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Microbiome, sex hormones and cardiovascular risk: a contribution to gender difference

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Summary. The gut microbiota (GM) is composed of all microorganisms living in the gastrointestinal tract. The development and composition of the GM are highly dependent on a multiplicity of environmental and host factors.
Through complex mechanisms, the changes in the GM composition and the related microbial metabolites affect the immune system and the metabolic functions, leading to several pathological conditions, such as obesity and associated disorders, atherosclerosis and cardiovascular diseases.
The recent literature highlighted the sex differences in the microbiome composition both in animal models and in human studies, together with a bidirectional cross-talk between the microbiota and the endocrine system. The GM composition, in fact, should be affected by the sex hormones levels; on the other hand, GM bacteria produce hormones (e.g., serotonin, dopamine and somatostatin), respond to host hormones (e.g., estrogens) and regulate the homeostasis of the hormones inhibiting the gene transcription (e.g., prolactin) or converting them in the host (e.g., glucocorticoids to androgens).
In the future, novel therapeutic strategies targeting the gut microbial metabolic pathways and/or metabolites, as well as altering the gut microbial composition, will offer the opportunity to modulate the susceptibility to – and the prevention of – cardiovascular diseases.

Key words. Microbiome, sex hormones, cardiovascular risk, gender difference.

Microbioma, ormoni sessuali e rischio cardiovascolare: un contributo alla differenza di genere

Riassunto. Il microbiota intestinale rappresenta l'insieme dei microrganismi presenti nel tratto gastrointestinale. Lo sviluppo e la composizione del microbiota intestinale dipendono fortemente da una moltitudine di fattori ambientali e specifici dell'ospite. I cambiamenti nella composizione del microbiota intestinale e dei metaboliti da esso prodotti influenzano le funzioni immunitarie e metaboliche dell'ospite, attraverso meccanismi complessi, che si traducono in diverse condizioni patologiche come l'obesità e i disturbi associati, l'aterosclerosi e le patologie cardiovascolari. La letteratura recente ha evidenziato, sia in modelli animali che in studi condotti nell'uomo, differenze sesso correlate nella composizione del microbiota. Un'interazione bidirezionale tra microbiota e sistema endocrino è stata descritta. La composizione del microbiota intestinale, infatti, è influenzata dai livelli di ormoni sessuali (per esempio, gli estrogeni) così come i batteri del microbiota intestinale, a loro volta, producono ormoni (per esempio, la serotonina, la dopamina e la somatostatina), regolano l'omeostasi degli ormoni inibendo la trascrizione genica (per esempio, la prolattina) o trasformandoli nell'ospite (per esempio, i glucocorticoidi in androgeni). In futuro, nuove strategie terapeutiche che abbiano come obiettivo le vie metaboliche e/o i metaboliti microbici intestinali, nonché il trattamento della disbiosi intestinale offriranno l'opportunità di modulare la suscettibilità e la prevenzione delle malattie cardiovascolari.

Parole chiave. Microbioma, ormoni sessuali, rischio cardiovascolare, differenza di genere.

Gender effects on the gut microbiota

Definition, development and composition of the gut microbiota

The gut microbiota (GM) is composed of all the microorganisms living in the gastrointestinal (GI) tract, such as bacteria and some viruses, bacteriophages and fungi and other species still to be identified.[1]

The development and composition of the GM are highly dependent on a multiplicity of environmental and host factors, especially those present in early life (i.e., birth conditions, mode of delivery, perinatal colonization, hospital environment and familial exposure).[2] Although GM core components tend to remain stable in adults, they are highly respondent to environmental alterations.[3] GM diversity increases from the perinatal period to adult life; in the older age this trend is drastically altered, showing less diversity if compared to a younger age.[4]

The GM community is mainly composed of five phyla (Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobia);[5] however, there is a considerable diversity in the species level and in their relative abundance.

