancreatic beta-cell function, sex steroid metabolism (estrobolome and testobolome), adipokine regulation, energy storage in fat, calcium-vitamin D homeostasis, and gut-derived melatonin production, with implications for PCOS and for fertility and growth hormone-IGF-1 axis dynamics. We also review the microbiome and metabolite related diagnostic biomarkers, sex- and age-dependent variations in gut-endocrine relationships, and evidence supporting probiotic, prebiotic, synbiotic, and fecal microbiota transplantations interventions. Although there is strong mechanistic evidence supporting the gut microbiota as an active endocrine regulator, as yet there are only small clinical trials available, with variable effects and with diet and medication as confounding factors. In conclusion, the gut-endocrine axis is a biologically coherent system that is not widely studied in clinical trials of humans, particularly one that needs to be sex-and age-stratified, and it is a system that is clearly interconnected and has therapeutic potential.

KEYWORDS: Gut microbiome, Endocrine gland, Growth hormone, thyroid gland, PCOS, Sex hormones

1. INTRODUCTION

The gut microbiota is an extremely dynamic and complex community of microbiota residing in the human gastrointestinal (GI) tract. It contains bacteria, viruses, fungi, archaea and other organisms. There are many factors involved in individual differences in this community composition including host genetics, food, age, exposure to medications and early life environmental factors. It may seem that the gut microbiota is dominated by the phyla Firmicutes and Bacteroidetes, yet the ecology of the gut is much more complex than the simple description. The microbial community of seemingly healthy individuals can vary greatly despite the fact that they have similar functional capacities [1-3]. Additionally, the biological significance of the gut microbiota exceeds its taxonomic compositions. The intestinal microbes can be metabolically versatile with the ability to ferment food material, generate vitamins, modify bile acids, degrade amino acids and chemicals provided by the host and form bioactive metabolites. Short-chain fatty acids (SCFAs), secondary bile acids, indole derivatives, and other microbial products are among these metabolites that might affect distant organs via metabolic, immunological, neurological, and endocrine pathways or act locally within the intestine [4,5]. Therefore, the gut microbiota can be thought of as a metabolically active part of human physiology rather than just a group of microorganisms.

2.Historical focus on the gut-brain axis:

Early studies in host–microbiota communication were centered around the gut–brain axis, a two-way communication system between the gastrointestinal tract and the central nervous system. It brought together endocrine, immunological and microbial-metabolite-mediated pathways with neurological pathways, particularly the vagus and enteric nerve systems. The discovery of how gut bacteria could influence neurotransmitter pathways, stress reactions, intestinal permeability, immunological activity and behaviour was a significant expansion of the traditional view of gastrointestinal physiology.
Consequently, the microbiota-gut-brain axis has become an important axis to investigate multiple issues such as obesity, mood disorders, neurodegenerative diseases, and functional gastrointestinal disorders. [6,7]. But microbiota-mediated communication to the brain can provide a partial view of biological events in the host. A large enteroendocrine system

exists in the gastrointestinal tract, consisting of specialized cells of the enteroendocrine system which are distributed throughout the intestinal epithelium. These cells identify the nutrients and microbial signals, and secrete hormones such as GLP-1, PYY, cholecystokinin, gastric inhibitory polypeptide, and other signalling molecules that regulate appetite, glucose metabolism, gastrointestinal motility, nutrient absorption, and energy homeostasis [8,9] (Figure 1).
In addition, products of microbial metabolism may directly affect the function of enterendocrine cells. Free fatty acid receptors (FFARs) on enteroendocrine cells can be activated by SCFAs and affect GLP-1 and PYY secretion. This indicates that endocrine mechanisms are not merely a function of the gut-brain axis but are also a vital mechanism in their own way.

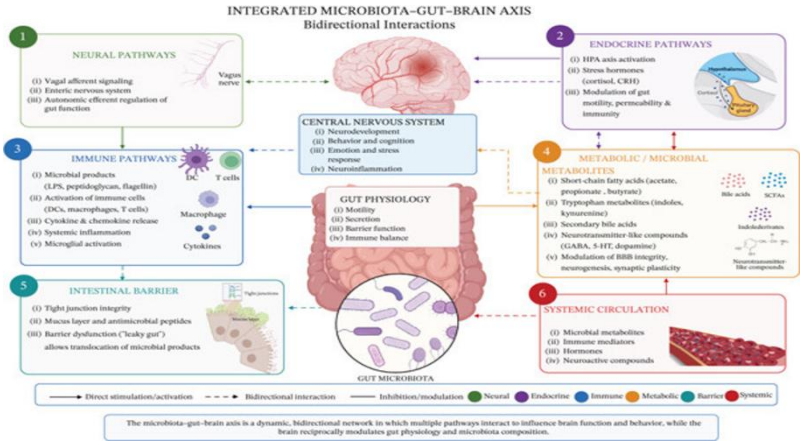

Figure 1: The term integrated microbiota–gut–brain axis (MGBA) describes the complex interactions between microbiota, gut, and brain. Bidirectional interactions between the gut microbiota and the central nervous system via interconnected neural, endocrine, immune, metabolic, and intestinal barrier pathways. Microbial metabolites such as short-chain fatty acids (SCFAs), metabolites derived from the breakdown of tryptophan, secondary bile acids, and neurotransmitter-like compounds, in addition to immune mediators and endocrine signals, regulate intestinal barrier integrity, systemic signaling, blood–brain barrier function, and neuronal activity. These are interconnected pathways that have overall effects on neurodevelopment, cognition, behaviour and neurological homeostasis. Solid arrows represent direct signaling pathways, and dashed arrows represent bidirectional interaction and feedback adapted from [10]

