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Metabolic syndrome and gut microbiota: there is a gender difference?

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Summary. The metabolic syndrome (MS) is a cluster of diseases that includes at least three of these conditions (high blood pressure, abdominal fat, high triglycerides, elevated blood sugar and low HDL cholesterol). The prevalence of metabolic syndrome in the adult population is on the rise with an estimated prevalence of 20-25%. In addition, patients have a five-fold greater risk of developing type 2 diabetes and an increased risk of death for cardiovascular causes.

In this review, we address the issue of the gender differences in metabolic syndrome trying to understand the pathogenesis of this difference. Genetic and hormonal factors and recent experiments with mice models are taken in consideration to understand these differences.

Moreover, recent studies on the direct effect of the gut microbiota on obesity by transplanting it from lean or obese mice into germ-free mice has demonstrated the important role of gut microbiota composition and its genetic background influence. Though the field is still young, studies demonstrate that diet, sex, and genetic background may each influence the composition of the gut microflora, and that the microbial community in turn impacts hormone levels, immunity, and metabolic homeostasis in the host.

New knowledge on the pathogenesis of the gender differences in metabolic syndrome could in the future help to develop more sophisticated drugs that may decrease the cardiovascular risk of patients with this disease.

Key words. Metabolic syndrome, gender differences, gut microbiota, hormonal factors.

Sindrome metabolica e microbiota intestinale. Esiste una differenza di genere?

Riassunto. Con il termine sindrome metabolica (MS) si identificano almeno 3 di queste condizioni (livelli di pressione arteriosa superiore al normale, presenza di grasso viscerale, alti livelli di trigliceridi, alterata glicemia a digiuno e bassi livelli di colesterolo HDL). La prevalenza della sindrome metabolica nella popolazione adulta è in aumento e si attesta sul 20-25%. I pazienti affetti da MS hanno un rischio di sviluppare diabete mellito cinque volte superiore rispetto alla popolazione normale ed un aumentato rischio cardiovascolare. Esiste una differenza di genere nella manifestazione clinica della malattia e in questo articolo cercheremo di capirne la patogenesi. Fattori ormonali e genetici svolgono un importante ruolo nel determinare questa differenza e recenti esperimenti su modelli animali hanno contribuito a dimostrarlo.

Recentissimi studi hanno evidenziato che il microbiota intestinale ha un effetto diretto nella patogenesi della obesità. In modelli animali mediante un trasferimento da topi magri o topi obesi in topi *germ-free* del microbiota intestinale era possibile dimostrare il ruolo del microbiota e la sua influenza sul background genetico.

Anche se il campo di studi è recente, esistono evidenze che dimostrano che la dieta, il sesso e il background genetico possono influenzare la composizione del microbiota intestinale, che a sua volta determina i livelli ormonali e l'omeostasi metabolica nell'ospite. Queste nuove evidenze, relative alla patogenesi della differenza di genere nella MS, potranno in futuro dare un impulso nuovo allo sviluppo di farmaci più sofisticati in grado di diminuire il rischio cardiovascolare in pazienti affetti da tale patologia.

Parole chiave. Sindrome metabolica, differenze di genere, microbiota intestinale, fattori endocrini.

Introduction

The metabolic syndrome (MS) is a cluster of conditions that includes at least three of these problems (high blood pressure, abdominal fat, high triglycerides, elevated blood sugar and low HDL cholesterol)[1-5]. In 1988, Reaven[6] proposed that insulin resistance was of fundamental importance in clustering abnormalities that not only increase the risk of type 2 diabetes, but also contribute to the development of cardiovascular disease. He speculated that a loss of, or defect in, insulin action and compensatory hyperinsulinemia was the linking factor for the condition, which he termed syndrome X. Since then, ample published data have shown that insulin resistance, detected by various methods, is indeed a key factor associated with the clustering of increased blood glucose, excess body fat, increased blood pressure, and cholesterol abnormalities, which have alternatively been named the *deadly quartet*, the *insulin resistance syndrome*, the *cardiometabolic syndrome*, and now most commonly, the *metabolic syndrome*. Genetics, physical inactivity, ageing, a proinflammatory state and hormonal changes may also have a causal effect.