In a healthy gut, anaerobic Bacteroidetes and Firmicutes represent more than 90% of the total bacterial species[5]. Bacteroidetes are the most prevalent phylum of gram-negative bacteria, and they are considered to be

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highly beneficial, due to their functional capability to degrade polysaccharides and regulate calorie absorption.[6]

In the specific case of Firmicutes, most gut bacteria representing this phylum are gram-positive, and are able to produce several short-chain fatty acids (SCFAs), contributing to the protective cardiovascular disease (CVD) phenotype.[7]

Through complex mechanisms, the changes in the GM composition and related microbial metabolites affect the immune system and the metabolic functions, leading to several pathological conditions, such as obesity and associated disorders, atherosclerosis and CVD.[8]

In fact, a dysbiotic intestinal microflora could impact the development of insulin resistance and the accumulation of fat. The GM modulates the mucosal immunity and systemic inflammation throughout several mechanisms. Moreover, it regulates gut permeability, maintaining the integrity of enterocytes, tight junctions and protective mucous layer.[9]

This is confirmed by the evidence that probiotics (such as *Streptococcus thermophilus* and *Lactobacillus acidophilus*) prevent any increases in permeability in the human intestinal epithelial cells, suggesting the importance of certain bacteria in maintaining a healthy gut mucosal barrier.[10]

Thus, the GM constitutes a real *ex-corpore* system that communicates with distal organs through multiple pathways.

Sex differences in the microbiome: bidirectional cross-talk between the microbiota and the endocrine system

The recent literature highlights the sex differences in the microbiome composition, both in animal and in human models.[11] Human studies suggest that women may host a higher ratio of Firmicutes/Bacteroidetes (F/B) in comparison to men.[12] F/B ratio is heavily influenced by the body mass index (BMI). Nevertheless, women show higher proportions of Firmicutes, adjusting for BMI, compared to men.[13] In addition, higher numbers of Proteobacteria, Veillonella, and Blautia have been found in women.[14] On the other hand, healthy male subjects show a higher abundance of Bacteroides-Prevotella than females, while the GM of post-menopausal woman is similar to the male one.[15]

In fact, sex modifies the relationship between diet and GM;[16] males and females have distinct microbial profiles, suggesting that the GM composition may be affected by sex hormones levels.[17,18] Figure 1 describes sex distinct microbial profiles and GM composition related to sex hormones levels.

As a matter of fact, bacteria are able to produce hormones (e.g., serotonin, dopamine, somatostatin), to respond to hormones (e.g., estrogens) and regulate the host's hormones homeostasis by inhibiting their gene transcription (e.g., prolactin) or by converting them (e.g., glucocorticoids to androgens).[19]

On the other side, environment, sex hormones and genetic factors have a significant effect on the GM composition, regulating the abundance of specific taxa; the resulting bidirectional cross-talk modulates the gender-related disease phenotype.[20] This suggests that the gender differences in the GM composition may be related to the dimorphism observed in the incidence and progression of metabolic and CV diseases. On the contrary, the loss of female sex hormones production in post-menopausal women levels out the gender differences in GM composition increasing the CVD incidence.[21] Moreover, sex hormones estradiol and testosterone may participate, directly or indirectly, in the gender bias in the GM composition, by shaping the gut mucosal immune environment.

In fact, estrogen may modify gut epithelial barrier integrity; experimental studies conducted on mouse models demonstrated that females are more resistant to gut injury compared to males.[22] The difference in GM composition between males and females could potentially contribute to the sex bias observed in autoimmunity.

During the puberty period, cells are exposed to higher levels of sex hormones, which affect the immune cell function and the signaling pathways. Therefore, the early host-microbe interactions during childhood could have deep and long-term consequences on the adult's health, through the development of the immune system and the induction of tolerance.[23] Sex hormones modulate the local immune environment: the impact of estrogens on the various immune cells contributes to a hyperactive immune habitat, while androgens (testosterone) maintain an anti-inflammatory condition.[24] Females' cells are generally more respondent to the same immunological stimulus than males'. This stronger response likely contributes to the female predominance in many autoimmune diseases.[25]