3. Microbial metabolites as signaling molecules:
The formation and alteration of bioactive metabolites is one of the most significant ways that gut microbes interact with the host. Of these, resistant fibers and carbohydrates in the diet are fermented to SCFAs, with the main ones being acetate, propionate, and butyrate. These metabolites can impact tissues that are not located in the Gl tract either through local action in the intestine or systemic action. SCFAs may modulate cellular transcription by inhibition of the histone deacetylase (HDAC) and bind to host G-protein coupled receptors (GPCR), such as free fatty acid receptor 2 (FFAR2/GPR43) and free fatty acid receptor 3 (FFAR3/GPR41). These processes play important roles in the regulation of immunological processes, intestinal barrier function, control of hunger, and glucose metabolism [11,12]. By affecting enteroendocrine cells, SCFAs also have an impact on endocrine signalling. In these cells, activation of FFAR2 and FFAR3 may lead to an increase in the secretion of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). PYY is involved in satiety and gastrointestinal motility, whereas GLP-1 is involved in the glucose-dependent insulin secretion and appetite regulation.
The other important class of microbial signalling molecules is secondary bile acids. The intestinal microbiota transforms most primary bile acids in the liver to secondary bile acids that have different biological properties. Such compounds bind to receptors in the host, including the nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5). The FXR signal is involved in the regulation of bile acid biosynthesis, lipid metabolism, glucose homeostasis, and intestinal function; activation of FXR in enteroendocrine cells can stimulate GLP-1 secretion. In this regard, the ability of microbiota to transform bile acids is an important connection between microbial metabolism and endocrine regulation. The transformation of bile acids by microbiota is therefore an important connection between microbial metabolism and endocrine regulation.
Another route of communication is the indole derivatives and metabolites of tryptophan. Dietary tryptophan is broken down by gut bacteria into a number of bioactive substances, such as indole, indole-3-propionic acid, indole-3-acetic acid, and other derivatives of indole. Furthermore, the microbial and immunological activity in the gut can modulate the amount of tryptophan in circulation, which can take part in the kynurenine pathway or the serotonin pathway or direct it to the microbial pathway, linking the intestinal microbial activity to immunological and neuroendocrine activities [13, 14]. Microorganisms associated with the molecular pattern LPS can stimulate inflammatory signaling, whereas beneficial microbial metabolites do not trigger inflammatory signaling. Gram-negative bacterial LPS can trigger Toll-like receptor 4 (TLR4) and subsequent inflammatory pathways.
Enteroendocrine cells (EECs) are an important link between the intestinal microbiota and the endocrine system. These specialized epithelial cells are able to sense nutrients and products of microbes in the intestinal environment and convert them into hormonal responses. The key populations of cells in EEC include L-cells, which secrete GLP-1 and PYY; K-

cells, which secrete the glucose-dependent insulinotropic polypeptide (GIP); and enterochromaffin cells, which secrete lots of serotonin (5-hydroxytryptamine, 5-HT). Specific receptors are present to allow direct microbial metabolite effects on EEC activity. EECs are of particular importance in the regulation of energy metabolism. Microbiota-derived signals may modulate GLP-1, PYY, GIP, serotonin, and other gut mediators, which in turn will impact appetite, insulin secretion, gastric emptying, intestinal motility, and energy balance. EECs could thus be considered as chemosensory endocrine intermediaries that transform the information they receive from the intestinal microbial ecosystem into hormonal signals of the host. [14,15].

Intestinal epithelium and associated immune cells are always in dynamic interaction with micro-organisms and their metabolites. Certain metabolites produced by microbes can facilitate this by modulating the differentiation of immune cells, production of cytokines and barrier function of epithelia, such as SCFAs and indole derivatives [16]. The intestinal barrier is important, since it regulates the extent of contact between the microbial products and the tissues. Together, tight-junction proteins, mucus, antimicrobial peptides, and epithelial cells limit movement of microorganisms and microbial molecules across the intestinal wall. The ability to preserve energy metabolism and barrier integrity in the epithelium is supported by SCFAs, especially butyrate, while disturbances in the diet, dysbiosis, and inflammatory diseases can impair these protective processes [16].

In the event of barrier disruption, LPS and other microbial-associated molecular patterns have increased access to immune cells and can enter the systemic circulation. Upon activation of TLR4 and other pattern-recognition receptors, inflammatory mediators, such as tumour necrosis factor α, interleukin-1 β, and interleukin-6, are produced. Chronic, low-intensity inflammation can then affect insulin signaling, adipose tissue metabolism, liver function, and more. Most importantly, there is a bi-directional relationship between microbiota, barrier integrity, immunity, and endocrine function. Hormonal changes affect intestinal physiology and the composition of the intestinal flora, and the intestinal flora and inflammation can affect hormonal production, metabolism, and signaling. Therefore, immune-mediated communication is not a distinct channel but a part of the wider gut-endocrine network [17,18].

