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Review

Gut Microsex/Genderome, Immunity and the Stress Response in the Sexes: An Updated Review

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Abstract: Sex has been universally acknowledged as a confounding factor in every type of biological study, while there are strong sex differences in morbidity along the lifespan. Humans have almost identical genomes (99.2%), yet minor variance in their DNA produces remarkable phenotypic diversity across the human population. On the other hand, metagenomic analysis of the human microbiome is more variable, depending on the sex, lifestyle, geography, and age of individuals under study. Immune responses in humans also exhibit variations, with an especially striking sexual dimorphism, which is at play in several other physiologic processes. Sex steroids have noticeable effects on the composition of the human microbiome along the lifespan, accompanied by parallel changes in immunity and the stress response. Gut microsex/genderome, a recently coined term, defines the sexually dimorphic gut microbiome. Apart from the sex steroids, the stress hormones are also at play in the proliferation of microbes. This review summarizes the concept of gut microsex/genderome under the prism of recent studies on the interrelations of the sexually dimorphic microbiome with immunity and stress.

Keywords: physiology; sexual dimorphism; liver; muscles; phenomena; stress system; microbiome; body composition; autoimmune disorders; obesity

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1. Introduction

The sex of a human being has always been a major element of her/his physical and psychosocial identity. Numerous physiologic processes are differentially expressed in the sexes, including sexual maturation, somatic growth body composition, immune function, and the stress response [1]. Lately, another key player in sexual differentiation has become the center of attention: the human microbiome. The latter term refers to the entire habitat of the commensal microorganisms (bacteriome, virome, mycobiome), their genomes, and the conditions of the environment they reside in [2,3]. "Microsex/genderome" describes the phenomenon of sexual dimorphism of the microbiome. It entails multidirectional interactions between the sex hormones, the various parameters of the microbiome, and the immune system [4–7].

Adolescence is characterized by a surge of sex hormones and there are numerous studies setting the onset point of autoimmune or autoinflammatory disorders in adolescence [8–10]. On the other hand, research implies a likely role for sex hormones in eliciting autoimmune processes, and in influencing the outcomes of autoimmune diseases [10]. These hormones may directly affect the metabolic processes of the bacteriome via steroid receptors, such as the estrogen receptor beta (ERβ) [11]. The gut bacteriome has β-glucuronidase activity and may deconjugates conjugated estrogens taken up by the liver and secreted into the gut via the bile. Gut microbiome estrogen deconjugation allows free estrogen reabsorption into the blood, which then circulates and affects multiple organs,

including those of the reproductive system, as well as the musculoskeletal, cardiovascular, and central nervous systems via specific estrogen receptors [12,13]. Additionally, relations between androgens and the gut microbiome have been reported. Animal studies concluded that the gut microbiome affects intestinal metabolism and deglucuronidation of androgens [14,15]. Male and female adults with excessive testosterone or estradiol concentrations, respectively, demonstrated a more diverse gut microbiome [16]. In androgen metabolism, the gut microbiome was a significant controller, while in the small intestine of lab animals, glucuronidated testosterone and DHT were high. In the distal intestine, increased concentrations of free DHT were observed, while noticeably augmented concentrations of unconjugated DHT were observed in the fecal matter of young adult males. In germ-free lab animals, glucuronidated testosterone and DHT were in increased concentrations in the intestine; however, decreased free DHT levels were found in its distal part. This implies that gut microbiome has distinct effects on the intestinal metabolism of DHT and testosterone [14,15]. However, also, gut microbiome seems to be influenced by the sex hormones. More specifically, sex hormones may regulate the diversity of the microbiome, further influencing gut permeability and trigger activation of important inflammatory pathways [17].