Hormones affect the autoimmune system: androgens and estrogens strongly modulate the Th1/Th2 balance. Androgens, such as testosterone, down-regulate the production of natural killer (NK) cells and tumor necrosis factor-alpha (TNF-α) and decrease the toll-like receptor 4 (TLR 4) expression in macrophage, while enhancing the production of anti-inflammatory IL-10.[26]

In males, testosterone has a suppressive effect on the T-cell proliferation, resulting in attenuated immune responses and a balanced immune system. Similarly, progesterone acts as a modulator of the immune system, inducing the synthesis of anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines.[27] By contrast, estrogens enhance the cell-mediated and humoral immune response, the NK cell cytotoxicity and the production of pro-inflammatory cytokines IL-1, IL-6 and TNF-α.[28,29]

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This explains the enhanced immune reactivity in females, which is associated with a more effective resistance to infections compared to males,[28] but which consequently also increases the susceptibility to autoimmune diseases.[30]

As well as the GM is influenced by estrogens, it in turn impacts on the estrogen levels. In this way GM become an important regulator of the circulating estrogen and estrogenic metabolites molecules.[31]

The enterohepatic circulation gives a further contribution to the homeostasis of sex hormones and their metabolites.

Sex steroid hormones and bile acids (BAs) have a structural similarity, since they are both derivatives of cholesterol, which contains the cyclic steroid nucleus. Similar to BAs, endogenous sex steroid hormones are derived from cholesterol. They can be recycled through the enterohepatic circulation process, in part regulated through the GM. Therefore, the GM action is crucial in defining whether steroid hormones must be excreted or recycled[31].

The interactions between estrogen signaling and BA metabolism emphasize the importance of sex steroid hormones on bile acid-GM homeostasis, contributing to sex-specific phenotypes.[31,32]

The aggregate of enteric bacterial genes, whose production is able to metabolize estrogens, is defined 'estrobolome'.[3] Circulating estrogens undergo phase I of hepatic metabolism: in the liver, estrogens and their metabolites (EMs) are conjugated, and excreted in the bile. They are de-conjugated by the GM β-glucuronidases, reabsorbed by the gut and translocated into the bloodstream, to act at distal sites (Figure 1). In this way estrobolome contributes to the host's total estrogen amount.

Therefore, the systemic estrogen metabolism (EM) profiles may be influenced by the estrobolome through multiple mechanisms, such as the distinct enzymatic activity regulating the balance between active and inactive steroids.[20] Thus, estrogens and the GM maintain physiological health and homeostasis, both locally and at distal sites.

A potential destruction of the estrobolome homeostasis induces a decrease in the circulating estrogens, as well as other metabolic effects of dysbiosis, leading to hypoestrogenic conditions: obesity, metabolic syndrome, CVD and cognitive decline.[33-36]

On the other side, hyperestrogenic conditions can also be driven by the estrobolome, through the increased abundance of β-glucuronidase-producing bacteria, or bacteria whose enzymatic activity is higher in the de-conjugative and hydroxylative functions. This condition results in increased circulating levels of free estrogens, which induce diseases such as endometriosis and cancer.[37,38]

Similarly, conjugated androgens can be hydrolyzed in the intestinal tract via bacterial β-glucuronidase into free androgens for reabsorption. The enhanced circulating levels of androgens may induce androgen-related diseases. Furthermore, glucocorticoids can be converted into androgens via the side-chain cleaving capacity of bacteria.[39,40]