Gut microbiota–endocrine communication can generally be described as a complex multilevel network of microbial metabolites, enteroendocrine cells, host metabolic enzymes, immune pathways, and neural and circulatory pathways. Signaling molecules are produced and modified by microorganisms, luminal signals are converted into endocrine responses in EECs, host hormones are modified by microbial enzymes, microbial and host signaling are integrated via immune pathways and distant organs are reached by signaling via vagal and humoral routes. These mechanisms underscore the idea of gut microbiota as an active endocrine regulator and offer a mechanism for the evolving gut–endocrine axis [19,20].

4.The gut microbiota and hypothalamic-pituitary-adrenal (HPA) axis.

It is now recognized that the hypothalamo-pituitary-adrenal axis is responsible for orchestrating the response to physical and psychological stressors. The research is still evolving, and many of the studies have been done in germ-free rodents, but a growing body of evidence suggests that the gut flora play a role in tuning the magnitude and rate of the HPA axis response to challenge from the organism. Influence of microbes on cortisol regulation. The initial observation in this area was made by studies of germ-free mice that lack any colonizing microbiota and thus demonstrated an exaggerated corticosterone response to mild restraint stress compared with normal mice [21].

Further studies in germ-free and gnotobiotic mice have extended this finding to provide evidence that the gut microbiota affects gene regulation in the glucocorticoid receptor pathway in the hippocampus, where it is critical for negative-feedback control of cortisol release; germ-free mice exhibit gene changes in the glucocorticoid receptor pathway in the hippocampus, alongside increased basal levels of serum corticosterone, that are associated with increased anxiety-like behavior [22]. In germ-free and colonized mice subjected to acute restraint stress, investigators have found that microbial status can influence gene expression within the pituitary and adrenal glands themselves, not just by some central node, including genes that regulate sensitivity of corticotropin-releasing hormone receptors and activity of steroidogenic enzymes [23], suggesting that microorganisms can modify the HPA axis at multiple anatomical levels. During dysbiosis, microbial metabolites have the potential to pass the blood-brain barrier (BBB) and influence the hypothalamus and hippocampus regions, while the breakdown of the intestinal barrier during dysbiosis can result in the entry of bacterial components (e.g. lipopolysaccharide) into circulation, which can then activate the axis via immune and inflammatory signaling, and vagal afferent signaling may provide a further non-humoral route by which luminal microbial activity can be communicated to central stress-regulatory circuits [24].

Microbiological changes, characterized by decrease in diversity, decrease in beneficial taxa, and increase in pro-inflammatory taxa, have been observed in humans after stress and in rodents after chronic psychosocial stress and chronic restraint stress, which are believed to be due to stress-induced alterations in gut motility, mucous secretion, intestinal permeability, and local immune activity [25]. This bi-directionality has implications in clinical and preclinical interpretation: it may be challenging to determine if a change in the microbes is a cause or a consequence of the dysregulation of the HPA axis in a particular disorder.

4.1 Gut Microbiota and Thyroid Function:

There has been an increase in the interest in the "gut-thyroid axis", as thyroid disease and gastrointestinal dysbiosis are often associated, and the gut microbiota is directly involved in multiple aspects of thyroid hormone synthesis, activation, and recycling. Absorption of iodine and selenium regulated by microorganisms. The gut microbiota affects both the bioavailability of iodine and selenium and is essential for the synthesis and activation of thyroid hormones. There are several ways by which intestinal bacteria impact iodine metabolism: modulation of the expression and activity of the

sodium-iodine symporter and the stimulation of deiodinase activity by bacterial lipopolysaccharide, which leads to the production of T3 and inhibition of TSH secretion from the pituitary, even outside of effects on nutrient absorption [26].
Microorganisms also need selenium to make selenoproteins, so host and microbial populations are competing for host-sourced selenium, and animal studies have shown that microbial processing of selenium may limit the amount of selenium available for host selenoprotein synthesis, including the iodothyronine deiodinases (types 1, 2, and 3) and glutathione peroxidases that are critical for protecting cells from oxidative stress [27,28]. In this regard, iron, zinc, and copper are also mentioned; all of them are cofactors involved in thyroid hormone synthesis or peripheral activation and gut dysbiosis has been associated with deficiency of these elements due to impaired absorption, changes in gut intestinal pH, and modification of the bioavailable, unbound form of the nutrient in the gut lumen [29]. Digestion of dietary fibre generates short-chain fatty acids (SCFA) which may have a complementary effect here, as these lower the pH of the lumen and can improve the bioavailability of iron in the colon, which in most people is an indirect benefit to thyroid hormone synthesis, provided they have sufficient fibre and the colonic microbiota is fermentation-competent [30].
Alterations in gut microbial composition have been broadly linked to autoimmune thyroid disease, including Hashimoto's thyroiditis and Graves' disease, with a decrease in genera that produce SCFA, which are important for intestinal health, and an increase in taxa linked to pro-inflammatory signaling [31]. The mechanism that has been proposed the most is increased intestinal permeability: a damaged epithelial barrier wall results in increased exposure to entering antigens and bacterial translocation that triggers innate and adaptive immune responses that may cross-react with thyroid antigens or simply create a systemic pro-inflammatory state that can lead to autoimmunity [32,33]. Low counts of one or more SCFA -producing bacteria also seem to be a common denominator amongst these conditions, and experimental studies demonstrate that supplementation with butyrate can normalize thyroid hormone levels in mouse models of GO, and that supplementing with B. fragilis and its metabolite propionate is effective in modulating the gut-thyroid axis in preclinical models of Graves' disease [34].