Additionally, during adolescence, the phenomena of synaptogenesis, synaptic pruning, changes in synaptic sensitivity, and fast-spiking interneuron connections are observed, in the brain along with increased incidence of stressful life events, differentially modifying grey matter and affecting the stress system of the brain during adolescence [18,19]. While gut microbiome composition also changes, paralleling the changes of the human organism [20], changes in the immune system are also observed, such as blood–brain barrier changes, astrocyte development and microglia priming [9]. More specifically, sex hormones have a significant impact on the function of lymphocytes and macrophages, in a direct manner, binding to surface hormone receptors, or in an indirect manner, via their effects on other targets, such as the hypothalamic–pituitary (HPA) axis that influence immune responses. As a result, puberty is a time period during which changes in immune function confer a risk (often sex-specific risk) to a number of immune related disorders, including autoimmune diseases, such as systemic lupus erythematosus or multiple sclerosis, and allergies such as asthma [21].

Recent data have demonstrated that gut microbiome is a major parameter in androgen production and metabolism, even influencing their crossing via the blood–testis barrier (BTB) to regulate spermatogenesis [22]. Another study demonstrated that microbiome alterations in young, commensally colonized lab rats, conversed testosterone and metabolite changes sufficient to oppose genetically encoded autoimmunity/autoinflammation, while preserving fertility [23]. Data from a human study demonstrated that apart from the sex-related differences in symptom presentation of the chronic fatigue syndrome, there was sex consistency in the microbial communities and sex-specific interactions between the gut microbiome and symptom expression [24]. Sex has been associated with major differences in many immune functions. Males are two to three times less likely to be diagnosed with an autoimmune or autoinflammatory disease, while they are quite prone to viral and cardiovascular diseases. During the last decade, these findings stimulated many researchers to conduct studies clearly demonstrating sexual dimorphism in immunity. This may be due to different genetic, epigenetic, hormonal, lifestyle and stress responsiveness-related factors [25].

The stress system response is indispensable to dealing successfully with environmental, or innate stressors without which the survival of an organism would be endangered. During this physiologic reaction, there is a surge of stress hormones, with specific effects on many tissues, including the immune system. Thus, acute stress enhances the immune system reaction, while chronic stress has deleterious effects on the immune response, causing a mild systemic inflammation or autoinflammation, and deteriorating the immunity against certain infectious organisms and cancer [26]. Additionally, it seems that there are sexually

dimorphic allostatic load differences between males and females in humans, but in other species, also [27].

In conclusion, gut microsex/genderome, immunity, and stress are seemingly interconnected and consist crucial parts of the homeostasis in mammalian organisms. These interrelations have not been extensively investigated, and this review aims at finding the gaps, combining the current knowledge, and pointing at research questions in further investigations (Figure 1).