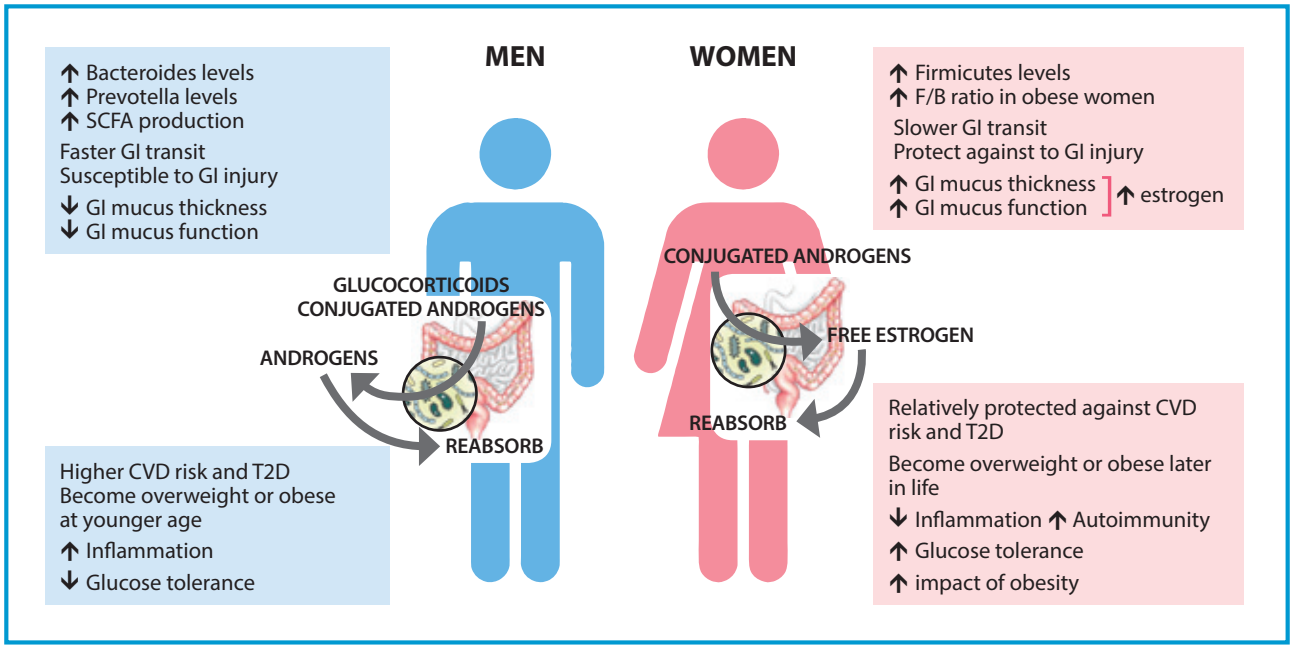

Figure 1. Sex differences in the cardio-metabolic disease and the gut microbiome (modified from Cross L et al. Mol Metab, 2018). SCFA: short-chain fatty acids, GI: gastrointestinal; F/B: Firmicutes/Bacteroidetes; CVD: cardiovascular disease.

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The role of gender on the relation between gut microbiota and cardiovascular disease

CVD is responsible for a large incidence of death cases in both men and women worldwide.[41,42] While age-adjusted CVD mortality rates are higher in men compared to premenopausal women,[43] nearly 50% of women in Western countries die due to coronary heart disease or stroke.[44]

The key differences in the epidemiologic and pathophysiologic CVD risk factors have been identified in men and women.

These differences underline the need to investigate the role of sex in the pathogenesis and progression of CVD.

Many studies demonstrated the association between specific GM and CVD. They mainly investigate the potential roles of bacteria in the pathogenesis of coronary heart disease, CVD and cardiometabolic disorders (Figure 2).[45-47]

Most of the studies investigating the link between GM dysbiosis, CVD risk factors and gender differences are conducted in mouse models, rather than in humans.

For example, in the experimental studies, ovariectomy and castration allow to evaluate the hormonal impact on the GM and the susceptibility to the disease.[48] In hypertensive animals, dysbiosis and decreased Bacteroidetes to Firmicutes ratio have been found.[49] In diet-induced obese mice, *Akkermansia muciniphila* abundance has been strongly correlated with lipid metabolism and inflammation markers in the adipose tissue.[50]

Although the correlation between sex hormones and GM composition has been largely demonstrated, as well as the role of the GM in the development and progression of diseases, only a few studies showed a differential analysis on sex/gender, mainly focusing on the irritable bowel syndrome (IBS) and on autoimmune diseases.[51,52]

The pathogenic mechanism of the gut microbiota and its metabolites in cardiometabolic diseases