4.2 The "gut-thyroid axis" concept

Taken together, the nutritional, immunological, and biotransformative roles of the gut microbiota described above have been synthesized into the concept of a "gut-thyroid axis," a term now used to describe the bidirectional relationship in which the microbiota shapes thyroid hormone synthesis, activation, and immune tolerance, while thyroid status in turn shapes gut motility, permeability, and microbial composition [35,36]. This framework was formalized in an influential review that catalogued the ways in which the microbiota affects iodine, selenium, and iron uptake, alters the availability and toxicity of thyroid medications, and differs systematically in composition between patients with thyroid disorders and healthy controls; the same review noted that germ-free rodents have smaller thyroid glands than conventionally raised animals, offering direct anatomical evidence that the microbiota is required for normal thyroid development and not merely for the fine-tuning of hormone levels in the adult animal [35].
Beyond autoimmune disease, the gut-thyroid axis concept has been extended to thyroid nodular disease and thyroid cancer, where a reduction in butyrate-producing bacteria and an enrichment of inflammatory bacterial taxa have been observed in tumor-associated microbiota, and specific intratumoral genera have been correlated with circulating thyroid hormone indices [37].

5 Microbiota, insulin secretion and sensitivity :

Some of the most convincing evidence for direct linkages of gut microbiota to beta-cell physiology, rather than to just correlate with metabolic disease, comes from a mechanistic study that demonstrated that intestinal lysozyme permits the trafficking of peptidoglycan derived from gut bacteria to the pancreas via the circulation, where it acts on the innate immune receptor Nod1 in beta cells, with this signal essential for normal beta-cell maturation and trafficking of insulin secretory granules, and resulting in impaired glucose stimulated insulin secretion in mice lacking this pathway, directly linking a bacterial cell-wall product to the intracellular machinery of insulin production [38].
A well established mechanism of microbial influence is through the conversion of primary bile acids into secondary bile acids, which are ligands for farnesoid X receptor and G-protein-coupled receptor TGR5, both of which are expressed on pancreatic islets, and activation of islet farnesoid X receptor has been demonstrated to improve insulin secretion and to prevent diabetes onset in genetically diabetic mouse models [39]. SCFAs have effects on beta-cell function. While effects of SCFAs on whole-body insulin sensitivity have been more consistently positive, the field remains far from settled on the directionality of SCFA-insulin relationship at the level of the individual beta cell, with some studies reporting stimulation and others inhibition, and a comprehensive review of this literature concluded that the overall picture is far from clear [40].
On the insulin sensitivity of peripheral tissues, human studies have correlated specific genera, such as Clostridium, Dialister and Phascolarctobacterium, with increased insulin sensitivity or secretion in overweight and obese adults, demonstrating that the human microbiota may play a role in insulin physiology beyond that demonstrated in animal models [41]. The consistent finding of an effect of transplantation of gut microbiota from lean humans with obesity/metabolic syndrome is that insulin sensitivity is transiently improved, and a series of studies in animals have found that this intervention can partially restore beta-cell function, although the results have been modest and short-term in humans [42].
Using primary murine colonic cultures, acetate and propionate were found to stimulate secretion of the incretin hormone GLP-1 from L cells, via the G protein-coupled receptor FFAR2 (GPR43), through activation of Gq signaling and an increase in intracellular calcium, and mice lacking FFAR2 exhibited a markedly reduced increase in circulating GLP-1 following an oral glucose challenge, establishing this receptor as a major connection between microbial fermentation products and incretin output in vivo [43]. The SCFA-FFAR2-GLP-1 axis, which promotes glucose-stimulated insulin

secretion, inhibits glucagon production, slows gastric emptying, and increases satiety, is a coherent mechanistic explanation for the well documented glucose lowering benefits of dietary fibre and fermentable prebiotics [44].
In vitro studies on butyrate have been demonstrated to prevent cytokine-induced beta-cell dysfunction, maintain glucose-stimulated insulin secretion and insulin content in inflammatory conditions that are known to reduce beta-cell output [45]. Dysbiosis is a disorder in Type 1 and Type 2 diabetes mellitus. LPS penetration of a damaged intestinal barrier triggers toll-like receptor 4 signaling in metabolic organs, leading to low-grade "metabolic inflammation" that is emerging as a key mechanism leading to insulin resistance and chronic insulin deficiency [46], and decreased commensal abundance of butyrate-producing bacteria eliminates a source of anti-inflammatory, insulin-sensitizing SCFAs. FMT is the most direct microbial-based therapeutic strategy, and, despite some tangible short-term benefits in peripheral insulin sensitivity after transplant of lean-donor microbiota into individuals with metabolic syndrome, the benefits are short-lived [47], requiring repeated FMTs, combination with dietary fiber to maintain the engrafted community, or application of defined bacterial consortia instead of whole community transplants to achieve durable benefit.