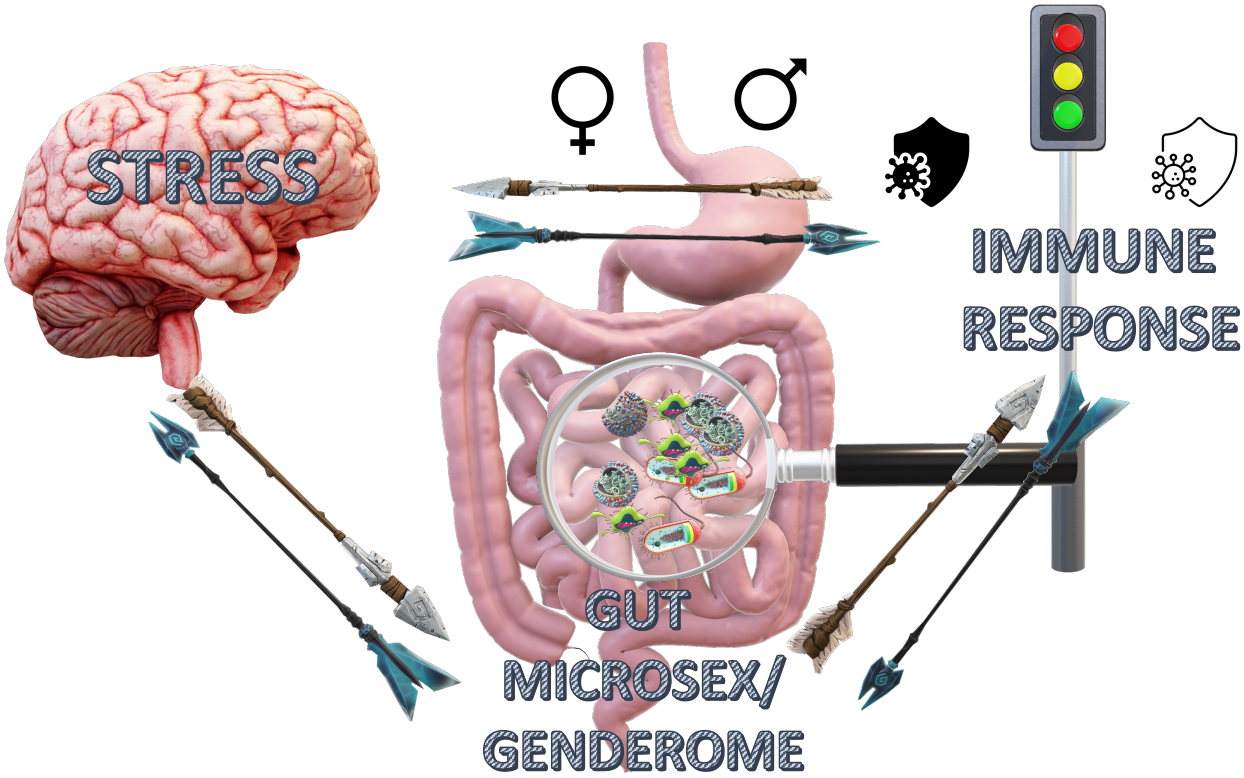


Figure 1. Concept of the study.

2. Materials and Methods

A search strategy was developed for PubMed; an algorithmic procedure resulted from the combination of the following *MESH* words: microbiome OR microgenderome OR microsexome AND estrogens OR androgens OR progesterone; immunity OR immune response OR autoimmunity OR immune cells AND sexual dimorphism OR gender OR estrogens OR androgens OR progesterone; stress OR stress response OR stress response OR allostatic load OR HPA axis AND sexual dimorphism OR sex hormones OR gender OR estrogens OR androgens OR progesterone. No restrictions were applied to language, or study design. "Snowball" procedure was employed; reference lists of relevant articles were hand-searched for potentially eligible studies to maximize the amount of evidence. Interventional, prospective, and retrospective studies, in vitro, animal, and human or cell studies, narrative, systematic reviews, and meta-analyses were included. SANRA scale was used to ameliorate the general quality of this review [28].

3. Results

3.1. Gut Microbiome in the Sexes: Gut Microsex/Genderome

During the first year of life, there are noteworthy differences in the concentrations of the sex hormones. Analysis of the gut microbiome of neonates show male infants had a lower α-diversity than females, while females exhibited higher abundance of *Clostridiales* (phylum *Firmicutes*), and lower abundance of *Enterobacteriales* (phylum *Proteobacteria*) [29]. Furthermore, a species, such as *Bifidobacterium* spp., comprising the most early and most

abundant colonizer, seems to be in different abundance between the sexes. A study conducted by Nagpal et al. demonstrated that male full-term babies had higher *Bifidobacterium populations* at the first day of life, than their female counterparts [30]. The gut microbiome however is similar in girls and boys but develops and differentiates in a dynamic gradual manner during childhood and adolescence. There is no specific time, but time periods, for these changes in gut microbiome, but they usually coincide with changes in daily life, such as introduction of solid foods, adrenarche, puberty, or beginning of increased social interactions, such as school attendance [29]. As far as species are concerned, *Bifidobacterium* spp. is in higher abundance during infancy, while *Clostridium* spp is profused during adulthood; yet, the simultaneous existence of these bacteria may either be representative of a contribution of each developmental stage to the composition of the gut microbiome community, or that there is an operative requirement for microbial metabolites during growth and development [4].

In a recent study, the fecal samples of healthy prepubertal children were abundant in *Bifidobacterium* spp., *Faecalibacterium* spp., and members of the *Lachnospiraceae*, while adults held greater populations of *Bacteroides* spp. From a functional viewpoint, significant variances were detected regarding the relative abundances of genes involved in vitamin synthesis, amino acid degradation, oxidative phosphorylation, and triggering of mucosal inflammation. The prepubertal gut microbiome was enriched in symbiotic functions, supporting continuing growth, while the gut microbiome of the adults was associated with systemic inflammation, and obesity and/or increased risk of adiposity [20].