The prevalence of metabolic syndrome in the adult population is on the rise with an estimated prevalence of 20-25%. In addition, they have a five-fold greater risk of developing type 2 diabetes. Adults with metabolic syndrome are twice as likely to die from, and are three times as likely to have a heart attack or stroke compared with people without the metabolic syndrome[7].

Sex differences in regional adipose tissue deposition

It is well known that there are inherent differences between men and women in fat distribution and properties of fat cells within anatomical depots (Figure 1). When normalized to waist circumference or to total body fat, men have more visceral adipose tissue (fat within the abdominopelvic cavity) than pre-menopausal women[8,9]. Men also tend to lose relatively more visceral adipose tissue due to calorie restriction than women[10]. By contrast, women typically have more subcutaneous adipose tissue (fat underneath the dermis)[9]. Numerous epidemiological studies have linked increased visceral fat to MS, and others have suggested that subcutaneous adipose tissue may even play a protective role against glucose dysregulation[10-14]. Thus, in the basal state, the higher ratio of subcutaneous/visceral adipose tissue composition in women may be a beneficial trait relative to MS development).

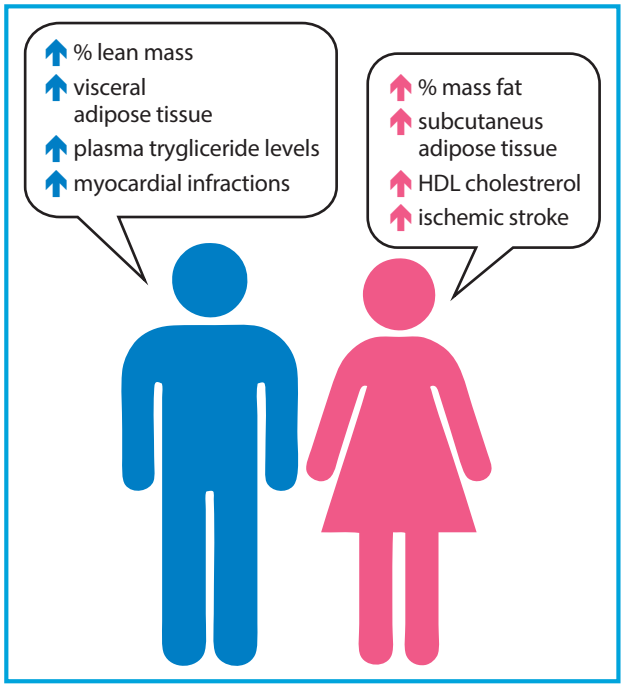

Figure 1. Sex differences in metabolic syndrome. Modified from Link JC, Reue K. Genetic basis for sex differences in obesity and lipid metabolism. Annu Rev Nutr. 2017; 37: 225-245.

Sex differences in metabolic syndrome

Sex differences exist in nearly all of the components of MS (Figure 1). For example, females have developed specific mechanisms to favor adipose tissue storage, whereas mobilization of fat stores tends to be more efficient in males[9-11]. Compared to men, women tend to have greater insulin sensitivity, and differences exist in lipoprotein profiles[10]. Moreover, women tend to have increased fat mass proportional to their body weight, increased subcutaneous adipose tissue, and elevated HDL cholesterol levels. Men generally have greater proportional lean mass, increased visceral adipose tissue, and elevated plasma triglyceride levels.

The levels of androgens also influence metabolic disease. Testosterone levels typically diminish in men with age, and low testosterone levels in men are associated with increased body fat and cardiovascular disease[3,15,16].

Cardiovascular disease incidence also differs, with women having higher incidence of ischemic stroke, and men higher incidence of myocardial infarction.