6. Gut Microbiome and Sex hormones

6. 1 Microbiota and Estrogen metabolism:

Estrogen metabolism is regulated by several microbial enzymes. In 2011, a term “estrobolome” was coined to define the entire suite of genes of gut bacteria that can metabolize estrogens , and this idea has since gained widespread traction in microbiome-endocrine studies. The mechanism involves enterohepatic recycling, which involves conjugation of the estrogens that are synthesized in the ovary, adrenal glands and fat tissue, primarily by glucuronidation to make them water-soluble for biliary excretion, followed by deconjugation by bacteria in the gut with reabsorption of unconjugated estrogens into the portal circulation and their reentry into the bloodstream [48].
The estrobolome has been involved in disease states at both extremities of the estrogen spectrum due to the both pathogenic and non-pathogenic activities of insufficient and excess β-glucuronidase activity. The decrease in microbial diversity and decrease in β-glucurononidase activity has been correlated with lower estrogen-reactivation levels and a rise in hypoestrogenic effects including menopause symptoms, lower bone density, and a rise in adverse cardiometabolic effects, while increases in the relative abundance of taxa that have higher levels of β-glucuronidase activity than Bacteroidota have been correlated with hyperestrogenic effects such as endometriosis and hormone-receptor-positive cancers [49, 50].

6.2 Microbiota and Testosterone/Androgen metabolism:

While estrogen metabolism has been studied more extensively than metabolism of the male hormones, androgens produced by gut bacteria have been much less investigated than estrogen metabolism, the field has come a long way in the past few years, and a similar "testobolome" was proposed as a gut bacterial tool for metabolizing testosterone and other androgens [51]. In addition, direct evidence for bacterial production of testosterone has been demonstrated, with Clostridium scindens shown to be capable of producing androgens from glucocorticoid precursors and studies of the mouse gut content have revealed significant amounts of glucuronidated testosterone and dihydrotestosterone in the small intestine with unconjugated dihydrotestosterone building up in the distal intestine, suggesting that, as with estrogens, deconjugation and reabsorption of androgens takes place throughout the length of the gut [52]. Gut microbiota transfer experiments further establish a causal link: transfer of gut microbiota from adult male mice to immature female mice resulted in increased circulating levels of testosterone in the recipient mice as well as changes in susceptibility to autoimmune diabetes, highlighting that the gut microbiota is not simply responsive to androgen status, but can also actively influence it [53].
The estrobolome and testobolome work together to control the bioavailable pool of circulating sex steroids, with plausible downstream consequences of either system disruption on fertility. A systematic review looking at the role of the estrobolome in the pathogenesis and associated infertility of endometriosis revealed consistent evidence that gut dysbiosis, high activity of the enzyme β-glucuronidase and increased estrogen levels due to this enzyme are likely contributing factors to the establishment and progression of ectopic endometrial lesions; however, the authors noted that most of the available evidence is association-based and not interventionally based, and a causal, mechanistic relationship between specific taxa and the development of lesions has not yet been definitively established . The interplay of these three pathological mechanisms (insulin resistance, hyperandrogenism and low-grade inflammation) of dysbiosis is hypothesized to converge on impaired folliculogenesis and anovulation, and microbiota-targeted adjuncts to fertility treatment may have a biologically coherent, though not yet substantiated, basis for their therapeutic use in Polycystic Ovarian Syndrome -related infertility [54,55].

7 Gut Microbiota and Adipose Tissue

7.1 Regulation of adipokines (leptin, adiponectin) by microbes:

The gut microbiota regulates leptin, the key adipokine involved in a host of convergent pathways that control satiety. In addition to their effects on the direct target of the intestine, they have been shown to stimulate adipocytes directly to express more leptin, thereby providing one mechanism through which fiber fermentation could affect central appetite regulation, and their effects on the direct target of the intestine are especially relevant for butyrate which directly enhances hypothalamic leptin sensitivity by increasing STAT3 phosphorylation in the arcuate nucleus, which is lost in leptin deficient animals, and restored by exogenous leptin administration, directly demonstrating that this microbial metabolite works through, rather than independently of, the leptin signaling pathway [56,57].
Since chronic low-grade inflammation as a result of bacteria-induced lipopolysaccharide is a known factor of leptin resistance, the gut-microbiota dysbiosis, characterized by increased gut permeability and endotoxemia, is believed to

play a role in the hyperleptinemic, leptin-resistant state characteristic of obesity, despite the growing absolute circulating levels of leptin [58]. Unlike leptin, adiponectin is generally decreased in obesity and dysbiosis, and the link between adiponectin and microbiota seems to be true bidirectional. Antibiotic-induced depletion of gut microbiota in high-fat-diet-fed mice was shown to affect the expression of adiponectin and resistin via epigenetic modifications of the Adipoq and Resistin gene promoters, suggesting a specific epigenetic pathway through which gut microbiota can long-term modify adipokine gene expression beyond transient modulation [59].