Changes in bacterial composition during adolescence to a firmer, adult-type composition is important for disease prevention, as microbial shifts could have a lasting effect on health through childhood and adulthood. The dominant bacterial genera found in the healthy gut microbiome of children include *Bacteroides*, *Prevotella*, and *Bifidobacterium* spp. Data from recent studies have demonstrated that the adolescent gut microbiome has significantly greater populations of *Bifidobacterium* and *Clostridium* in comparison with the seemingly healthy adult gut microbiome [31]. In people aged 70 years of age, or older, however, when there is an apparently decreased secretion of sex steroids, no changes in gut physiology have been recorded. In a study of 35,292 adults, total populations in colony-forming units did not exhibit age- or sex-related changes. However, individual bacterial species varied according to age: *Escherichia coli* and *Enterococci* spp. both increased, and *Bacteroides* spp. lessened with age. In fact, another study recorded that maintaining a high *Bacteroides* dominance into older age, or having a low alpha diversity, predicts decreased survival in a four-year follow-up [32]. *Lactobacillus* and *Bifidobacterium* spp seemed to be constant throughout adult life [15].

In adults, the factor of sex is a strong predictor of diversity and, therefore, it should not be overlooked in diversity analysis, particularly for key phyla such as: *Actinobacteria*, *Bacteroidetes*, and *Firmicutes*. Composition of species is dependent on the sex, since, there seem to be sex-specific bacterial species for each sex [33]. Ovary-derived estrogens, or estrogens derived from the adrenal glands and/or adipose tissue, or food-derived estrogens can be further managed by the gut microbiome into estrogen-like metabolites influencing host physiology, hence coining the term "estrobolome" [13]. Additional studies support sex hormones as distinct players in the microbiome composition, as differences in microbiome profiles between male and female NOD mice disappeared after castration of the males, also, suggesting the strong involvement of testosterone [34,35].

In a study by Koliada et al. [36], the investigators revealed relative abundances of *Firmicutes* and *Actinobacteria*, as evaluated by qRT-PCR, to be significantly augmented, while those of *Bacteroidetes* was significantly reduced in the females vs. the males. The *Firmicutes* to *Bacteroidetes* (F/B) ratio was significantly augmented in the females in comparison with the males. Females had 31% higher odds of having F/B ratio more than 1 than males. This trend was apparent in all age groups, from adolescence to the middle age. The difference between sexes was even more distinct in the elders (50 years of age or more). More specifically, in this age group, females presented with 56 % higher odds of having

F/B ratio > 1 than the males. In other studies of human populations, sex differences in fecal microbiome were proved principally at lower taxonomic levels [37]. Others found that males had three times higher odds than females of fecal matter of smaller populations of *Bacteroides* and higher of *Prevotella* [38]. The reduced representation of the *Bacteroidetes* phylum and correspondingly higher populations of members of the *Firmicutes* phylum, recognized to supply energy from food, are characteristic features of the "obese gut microbiota" [39]. Sex-specific gut microbiome differences were discovered to be BMI-related, with higher F/B ratio in obese females than that of obese males. More specifically, no differences in F/B ratio were observed between the sexes, when considered independently of BMI. However, when all study participants were stratified according to BMI, higher F/B ratio was observed in males who had BMI < 33 than in females of the same BMI group, whereas, males had a significantly lower F/B ratio than females in the BMI > 33 group [35].

3.2. Immunity and the Sexes

Estrogen, progesterone, and the androgens produce direct effects on the function and inflammatory ability of immune cells. Males are more vulnerable to most viral infections, but females possess immunological qualities that render them more prone to distinct immune-related disease outcomes. Sex chromosome complements and related genes, together with sex steroids, play chief parts in mediating the expression of sex differences in immunity to viral illnesses. The epigenetic changes are, also, reflected by changes in the function of the immune cells (Table 1) [25,40]. This is in accordance with latest findings about COVID-19 infection and its post-viral period [41].