The GM can impact the host's processes via bioactive metabolites that may, directly or indirectly, affect the distal organs.[53] The GM interacts with the host through different pathways, including the trimethylamine (TMA)/trimethylamine N-oxide (TMAO), SCFAs and primary and secondary bile acid (BAs) pathways. Some of these molecules have been proved to functionally interact with sex hormones, explaining the gender dimorphism in the CV risk and the CVD outcomes.[54,55]

Under particular conditions, such as gut wall barrier function damage, lipopolysaccharides (LPS) and peptidoglycans (structural components of the microbiota) can trigger numerous downstream signaling processes involving host's receptors both at the epithelial cell border and in the blood vessel.[56]

Dietary foods containing choline, phosphatidylcholine and carnitine are converted by GM enzymes (TMA lyases) to trimethylamine, which is subsequently oxidized by hepatic flavin monooxygenase 3 (FMO3) to generate TMAO. Circulating TMAO levels reveal a positive correlation with the atherosclerotic plaque size, although this correlation is not proven with triglyceride, lipoproteins, fasting glucose, and hepatic triglycerides.[54]

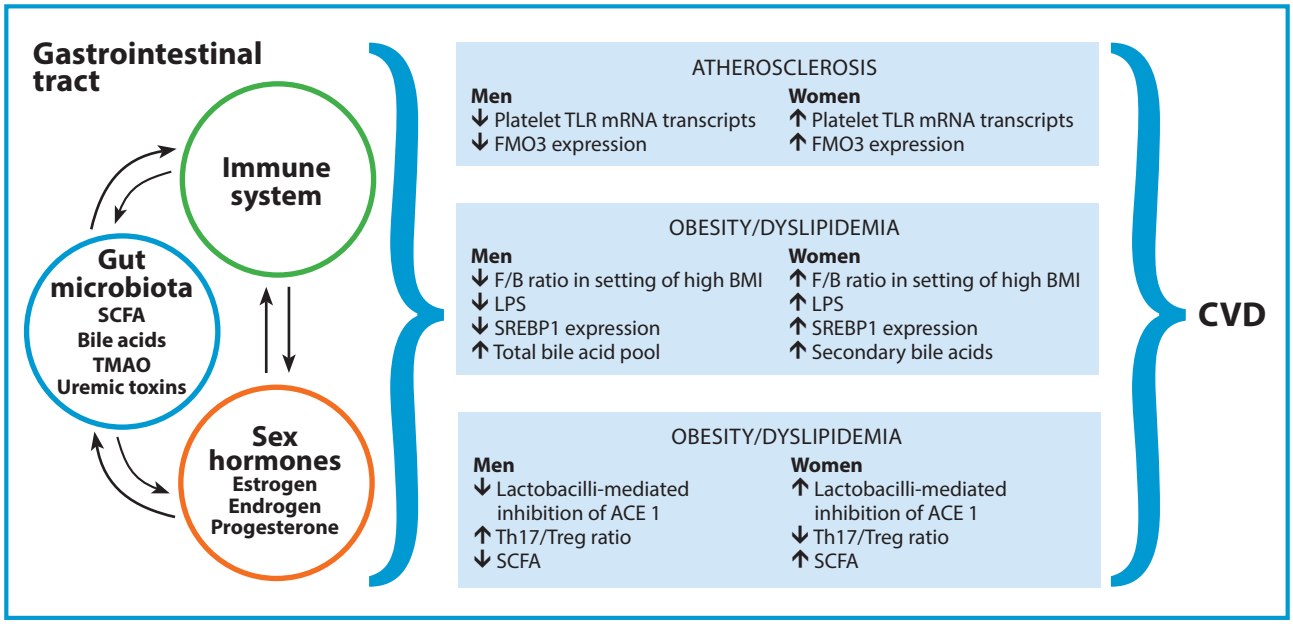

Figure 2. Interconnections between immune system, gut microbiota and sex hormones as the possible mechanisms by which gut microbiota mediate the sex differences in the cardiovascular disease risk. SCFA: short-chain fatty acids; TMAO: trimethylamine N-oxide, TLR: toll-like receptor; FMO3: flavin monooxygenase 3; TH17: T helper 17; CVD: cardiovascular disease.