Firmicutes-to-Bacteroidetes ratio in obesity compared to lean individuals, increased fecal concentrations of SCFAs, and elevated breath excretion of ethanol, all of which have been proposed as indirect measures of an increased ability for microbial energy extraction from ingested carbohydrate [60,61], but others have not replicated a consistent signature of Firmicutes-to-Bacteroidetes, and the ratio is now thought of as an oversimplified measure of a more complex functional shift in microbial community metabolism. The gut-adipose relationship expands to the full burden of metabolic syndrome by a complex and interwoven network of simultaneous actions of SCFAs, bile acids in adipose, liver, and pancreas. A thorough investigation of this cross-talk between adipokines and metabolites from gut bacteria identified six adipokines, among which adiponectin, leptin, resistin, interleukin-6, MCP-1 and PAI-1, were consistently dysregulated in obesity and whose expression was regulated by metabolites derived from gut bacteria, and the adipokine imbalance directly involved in the low-grade pro-inflammatory state that is associated with obesity, insulin resistance and the vascular complications of metabolic syndrome [62]. Long-lasting effects on the gut microbiota, has provided the strongest evidence to date that altering the gut microbiota can directly impact adipokine and metabolic syndrome parameters in addition to weight loss.

Gut microbiome interaction with calcium homeostasis:

Multiple mechanisms have been suggested to account for the regulation of calcium bioavailability by the gut community upstream of the parathyroid gland. The bacterial strains that express 7-beta-hydroxysteroid dehydrogenase like some Ruminococcus spp. convert primary into secondary bile acids that increase the expression of intestinal vitamin D receptors, which allows the transcellular transport of calcium. The calcium-sensing receptor is the dominant regulator of PTH secretion and changes in absorptive efficiency can, therefore, influence parathyroid secretion, while clinical associations between the amounts of microbes in the body and levels of circulating PTH are consistent with this feedback mechanism. Vitamin D directly affects the intestinal microbiota via its antimicrobial and barrier-supportive effects mediated by the vitamin D receptor, while the shift on one side of the axis is likely to amplify that on the other [63].

The hypocalcaemic state and the greatly disturbed vitamin D metabolism of germ free mice, with low levels of all three metabolites, are normalised after conventionalisation within 1-2 weeks . The mechanism seems to be mediated primarily through the phosphaturic hormone fibroblast growth factor 23 (FGF23) which is significantly elevated in germ-free animals. Colonisation results in a short-term increase in colonic tumour necrosis factor (TNF) alpha, leading to decreased FGF23 production, which allows renal 1-alpha hydroxylase activity to return to normal and normalises 1,25-dihydroxyvitamin D and serum calcium . The microbiota also influences the actions of the skeletal parathyroid hormone (PTH) downstream. The bone-anabolic arm of the response to PTH administration in mice is reduced by broad-spectrum antibiotics in both hyper- and hypocalcaemic trials, and microbially derived butyrate has been shown to be required for this effect, in part through expansion of regulatory T-cells and Wnt-beta-catenin signalling in osteoblasts [63,64].

8 The Pineal Gland and the Interactions of Pineal Gland and Microbiota:

Melatonin is a most abundant reservoir of production, with concentrations of melatonin in enterochromaffin cells and other gut sources being reported to be several hundredfold more than that of the pineal gland [65]. Pineal melatonin in systemic circulation has chronobiotic effects which are different in several ways from the antioxidant, anti-inflammatory and barrier-protective actions of locally synthesised melatonin, which is mainly paracrine. Experimental pinealectomy in pigs does not alter gut melatonin levels and the endogenous melatonin does not alter the gut microbiota, while exogenous melatonin does alter the gut microbiota; this dissociation suggests a much more independent regulation of gut melatonin production compared to pineal/suprachiasmatic regulation [66].

Trytophan is a precursor of both serotonin and melatonin, which is extensively metabolized in the gut, and some commensal genera, such as some species of the Lactobacillus and Bifidobacterium genera, seem to be able to directly modulate local melatonin production or to stimulate host production by inducing Toll-like receptor and MyD88-dependent signalling in epithelial cells of the colon. On the other hand, when the microbiota is depleted by antibiotics or in germ-free animals, there is a shift in the balance of melatonin in the bloodstream and in the colon, suggesting that the gut flora has a role in regulating the distribution of melatonin between blood and colon. Since the secretion of melatonin is also under a light-entrained circadian rhythm, and since the gut microbiota itself exhibits a diurnal oscillation in composition and function, chronodisruption (whether due to shift work, jet lag or irregular feeding) tends to produce dysbiosis, which in turn can dampen the amplitude of host circadian gene expression, thus forming a vicious circle that has been linked to obesity, inflammatory bowel disease, and mood disorders [65].

9 Growth Hormone/IGF-1 Axis and Microbiota

Specific taxa also seem to exert different mechanisms: colonisation by Prevotella copri increases the production of interleukin (IL)-13, leading to hepatic upregulation of insulin-like growth factor (IGF)-1 through the IL-13 receptor-JAK2-STAT6 pathway, whereas bacterial cell-wall components of Lactobacillus plantarum activate the pattern-recognition receptor NOD2 to stimulate IGF-1 production and promote bone growth, which is impaired in NOD2-deficient animals. The ability of Lactobacillus plantarum to restore linear growth appears to be mediated primarily by

this IGF-1-dependent pathway and is relevant to the connection between undernutrition in childhood, microbial dysbiosis and stunting.