Sex-specific transcriptome and methylome have been identified within several studies, independently of the well-described phenomenon of X-chromosome inactivation, suggesting that sexual dimorphism, also, occurs also at the epigenetic level. Furthermore, distinct adjustments to the transcriptomic and epigenetic landscape transpire in alliance with changes in hormonal concentrations, occurring in puberty, pregnancy, menopause, and exogenous hormone therapy. Autoinflammation refers to primary dysregulation of innate immunity with cells involved encompassing phagocytic cells (neutrophils, eosinophils, basophils, monocytes/macrophages, and dendritic cells), mast cells, epithelial and endothelial cells, natural killer cells, innate lymphoid cells, and platelets, together resulting in the production of inflammatory cytokines, such as IL-1β, and IL-18. These autoinflammatory diseases typically lack autoantibodies or MHC associations, and they seem to have a slight predominance in females [25].

Estrogen, progesterone, and testosterone intermingle with nuclear hormone receptors in many cell types, including the cells of the immune system. Thus, it seems that several genes are controlled by sex hormones. In addition, sex hormones can also have effects on gene expression through other mechanisms, comprising G-protein coupled receptor signaling, and rapid membrane signaling [42]. Autoimmunity refers to a loss of self-tolerance and a state of immune responsiveness to self-antigens. Autoimmunity causes damage in various tissues, and results in diseases termed as "autoimmune diseases" [43].

General and tissue-specific body changes have been associated with irritable bowel syndrome (IBS) via mechanisms of dysfunction of barrier permeability of the intestinal epithelium and changes of the immune system. Other studies advocate a female predominance of IBS, implying sex hormones of the females as drives in its pathogenesis. Transit duration of the GI tract also has been described to vary according to the phase of the menstrual cycle, pregnancy, and postpartum. Estrogen, and testosterone seem to directly alter both the gut microbiome and immune cells. Increased concentrations of β-estradiol cause the production of IL-12 and IFN-γ, via the stimulation of the dendritic cells. Thus, activation of inflammatory pathways are activated increasing of proinflammatory cytokine concentrations. Estradiol prolongs the survival of polyclonal B cells generating a proinflammatory environment and resulting in altered intestinal gut permeability, causing the migration of gut microbiota into the lamina propria, which, in turn, promotes local inflammatory processes [15]. In summary, testosterone and progesterone

seem to be anti-inflammatory, suppressing several aspects of the immune response necessary for inflammation, whereas estradiol has bi-potential effects: proinflammatory at low concentrations and anti-inflammatory at high concentrations [44,45].

Table 1. Sex hormones in relation to gut microsex/genderome, immune cells, and the HPA axis.

Factor	Estrogens	Androgens	Progesterone
T cells	↑ Th1 differentiation, ↑ TNF, IL-1β, IFN-γ, IL-4 ↑ Treg activation ↑ T-cell apoptosis	↓ Th1 response ↓ T-cell proliferation ↓ IL-4 production ↓ Treg cells	CD4+: ↑ IL-4 ↑ Treg differentiation ↓ IFN-γ ↓ proliferation ↓ T-dependent Ab responses ↓ Th17 differentiation ↓ IL-6 receptor CD8+: ↑ IFN-γ (MPA) ↓ cytotoxicity (MPA)
B cells	↑ Activity ↑ Antibody production	↓ Antibody production	↓ CD80 ↓ CD86
Macrophages	↑ Phagocytosis ↑↓ TNF, IFN-γ, IL-6, IL-10 ↑ TLR expression ↓ Nitrite	↓ Phagocytosis ↓ TNF, iNOS, NO ↓ TLR expression ↑ IL-10, TGFβ	↓ iNOS, NO ↓ TNF, IL1β ↓ FcγR expression ↓ microparticle release
NK cells	↑ IFNγ ↑ Granzyme B ↓ FASL	ND *	↑ Apoptosis (Caspase dependent) ↓ cytotoxicity ↓ IFN-γ
DCs	↑ Maturation ↑ Activation ↑ TLR-7, TLR-9 ↑ CCL2, IL-6, IL-10, CXCL8	↓ IL-1β, IL-10, TNF	↓ CD40, CD80, CD86 ↑ IL-18, IL-10 ↓ TNF, IL-1β
Neutrophils	↑ Numbers ↑ Degranulation ↑ Elastase release	↑ Numbers ↓ Kinases ↓ Leukotriene formation	↓ superoxide release ↓ apoptosis ↓ chemotaxis
Eosinophils	↓ Numbers ↓ Degranulation ↑ Mobilization	↓ Degranulation	↑ Numbers ↑ Degranulation