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Mouse models confirmed that the dietary supplementation with choline increases TMAO levels, macrophage foam cell formation, and the development of atherosclerosis. The enhanced atherosclerotic effects of the phosphatidylcholine metabolism depend on the GM, since germ-free conditions eliminate the development of atherosclerosis.[57] The L-carnitine diet supplementation showed similar effects.[54] The association of TMAO levels with the adverse clinical consequences observed in numerous clinical studies[58,59] confirm that TMAO is a cardiovascular risk predictor. In a large independent clinical cohort (n = 4,007), patients in the highest quartile of plasma TMAO levels had a 2.5-fold higher risk of a major adverse cardiovascular event than patients in the lowest quartile.[60] Moreover, TMAO circulating levels predict a 5-year mortality in patients with stable coronary artery disease.[61]

The GM-mediated gender difference in thrombotic risk has also been studied. Women show a greater thrombotic risk compared to men, depending on the different mechanism involving the GM and the steroids hormones. Women show an increased TLR and trimethylamine N-oxide activation of platelets.[62,63] Trimethylamine N-oxide production is accelerated in women compared to men. Another mechanism involved in the enhanced prothrombotic risk in women consists in the gonadal hormone regulation of the hepatic FMO3 expression.[64]

Moreover, TMAO enhances the platelet responsiveness to multiple distinct agonists (ADP, thrombin and collagen) by facilitating the release of Ca2+ from the intracellular stores and by inducing a pro-thrombotic effect *in vivo*. This effect is blocked when choline is fed to germ-free mice, or to mice treated with oral antibiotics.[65]

Thrombosis caused by potential platelet hyper-reactivity is a transmissible trait, as demonstrated by studies on caecal microbiota transplant using mouse models as caecal microbial donor strains and germ-free mice as recipients. In a human cohort, a dose-dependent association between plasma TMAO levels and platelet aggregation has been demonstrated. Thus, the effects of TMAO directly observed on atherosclerosis and platelet aggregation partially explain the increased risk of cardiovascular events in the presence of GM-generated high TMAO levels.[66]

Gut microbiota, gender difference and cardiovascular disease risk factors

Dyslipidemia, dysglycemia, hypertension, and obesity may all induce GM changes and, vice versa, the GM may induce changes in the aforementioned conditions.[67]

Clinical studies demonstrated an increased susceptibility to dyslipidemia in men compared to women.

One of the supposed mechanisms underlying this gender difference is related to the 17β-estradiol-mediated increase in PPAR-γ (peroxisome proliferator-activated receptor gamma) receptor expression.[68] In fact, pioglitazone, a PPAR-gamma agonist, shows a stronger efficacy in female mice compared to male.[68,69]

Dysglycemia, glucose intolerance and insulin resistance are associated with the absence of TLR2 signaling, which may be attributed to an increased serum lipopolysaccharide (LPS) activation TLR4 in the muscle, liver, and adipose tissue.[70] This association has been demonstrated in TLR2 knockout mice presenting higher proportions of Bacteroidetes and Firmicutes, coupled with a lower proportion of Proteobacteria phyla.[71]

Estrogens, progesterone and testosterone regulate LPS-mediated signaling through TLR4, a mechanism by which gut dysbiosis could generate insulin resistance. In particular, testosterone decreases the TLR4 expression in macrophages[72] and the TLR2 signaling.

Progesterone diminishes the LPS-mediated TLR4 signaling,[73] while the estrogenic treatment in mice increases the cell membrane expression of TLR4.[74]

These results suggest that the GM may play a key role in the steroid hormone changes across the lifespan underlying the CVD risk; for example, the reduction in menopausal estrogen levels and the consequent pro-atherogenic shift of the cardiometabolic profile in women.