Some studies have demonstrated that post-menopausal women have altered body fat distribution and increased incidence of cardiovascular disease, hypertension, diabetes and other disorders[17,18]. It is well known that estrogens are involved in a plethora of mechanisms regulating body fat distribution and glucose and lipid metabolism.Thus, the metabolic and hormonal changes of menopause occur over several years, extending into the postmenopausal period, and vary widely among women. In contrast, fluctuation in nonreproductive hormones produced by the thyroid, parathyroid, and pancreas noticeable after menopause are considered a result of chronological aging without a significant relationship to menopause itself[19].

However, even in the absence of weight gain, postmenopausal alterations in fat occur with a preferential increase in visceral adiposity even after accounting for age and baseline total adiposity. Lovejoy et al[20] demonstrated that among initially healthy premenopausal women followed longitudinally, all women gained subcutaneous adipose tissue with age, irrespective of menopausal status, whereas visceral adipose tissue increased only in women who became postmenopausal and in parallel with a decline in estrogen. Furthermore, this increase in visceral fat has been shown to correlate positively with an adverse inflammatory and thrombotic profile and to correlate negatively with concentrations of adiponectin[21].

Visceral fat accumulation, when it does occur, is generally accompanied by insulin resistance, increased free fatty acid concentrations, and secretion of apolipoprotein B-containing particles, leading to hypertriglyceridemia and increased hepatic lipase activity. This cascade ultimately results in a preponderance of small, dense LDL particles and a reduction in large antiatherogenic HDL_2 particles.

A similar pattern emerges with menopause, in that LDL particle composition shifts from a low prevalence of small, dense atherogenic LDL particles in premenopausal women (10%-13%) increasing to as much as 30%-49% after menopause. These lipid changes (increased TG, low HDL cholesterol, and increased small, dense LDL) are indicative of increased cardiovascular risk and contribute to the number of women meeting a diagnosis of MS.

Nonetheless, several mechanisms may contribute to the development of hypertension in postmenopausal women including endothelial dysfunction, inappropriate activation of the renin-angiotensin and sympathetic systems, oxidative stress, and inflammatory mediators.

Studies in American[22] and Finnish[23] elderly subjects demonstrated that metabolic syndrome was not an independent predictor of total mortality.

In elderly Italian individuals, the prevalence of metabolic syndrome over 75 years of age decreases in men, whereas it increases in women; women more frequently had two or more components of the metabolic syndrome compared with men; and women showed a higher prevalence of high triglycerides and low HDL cholesterol than men[24].

Sex differences and genetic factors

Genetic factors, in particolar sex chromosomes, could also contribute to sex differences in metabolic traits[25]. Some studies on individuals with sex chromosome anomalies (Turner syndrome or Klinefelter syndrome) reported increased adiposity and other features of MS[26-28].

Studies performed using mice allow understanding the effects of high and low gonadal hormone levels on the identical genetic background. The action of gonadal hormones can be classified into two classes:

1. the permanent effects of gonadal hormones that lead to the development of sex differences during fetal and neonatal development;
2. the acute actions of gonadal hormones that cause specific responses in numerous processes throughout life. The acute effects of gonadal hormones are reversible, and a standard way to identify acute hormone effects is to compare adult mice with intact gonads with those from which gonads were removed in adulthood. Those sex differences that are caused by acute hormonal effects will be abolished in gonadectomized mice, whereas sex differences resulting from the permanent effects of gonads during development will remain.

The origin of male and female gonads and the hormones they produce traces back to the presence of either XX or XY sex chromosomes. Furthermore, the presence of either XX or XY chromosomes leads to sex differences at the cellular level because of the differential action of genes on the X and Y chromosomes.

For example, during early embrionic growth before the development of gonads or gonadal hormones, male embryos are larger than female embryos in mice, humans, and several other mammals. In mice, these differences have been attributed to a combination of effects from the presence of the Y chromosome in male embryos and the sexual imbalance between the number of X chromosomes in males vs females[29-31]. Following gonadal differentiation, it is difficult to make a clear-cut distinction between the effects due to hormones and those resulting from sex chromosomes. In mice, males also have greater body weight, but the degree of body fat is dependent on diet and strain. In some strains, a high fat diet leads to similar adiposity, whereas in others one sex has greater adiposity than the other[32,33].