Table 1. *Cont.*

Factor	Estrogens	Androgens	Progesterone
Autoimmunity/ Autoinflammation	↑	↓	Dose -dependent action: Too high—↓ Too low—↑
Firmicutes/Bacteroidetes ratio	↑	↓	ND *
Virome	Decrease in females	ND *	ND *
Mycobiome	ND *	ND *	ND *
Acute Stress Response (HPA axis—Cortisol, norepinephrine and epinephrine)	Upregulation of stress response, However, supportive of spatial memory during acute stress event	Suppression of HPA axis stress response in males	Progesterone results in inhibitory effects on HPA axis reactivity in females.
Chronic Stress Response (HPA axis—Cortisol, norepinephrine and epinephrine)	Upregulation of stress response, However, supportive of spatial memory during acute stress event	Suppression of HPA axis stress response in males	Downregulation of the stress response/Upregulation of the GABAminergic system

* ND: No data. [12,14,44,46–52].

3.3. Stress Response in the Sexes

The hypothalamic–pituitary–adrenal (HPA) axis, a neuroendocrine complex that holds control of hormonal reactions to internal and external cues, acting like stressors, and it exhibits sex-biased activity [53]. Data from animal studies have demonstrated progesterone and its products, the neuroactive steroid allopregnanolone, as central parts in stress and in stress-related psychopathology. These hormones are mainly produced in the brain but, also, in the periphery during stress and they downregulate anxiety symptoms and HPA axis activity in lab animals. While 5α-dihydroprogesterone seems to have a downregulatory action on subjective anxiety via the progesterone receptors, allopregnanolone acts on GABA-A receptors, decreasing subjective anxiety, along with the ability to learn and memorize, as well as saccadic eye velocity, both via a decrease in corticotropin-releasing hormone (CRH) release and arginine vasopressin (AVP) secretion, resulting in motivation for affiliation during times of stress [48]. This phenomenon seems to be exacerbated when the concentrations of progesterone are high [54].

Estrogens upregulate HPA axis action, increasing the release of the stress-related secretagogues at multiple sites due to the broad expression of estrogen receptors (ERs). In the adrenal gland, estradiol increases the adrenal response to adrenocorticotropic hormone (ACTH) administration [55], while androgens are consistently reported to inhibit HPA axis activation and action [53,56,57]. A quite recent study revealed stress-induced activation of the HPA axis may be triggered by estrogen-dependent upregulation of AVP in the median eminence of female rats [58]. Most likely, estradiol instigates dysregulation of the HPA axis feedback, as evidenced by the inability of dexamethasone to suppress diurnal and stress-induced ACTH and corticosterone secretion, as demonstrated in female rats. In addition, the ability of estradiol to hamper glucocorticoid negative feedback occurs specifically via ERα acting at the level of the paraventricular nucleus (PVN) of the hypothalamus [59].

Androgens have an inhibitory effect on basal and stress-induced glucocorticoids (GCs) concentrations via central and peripheral actions, while estrogens have a stimulatory effect not only by impairing glucocorticoid negative feedback, but also by centrally stimulating the HPA axis. As shown by Vamvakopoulos and Chrousos, the CRH gene has estrogen-response elements in its promoter and responds to estrogen stimulation [60,61]. This effect of estrogens is effected by the presence or absence of progesterone that subsidiarily counteracts estrogen stimulating action [62,63].