Growth hormone and IGF-1 status also affects microbial community structure, in the reverse direction. Growth hormone excess and deficiency is associated with differences in the microbial composition and diversity of mice compared to littermate controls, and the impact of growth hormone excess action on the microbiome varies by age, indicating that there is an interaction with the overall ageing phenotype of growth hormone excess somatotropic overactivity [67]. In children with GH deficiency, levels of fecal butyrate and Bifidobacterium spp. are often decreased, and the supplementation with probiotics of Lactobacillus plantarum, high fibre diet or, less experimentally, FMT have been shown to be effective in animal models and small clinical trials, but ethnic and dietary diversity in baseline microbiota may make it challenging to compare across populations and plan trials [68].

The use of microbiota as a Biomarker for Endocrine Dysfunction

The stability of some compositional signatures within the cohorts has sparked the interest in the gut microbiome as a diagnostic or prognosis biomarker in endocrinology. Reduced alpha-diversity and loss of butyrate-producing bacteria like Faecalibacterium prausnitzii and Roseburia species, as well as increased levels of Proteobacteria, are frequently reported across all metabolic-endocrine diseases including type 2 diabetes, obesity, PCOS and growth hormone deficiency, and are sometimes considered to represent a 'dysbiotic signature' that is common to all metabolic-endocrine diseases [69].

Advances in shotgun metagenomic sequencing and machine-learning classification are starting to enable prediction of glycaemic response to specific foods, disease-state classification in type 2 diabetes and even risk-stratification for certain conditions like gestational diabetes, with accuracy that is approaching that of conventional clinical predictors in some cohorts, though external validation in ethnically and geographically diverse populations remains the main hurdle to clinical translation. Although there is currently no gut-microbiome derived test in routine endocrine practice, enthusiasm for microbiome biomarkers should be tempered by the understanding that the composition of the gut microbiome is highly sensitive to diet, medication (including metformin and proton-pump inhibitors) and the technique used to collect the sample, which could all impact cross-study comparisons [69].

Sex and Age-Related Variation in Gut-Endocrine Interactions:

There is also some difference in microbial diversity and composition between men and women, with women having higher relative abundances of Akkermansia and Ruminococcus, and men having higher relative abundances of Prevotella and Fusobacterium, with little difference between men and women before puberty and after menopause [70]. Gonadal hormones seem to be one of the major contributors to this dimorphism: gonadectomy in rodents causes a trend towards a microbiota profile more like that of intact male and female mice, the harmful metabolic effects of which are more marked in females (with overnutrition) [71].

Gut bacteria expressing beta-glucuronosidase and other enzymes, collectively called the ‘estrobolome', can deconjugate estrogen metabolites that are intended for excretion, and allow reabsorption of estrogen metabolites through enterohepatic circulation; thus, the composition of the bacterial subset can influence circulating estrogen exposure throughout the menstrual cycle, during pregnancy and menopausal transition [72]. The clinical relationships that have been most thoroughly investigated include those involving PCOS and the relationship between dysbiosis, hyperandrogenism, and insulin resistance and between estrogen withdrawal and microbial shift and increased bone resorption in postmenopausal osteoporosis [73]. These sex differences are exacerbated by aging. Progressive loss of SCFA-producing taxa, expansion of pro-inflammatory Proteobacteria, and reduced production of protective metabolites like indoles and polyamines collectively contribute to the low-grade inflammatory state, also known as 'inflammaging,' exhibited by older adults.

The Role of Probiotics, Prebiotics, and Synbiotics in Endocrine Disease Management:

Interventional studies of the gut microbiota have been the most extensive in PCOS and to a lesser extent in thyroid disease. In 2024, a systematic review of 11 RCTs, primarily with Iranian participants, revealed a uniform decrease in the homeostatic model assessment of insulin resistance (HOMA-IR) with probiotic and synbiotic supplements, with synbiotic mixtures showing greater efficacy than probiotics or synbiotics alone, and a modest beneficial effect on lipid profile parameters [74]. In overweight and obese women with PCOS, a follow-up 6-months randomized study of synbiotic supplementation with lifestyle modification (LM) alone showed that synbiotic showed slight but significant additional benefits on metabolic and androgen indices compared to LM alone [75].

However, not all trials have been successful: in people with PCOS, free T, the pre-specified primary outcome, was not significantly changed with probiotics compared with placebo and metformin in a phase IV randomized study of probiotics versus placebo and metformin [74]; and reproductive-endocrine endpoints have seemed to be less responsive to microbiota-targeted intervention than metabolic endpoints. Combination regimens of probiotics together with metformin have been found to be effective not only as an additive metabolic effect, but as a way to alleviate any gastrointestinal side effects that may be a barrier to metformin adherence, proposed to be through short-chain fatty acid restoration and activation of the AMPK pathway [76]. The literature on probiotics and synbiotics in endocrinological investigations is more convincing for insulin-resistant states and less for direct modulation of circulating hormone levels and is even more heterogeneous in design.

Fecal Microbiota Transplantation: Evidence and limitations.