Hypertension

Hypertension is the most prevalent modifiable risk factor for CVD. The role of the GM in hypertension has been evaluated both in animal and human studies.[75-78] Li et al. described a decreased microbial richness and diversity in pre-hypertensive and hypertensive populations; fecal transplant from hypertensive individuals to germ-free mice showed an elevated blood pressure, thus demonstrating a direct correlation.[79]

A recent study showed a blood pressure-lowering effect in treatment-resistant hypertension patients treated also with antibiotics.[80] Furthermore, a meta-analysis demonstrated a significant decrease in blood pressure in patients treated with Lactobacillus probiotics.[80-82]

The GM can potentially affect the host's blood pressure through multiple mechanisms. The microbiota production of SCFAs plays a pivotal role in the relationship between the GM and hypertension. The lowering effects on blood pressure of a high-fiber prebiotic and probiotic diet may act through the increase of acetate-producing bacteria in the gut.[83,84]

In addition, the production of SCFAs[85,86] by the GM impacts on renal sensory nerves and blood pressure, inducing vasodilation or vasoconstriction.[87] In this way, sex differences in the renal functions that regulate blood pressure[88,89] may be derived in part from microbiome variations.

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The Lactobacilli effect on the blood pressure-lowering mechanism may be exerted by the secretion of peptides, that inhibits the angiotensin-converting enzyme, with a decreased ability to convert angiotensin I into angiotensin II, a strong vasoconstrictor. Women have higher levels of Lactobacilli in the gut:[90] this may partly explain the lower pressure levels in fertile women, compared to men of the same age. In addition, men show larger increases in blood pressure in response to angiotensin II compared to women.[91,92]

The GM also acts on hypertension through immune response and inflammation.[93]

The GM contribution to sex differences in hypertension may involve immune-related processes. In fact, proinflammatory T helper (TH) 17 cells are released from GM[94] and could trigger arterial hypertension.[95,96] It has been demonstrated that hypertensive male rats present more TH17 cells compared to female rats.[91]

Moreover, the GM Lactobacilli reduction is related to an increase in TH17 cells.[97] Since women may have more Lactobacilli than men,[97] and men have a higher number of TH17 cells,[91] the depletion of the protective strain in women may be of greater magnitude, resulting in a larger relative increase in TH17 cells, with a corresponding greater effect on blood pressure. Generally, inflammation is identified as a cause and a consequence of hypertension. A reduced GM diversity can lead to low-grade inflammation, which contributes to the development of hypertension.[98] Conversely, estrogens can reduce inflammation,[99-101] concurring to the maintenance of normal blood pressure values during the fertile age.

Dysbiosis is associated with hypertension, due to an increase in the sympathetic drive. The latter mediates the inflammatory responses by affecting gut permeability.[102] GM products are implicated in the sympathetic activation and the maintenance of an influx of lymphocytes to the intestinal tissue. Communication between the gut enteric nervous system and the central nervous system has similarly emerged as a potential connection to blood pressure.[103,104]

Overall, these data confirm a strong association between gut microbial dysbiosis, hypertension and gender.

Myocardial infarction and heart failure

Some studies confirm the relationship between GM dysbiosis and the pathogenesis of atherosclerosis (A), myocardial infarction (MI), coronary artery disease (CAD) and heart failure (HF) in humans. Nevertheless, all data are provided without age and gender differentiation.

The GM of CVD patients may be fostering inflammation by producing proinflammatory molecules. Atherosclerotic plaques include bacterial DNA, mostly of Proteobacteria, and these bacteria have been found in the same individual's gut,[105] suggesting a disruption in the intestinal epithelial barrier. Thus, the GM communities may be a source of plaque bacteria.[106]

GM Bacteria may affect plaque stability and the development of CVD, through the disruption of the intestinal epithelial tight junctions caused, at least partially, by ammonia and ammonium hydroxide.[107] Moreover, the presence of vulnerable coronary plaque, plaque rupture, and long-term risks of incident cardiovascular events in patients with acute coronary syndrome (Figure 2) were associated with high circulating TMAO levels.[108,109]

Thus, TMAO could be a marker for coronary plaque vulnerability and progression.

Human studies on more than 1,800 stable cardiac patients undergoing elective coronary angiography demonstrated that all TMAO-associated metabolites had a positive association with prevalent CVDs and incident cardiovascular events. TMAO can also predict adverse outcomes of all-cause mortality or re-infarction 2 years after a MI.[110] These data emphasize that TMAO acts as a direct participant in an enhanced risk for atherosclerosis and myocardial infarction.