It seems that sex chromosomes do influence sex-specific biology in utero, even if the data is scarce [64]. A rise in testosterone concentrations in male fetuses starts shaping the male brain during the prenatal period differently than the female brain. These "organizational effects" possibly occur before puberty. The cerebral regions involved in glucocorticoid regulation at rest and after stress are, thus, entangled in a sex-specific manner. After puberty, the increased concentrations of all gonadal hormones will cooperate with glucocorticoid hormones in specific crosstalk through their nuclear receptors. In addition, stress occurring early in life, during the prenatal period, and in adolescence will prime the long-term glucocorticoid stress response through epigenetic mechanisms, in a sex-specific manner. Overall, different molecular mechanisms explain sex-specific glucocorticoid stress responses that do not omit important gender effects in humans [65].

4. Discussion

In this review, we found that females exhibit a more "obesogenic" gut microbiome profile, along with a distinct propensity for autoimmune/autoinflammatory disorders and an upregulated HPA axis, even if they seem to be more protected against viral diseases, when compared to their male counterparts.

The importance of the microbiome in immune system development mainly emanates from data related to microbiome risk factors. Inadequate microbial component exposure, excessive antibiotic exposure [66], and premature birth [66,67] are risk factors for dysbiosis. The colonization of human intestinal tract starts at the critical neonatal period of life. During the first year of life, there seems to be no significant difference in gut bacteriome composition, associated with any clinical outcome, independently of the type of delivery [68].

The sex-specific associations raise questions about intestinal dysbiosis in women with the chronic fatigue syndrome, assessing whether higher populations of *Clostridium* spp aggravate symptoms in females, and the potential benefits of targeting treatment to restore intestinal balance. In male patients with chronic fatigue syndrome, observations about *Lactobacillus* and *Streptococcus* genera sustain increased concentrations of D-lactate as a contributing factor to the onset of symptoms. This hypothesis describes the neurological symptoms of chronic fatigue syndrome as a consequence of neurotoxic effects of bacterial metabolites, since D-lactic acid is produced by most species of *Lactobacillus* and *Streptococcus*) with effects not only on the brain and but also on the rest of the nervous system parts [24,69].

Data may be sparse, but robust evidence demonstrates the drive of the immune system response by the microsex/genderome, in both sexes. The taxa of *Firmicutes*, *Actinobacteria* and *Proteobacteria* process and, consequently, control homeostasis of sex steroid hormones through genes, encoding hydroxysteroid dehydrogenase (HSD) enzymes. *Clostridium* spp, *Lactobacillus* spp, and *Streptococcus* spp demonstrate interesting sex- interactions. More specifically, *Clostridium* spp populations seem to be directly connected to some symptoms in females, such as insulin resistance, bloating, and other gastrointestinal symptomatology. *Clostridium* spp has been associated with increased concentrations of inflammation markers. Increases in *Firmicutes* have also been associated with the female sex and westernized diet, while populations of the opportunistic species *Clostridium difficile* and *Clostridium perfingens* increase with heavy intakes of sugars. It seems that females demonstrate a propensity to have increased F/B ratio, especially during the reproductive years, as they need more adipose tissue to produce sex steroids and the normal physiology of the menstrual circle.

Last, but not least, the gut microbiome along with their metabolites, communicate with distant organs, such as the adipose tissue, the skeletal muscles, the liver and the brain. Short-chain fatty acids (SCFAs) derived from the fermentation of gut microbiome, lipopolysaccharides (LPS), bile acids and branched-chain amino acids (BCAAs) play vital roles in inter-organ crosstalk by regulating the integrity of the gut barrier and influencing peripheral tissue function and metabolism; all potentially contributing in the case of dysbiosis, to development of obesity and insulin resistance [70].