This led to the generation of mouse models to distinguish gonadal and chromosome sex effects such as the Four Core Genotypes (FCG) mouse model. This model generates mice having XX chromosomes in both males and females and XY mice on male and female gonadal backgrounds. In gonad-intact, male mice (with testes, either XX or XY) have greater body weight than female mice (with ovaries, XX and XY). In addition, XX mice weigh more than XY mice of the same gonadal sex. After gonadectomy (GDX) of adult mice, male-female sex differences are reduced, indicating that acute effects of gonadal hormones contribute to male-female differences in body weight. Weeks or months after GDX, however, the body weight of XX mice increases more than that of XY mice, and XX mice eventually have nearly twice as much body fat[34]. These results suggest that the presence of two X chromosomes, and/or the absence of the Y chromosome, leads to enhanced body fat. The XY model resolves this question in favor of the X chromosome dose. Mice with two X chromosomes (XX or XXY) have greater body weight than mice with one X chromosome (XY or XO)[34]. XX mice after GDX also have accelerated weight gain on a high fat diet, with increased food intake[34,35]. XX mice also develop deeper fatty liver, greater evidence of insulin resistance and higher circulating cholesterol levels than XY mice when stressed with fat- or cholesterol-enriched diets. Thus, the number of X chromosomes has a substantial effect on obesity and related morbidities. The use of these mice models could allow understanding the role of genetic factors in determining these metabolic sex differences to optimize prevention, diagnosis, and therapeutic intervention for both sexes.

Gut microbiota and sex differences

To date, the human intestinal microbiota has gained increasing interest for its equivocal impact on human health, such as its comprehensive physiological and pathological functions[36-39]. A plethora of microorganisms

have colonized the gastrointestinal tract by the time that we are born, and they play a crucial role in building our future physiology and immunity, leading to homeostasis of the internal environment. The role of bacteria in shaping immunity and gut structure has emerged over the last decades. The human intestinal microbiota composition is the result of a bi-directional interaction between the host and its microbial consortium. Immune factors, such as secretory IgA and endogenous secretions, end up in the bowel and have been proven to affect the composition of gut microbiota[40,41]. Current views suggest that low-grade chronic systemic inflammation contributes to the development of insulin resistance, diabetes, and obesity. The relative proportion of some major phyla of gut bacteria, such as Bacteroidetes and Firmicutes (a smaller proportion of Bacteroidetes and greater abundance of Firmicutes), was associated with metabolic syndrome[42]. Ferrer et al. conducted an investigation of gut microbial communities in fecal samples taken from an obese adolescent and a lean adolescent by analyzing the diversity of 16S rDNA amplicons, 22 Mbp of consensus metagenome sequences and the expression profiles of 613 distinct proteins. They found that in the obese gut, the phylum Firmicutes (94.6%) was more abundant in the total microbiota than Bacteroidetes (3.2%), whereas the lean gut showed a remarkable shift towards Bacteroidetes (18.9% of total 16S rDNA), which became the most active fraction (81% of proteins)[42]. These facts generally implicated the role of the gut microbiota in the pathophysiology of metabolic syndrome.

In addition to these endogenous modulations, the composition and stability of the gut microbiota are determined by nutrition or other factors, such as probiotics, prebiotics, antibiotics, drugs, and diseases. Current studies suggest that manipulation of the gut microbiota could be a promising approach for the prevention and management of metabolic syndrome[43].

A direct effect of gut microbiota on obesity was elegantly demonstrated by transplanting gut microbiota from lean or obese mice into germ-free mice. Mice that received microbiota from diet-induced or genetically obese mice gained weight compared to recipients of microbiota from lean donors[44, 45]. These findings suggest that gut microbiota have the capacity to dramatically influence host metabolism, including effects on energy acquisition and storage.