FMT is the most direct way to modify the makeup of the gut community and is the most well-studied method for obesity and type 2 diabetes. Stool transplantation from lean donors to patients with metabolic syndrome yielded short-term improvements in peripheral insulin sensitivity, and the benefits were strongly correlated to the diversity of the recipient's own gut flora [77] and not with any particular donor factor. Later randomized trials demonstrated a greater metabolic

improvement with the combination of FMT and dietary fibre compared to FMT alone [78] and this improvement was maintained for a longer period of time than with FMT alone.
A study showed the pooled effects on fasting glucose, insulin resistance, and body mass index are generally small, heterogeneous across studies, and not statistically significant, except that for the subgroup of patients already carrying a diagnosis of diabetes, there may be a slightly more consistent advantage than in obesity or metabolic syndrome alone [79,80]. In addition, a focused review of FMT in the entire endocrine disorders field has revealed its theoretical potential in both diabetes mellitus types, with its use in type 2 diabetes being associated with a modulation of insulin resistance, and in type 1 diabetes, to a dampening of the autoimmune process leading to beta-cell destruction; and explicitly warned of variability in the donor-microbial cells, the lack of standardisation of preparation and dosing, and the transient engraftment of the microbial cells.
The future for translation of this field is not dependent on any single probiotic or transplant approach but on the incorporation of microbiome information within a precision-medicine framework that also includes host genomic, metabolomic, and clinical data. This proof-of-principle with machine-learning models trained on metagenomic and metabolomic data has already been demonstrated to have an improved ability to predict glycaemic responses to the same meal compared to models trained on macronutrient-based data alone and has driven interest in similar modelling approaches for other endocrine outcomes such as the prediction of risk for gestational diabetes and response to growth hormone treatment in children with short stature [81].

Future Perspectives:
The evidence gathered throughout this review marks the gut microbiota as a coordinated axis of regulation rather than an “extra” endocrine system influencing specific axes in isolation, but rather a complex system that interacts with the HPA axis, thyroid, endocrine pancreas, gonads, adipose tissue, calcium-vitamin D system, pineal gland and somatotropic axis all at once. The current problem facing the field is the translational one is that the majority of the mechanistic knowledge comes from germ-free or gnotobiotic rodent models and interventional information in humans is scarce and comes from small-sized studies with difficult to characterize endpoints measured over short periods of time. In addition to association studies, there is a need to move away from cross-sectional studies to well-powered, sex- and age-stratified randomized studies of specific microbial consortia, specific metabolites, and dietary interventions against clinically meaningful endocrine outcomes, not compositional shifts alone. The integration of multiple omics is expected to be the next big leap.
The extension of combining metagenomic, metabolomic, host genomic, and clinical data – as previously shown in prediction of glycaemic response – to gestational diabetes risk, responsiveness to GH therapy, progression of thyroid autoimmunity and phenotyping of PCOS could also be achieved. Biomarkers at the metabolite level (circulating short-chain fatty acids, bile acid profiles, TMAO) seem to be more mechanistically tractable and reproducible than taxonomic signatures and should be prioritized in biomarker development pipelines. The proposed organizing concept of homeostasis vs dysbiosis is conceptually helpful but needs to be tested in a prospective fashion prior to clinical use. Therapeutically, there are likely to be defined bacterial consortia, engineered strains, or purified microbial metabolites (e.g., butyrate, secondary bile acid analogues) delivered via precision dosing, away from whole community approaches such as unmodified FMT, which have been constrained by donor variability, short-term engraftment and inconsistent efficacy. Combination interventions (e.g., fiber co-supplementation with FMT or probiotic-metformin synergy) demonstrate more persistent benefits than individual modality interventions and are promising for further investigation. It is also important to consider sex and age-specific dietary and biotic recommendations as there is clear evidence for divergence in microbial composition between sexes and throughout the lifespan, and the profile of endocrine-metabolic risk are also distinct.

CONCLUSION:
The gut microbiota is an active, metabolically and immunologically engaged endocrine modulator that communicates with host tissues via microbial metabolites, enteroendocrine cell signaling, immune-dependent and barrier-dependent pathways, and neural and humoral pathways. This review has demonstrated that this effect is not limited to the gut-brain axis and includes adrenal steroidogenesis and HPA axis tone, thyroid hormone synthesis and autoimmunity, pancreatic beta-cell function and insulin sensitivity, sex steroid metabolism through the estrobolome and testobolome, adipokine regulation and energy storage, calcium and vitamin D homeostasis, melatonin distribution, and the growth hormone-IGF-1 axis. In each of these systems, similar themes emerge: the role of SCFA-receptor signaling, bile acid transformation, barrier integrity and endotoxemia, and the two-way crosstalk between changes in the microbial community structure and the hormones of the host. The intactness of such a gut-endocrine axis is substantial, but clinical translation is still in its infancy and is hampered by the sensitivity of the microbiome to diet, medication and methodology as well as the challenge of proving causality from data largely correlative in humans. To make full use of the diagnostic and therapeutic potential of this axis will require extensive and hypothesis-driven human trials to bridge the gap between description and mechanism and to translate into clinical applications.
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Conflict of Interest:
Nil

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