Health disparities during lifespan between sexes are, also, partly dependent on the immune response. Innate and adaptive immunity either in males and females are the product of interactions between behavior, age, comorbidities, genetic predisposition, geographical distribution of pathogens, health behaviors, sex chromosomes and sex hormones. Males and females seem to have different lifestyles, and thus environmental stressors, nutritional requirements, and different sex hormone profiles. Sexual dimorphism of the immune response is well documented. Females exhibit lower infection rates than their male counterparts for a variety of bacterial, viral, and parasitic microorganisms. Females present with substantially increased incidence of autoimmune diseases, compared to males. Thus, females present with a more sensitive immune reactivity to self and non-self-molecular patterns, when compared with males. However, the molecular means driving the sexually dimorphic immune response are not fully understood. Autoimmune diseases are managed in a sex-neutral manner.

Sex hormones, sex-chromosome-encoded genes and environmental exposure seem to be determinants of immunity, directly contributing to the immune cell range of action in response to any injurious agent. These factors have a direct effect on DNA methylation, expression levels of miRNAs, and chromatin remodeling, and influence microbiome composition, potentially shaping the functional profile of immunity. The consequences of altered immune cell phenotype have several effects on sex-specific responses to vaccination, risk for autoimmune disorders and susceptibility to pathogens. Therefore, differences between the sexes must be considered when therapeutic intervention strategies against infections and autoimmune diseases are concerned in both sexes.

A few studies support the existence of increased activity of phenoloxidase (PO) in females. PO participates in wound healing and immune reactions against parasitic infections. This difference is followed by concomitant sex differences in the expression of genes in the PO-activating cascade. It seems that there is considerable plasticity in female PO phenotypic activity with regard to mating. Experimental evolution under enforced monogamy (low remating rates and reduced sexual conflict) rapidly decreases female (but not male) PO activity, as demonstrated in many studies. Thus, it seems that selection pressures molded by mating interactions results in a sex-specific mixture of immune responses with significant repercussions for host-pathogen equilibria in sexually reproducing organisms [71]. Future studies need to report the sex of cells, animals, and subjects to expand the knowledge on the pathogenesis of diseases and, thus, personalize the therapies for the sexes. Until present, data on sex different responses to anti-viral therapy and prophylaxis are scarce, suggesting the need for additional basic biomedical research in this topic [72].

Stress system dysregulation due to chronic stress may result in depression, anxiety, asthma, obesity, diabetes, metabolic syndrome, cardiovascular diseases, panic attacks, autoimmune disorders and disorders of body composition, such as osteosarcopenia and altered lipid partition [73–77]. To enhance survival and reproduction, the HPA and the hypothalamic—pituitary–gonadal (HPG) axes collaborate to integrate environmental, psychological, reproductive, and genetic cues. Both axes exhibit remarkable sex differences, which are structured and triggered by dynamic variations in sex and stress hormones across the lifespan. It can be argued the developmental programs defining sex differences in the HPA axis may affect susceptibility to develop disorders prompted by stress in adulthood.

For the maintenance of homeostasis, the neuroendocrine system constantly adjusts the concentrations of gonadal steroids, using sex steroid receptors in the hypothalamus. Hypothalamic neurons expressing gonadal steroid receptors are of great significance for the proper regulation of the HPA and HPG axes, and thus, the composition of these cells requires further investigation. Dysregulation of these axes may end in compromised responses to stressors, and to immune responses. Overall, the HPG and HPA axes work in a correspondingly fashioned pattern, to effectively preserve the survival, minimizing the total allostatic load. Although tremendous progress has been achieved lately, there are still unanswered questions [78].

5. Conclusions

The causes of sex differences in the intestinal microbiota composition are probably multifold. There are a few studies, supporting a correlation between microbiome and gut immune cell populations occurring in a sex- and strain-specific manner [79,80]. Gut microsex/genderome, immunity and the stress response seem to be highly interconnected and orchestrated in a fine-tuned manner, according to genetic, epigenetic, and environmental cues in each sex [81,82]. There are a lot of hypotheses to examine about the microsex/genderome, such as the as yet unexamined virome and mycobiome, both seriously neglected parts of the gut microbiome, along with immunity and the stress response [82,83], while there is a cumulative body of evidence and knowledge in the last 50 years about the gut microbiome, immunity and stress biology, sex differences are in their interrelations have been barely addressed [65]. Studies about the interrelations of the microbiome, immunity and the stress system of the brain are currently lacking.

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