Although the field is still young, studies demonstrate that diet, sex, and genetic background may each influence the composition of the gut microbiota, and that the microbial community in turn impacts hormone levels, immunity, and metabolic homeostasis in the host.

These changes were dependent on the specific mouse strain, indicating that genetic background influences gut microbiota composition. Furthermore, some genera (*Akkermansia*, *Lactococcus*, and *Allobaculum*) were correlated with the gain in body fat due to diet, highlighting the connection of gut microbes with metabolic health. Feeding a high fat diet (61% calories from fat) for 8 weeks suppressed the diurnal fluctuations in microbial composition and reduced species, which may be detrimental to overall health[44]. One hypothesis is that metabolites produced by the gut microbiota, including catabolized complex carbohydrates and bile acids, may signal to and alter host metabolism.

A recent study investigated the effects of sex on gut microbial communities[45]. Of 89 strains of mice examined, 7 strains had significant sex differences in abundance. To determine how these sex differences were affected by nutritional excess, the authors examined male and female mice on a high fat/high sucrose diet for 8 weeks. They identified a sex-by-diet interaction in microbiota composition, suggesting that specific taxa respond to diet in a sex-dependent manner. In addition, gonadectomy revealed that circulating sex hormones regulate the gut microbiota in a strain- and diet-dependent manner.

While many factors influence microbial composition, the gut microbiota itself remarkably affects testosterone levels in both males and females[46]. Germ-free females had higher levels of testosterone compared to females, while germ-free males had reduced levels of testosterone.

Perhaps most strikingly, transplantation of microbiota from the adult male cecum to the female cecum resulted in a significant increase in testosterone at 7 and 14 weeks of age. At 34 weeks of age, the microbial community reverted to a population resembling female gut microbiota. The implications of this manipulation were reflected in protection of type 1 diabetes in nonobese diabetic (NOD) mice. Female mice that had received male cecal bacteria were protected from autoimmune destruction of pancreatic β cells, while those that had received female cecal bacteria were not. In addition, treatment of an androgen receptor antagonist eliminated the protective effects of male cecal bacteria, suggesting that the transfer-mediated enhanced testosterone levels were required for protection from type 1 diabetes[47].

Future perspective

Given that sex is one of the most profound biological determinants, it is unfortunate that it has not always received due attention in studies. Both pre-clinical and clinical studies have traditionally focused on a single sex, and more often than not, this has been the male sex. A frequent justification was the hormonal fluctuations that occur during the female reproductive cycle. In recent years, the need to include both sexes in pre-clinical studies has been recognized and voiced. It is hoped that these discussions will lead to a greater transparency

in reporting the sexes used in pre-clinical studies, and increased inclusion of both sexes in both pre-clinical and clinical studies.

The new knowledge related to the pathogenesis of the gender differences in metabolic syndrome could in the future help to develop more sophisticated drugs that may decrease cardiovascular risk and mortality in patients with this disease.

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Key messages

- Sex differences exist in nearly all of the components of metabolic syndrome. Men have more visceral adipose tissue than pre-menopausal women. Men also tend to lose relatively more visceral adipose tissue due to calorie restriction than women; by contrast, women typically have more subcutaneous adipose tissue. Some studies have demonstrated that post-menopausal women have altered body fat distribution and increased incidence of cardiovascular disease, hypertension, diabetes and other disorders.
- Genetic factors, in particular sex chromosomes, could also contribute to sex differences in metabolic traits.
- The use of the mice models could allow to understand the role of genetic factors in determining these metabolic sex differences.
- A direct effect of gut microbiota on obesity was elegantly demonstrated by transplanting gut microbiota from lean or obese mice into germ-free mice. Mice that received microbiota from diet-induced or genetically obese mice gained weight compared to recipients of microbiota from lean donors. These findings suggest that gut microbiota have the capacity to dramatically influence host metabolism, including effects on energy acquisition and storage.
- New knowledge related to the pathogenesis of gender differences in metabolic syndrome could in the future help to develop more sophisticated drugs that may decrease the cardiovascular risk of patients with this disease.

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