Recently, a mechanistic link between the gut microbiota and the severity of myocardial infarction has reported in rats.[111,112] The use of broad-spectrum antibiotics has been shown to affect the circulating levels of leptin and the analytes produced during the aromatic amino acid catabolism, with an associated reduction in the myocardial infarct size.[111,112] Similarly, *Lactobacillus plantarum* suppresses the production of leptin, improves the left ventricular function and ultimately decreases the myocardial infarct size after MI.[111] Another animal study showed that the administration of the *Lactobacillus rhamnosus* GR-1 attenuated the left ventricular hypertrophy and the heart failure after experimental MI.[113] The reduction in the metabolites of the aromatic amino-acids phenylalanine, tryptophan and tyrosine can decrease the severity of induced MI.[112]

HF is a disease with a high morbidity and mortality,[114] where about half of the patients die within 5 years from their diagnosis.[115] Changes in the composition and diversity of the GM have been observed in patients with HF. There is a growing literature supporting the role of GM in the pathogenesis of HF – the so-called "gut hypothesis of HF". The latter implies that a decreased cardiac output and an elevated systemic congestion can induce intestinal mucosal ischemia and/or edema, leading to the disruption of the intestinal barrier and to an increase in bacterial translocation and circulating endotoxins, contributing to the underlying inflammation in HF patients.[116-118]

Niebauer et al. found that HF patients with peripheral edema had higher plasma concentrations of endotoxin and inflammatory cytokines, compared to those without edema.[119] In another study, HF patients with

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lower intestinal blood flow showed higher serum concentrations of immunoglobulin A-anti lipopolysaccharide, which in turn was correlated with an increased growth of the bacteria obtained from the biopsies of colonic mucosa, but not by stool bacteria.[120] The nature of the bacterial flora in these subjects also appeared to be different from controls, as recently confirmed by Pasini et al.[121]

Moreover, microbial metabolites – especially those derived from dietary nutrients – can generate paracrine and endocrine effects, leading to an increased susceptibility to HF. In fact, TMAO and choline are associated with the severity of HF, since circulating TMAO levels are higher in HF patients compared with age- and gender-matched healthy subjects.[122] In addition, an elevated TMAO level is relevant to the severity of HF, and indicates a worse prognosis,[122] even after adjusting for the traditional risk factors[60].

At present there are no data reporting the effect of GM dysbiosis on the development of HF related to gender dimorphism.

Conclusions

Relations between the gut microbiome and the host have been assumed in CVD and associated metabolic conditions. The GM may be the key mediator or modulator of the observed sexual dimorphism in the onset and progression of cardiovascular disease. Gut microbiome-dependent metabolites may interact with important biological pathways under the sex hormone control, since male and female sex hormones have differential effects on the GM. Endogenous sex hormones and microbiota affect each other: the hormonal milieu modulates the composition and diversity of the GM which, in turn, affects the metabolism of the sex hormones, with systemic implications. The assessment of the intestinal barrier function may lead to a greater comprehension of gut-directed CVD risk prevention and therapy.

Further human studies, highlighting the effect of gender on the relationship between GM dysbiosis and CVD, should be pursued in order to pave the way to potential low-risk interventions involving microbiota to reduce the CVD risk throughout the lifespan.

Key messages

- Changes in the gut microbiota (GM) composition and the related microbial metabolites affect the immune system and the metabolic functions of the host, leading to several pathological conditions, such as cardiovascular diseases (CVD).
- Sex differences in GM are involved in the risk for CVD and for CVD dimorphism.
- Sex hormones are a pivotal modulating factor of the mammalian microbiota composition.
- Systemic estrogen metabolism profiles may be influenced by the composition and diversity of the GM.
- A bidirectional cross-talk between microbiota and sex hormones has been described; bacteria can produce hormones, responding to the host's hormones regulating its homeostasis and suggesting the potential improvement of CVD outcomes by altering the gut flora.

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