Review Article

Gender difference in the neuroimmunomodulation of obesity: A mini review

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Abstract

Obesity along with its comorbidities is escalating rapidly in epidemic fashion worldwide. Sex differences exist in the etiopathogenesis of obesity-mediated diseases, which is primarily mediated by the distribution of adipose tissue and alterations in the neural regulation. In this review, we have emphasized the role of gender in the development of obesity, and its alterations in the neural and its associated inflammatory pathways.

Key words: Gender, immunomodulation, obesity

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INTRODUCTION

Obesity has become a global primary health concern due to the increased risk of mortality associated with its comorbidities. The prevalence of obesity among both the gender differs widely between the countries and within the country.[1] Studies have also reported gender difference in the tendency to develop obesity and its related complications.[1] Moreover, these gender differences in obesity are more among the females when compared with the males, especially in the developing countries.[2]

Although obesity *per se* is independent of gender, there exists a gender difference in the body fat distribution, body composition, immunity, and feeding behavior.[3,4] An epidemiological study that investigated the 5-year incidence of obesity showed that men were 1.6 times more likely to become obese than women.[5] For a given body mass index, men were reported to have more lean mass and women to have higher adiposity. Furthermore, men were found to have more visceral adipose tissue, whereas women have more of subcutaneous adipose tissue.[6] The risk of obesity was less in both men and women with higher educational and socioeconomic status, whereas higher occupational status was associated with a lower risk of obesity only in women.[7] Males had more weight gain with higher energy intake than did females. Male rats pair-fed with control females showed a significant increase in body weight gain.[4,5,8] Male rats on high-fat diet (HFD) became obese much earlier than female rats on HFD.[9,10]

DIFFERENTIAL FAT DISTRIBUTION

Gender difference in the distribution of fat has been observed even before the onset of puberty. Although both females and males display a persistent increase in their body fat content throughout the development, males are known to have the maximum body fat percentage during puberty. Moreover, in females, it is mostly the subcutaneous fat that accumulates, whereas in males, it is more of visceral fat. However, this gender difference in the

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distribution of visceral fat is abolished as age advances, and it is found that postmenopausal females are known to have more of visceral fat rather than subcutaneous fat.[1]

The basal metabolic rate per kilogram of fat tissue is greater in females than in males, which may be due to the differential expression of mitochondrial genes between obese males and females. When both males and females were subjected to HFD, it was found that males had a significantly greater body weight gain and fat mass index when compared to females.[1] Further, the fat oxidation is also less in females compared to males, enabling females to store more fat.[11] Therefore, all these variations in the net regional fat deposition between male and female play an important role in mediating the fatty acid metabolism, adipokines production, inflammatory response, and mitochondrial function.

NEURAL REGULATION IN OBESITY: ROLE OF GENDER

The ventromedial hypothalamus shows gender differences in its neuronal morphology, neurochemistry, and feeding behavior.[4,8,12] Similarly, amygdala also shows a gender difference in the feeding behavior, male rats having greater weight gain than female rats.[13] Not only eating behavior patterns differ widely between obese men and women but also there exists a gender difference in the cognitive, emotional, and reward processing functions of the brain. Several anatomical differences in the brain structure between obese and lean persons have been reported, of which the cerebral white matter changes correlated significantly with increased body weight in men compared with women. In the fasted state, neurons in the visual and attention regions of the brain showed increased activity in obese men, whereas obese women showed greater activation in the affective and reward-related processing regions such as the caudate nucleus.[14]

IMMUNOMODULATION IN OBESITY: ROLE OF GENDER

Influence of gender on immunological responses and inflammatory conditions has been well established.[4] A recent study has shown a significant gender difference in the level of inflammatory markers in prepubertal children. Immune response to infections is generally well tolerated by females than males. It has been reported that autoimmune diseases are more common in women than men and women were found to have higher titers of all classes of circulating autoantibodies than men.[15] Studies have demonstrated the role of sex hormones in immune response modulation.[16] Obese females were found to have higher complement C3 and C4 levels than obese males. Furthermore, inflammatory marker C-reactive protein concentrations were significantly higher in both obese and morbidly obese women, unlike male it was increased only in morbidly obese conditions. sE-selectin and leptin levels were found to be significantly elevated in both obese women and men.[17] The cellular and the humoral immune response were found to be more powerful in a normal adult woman than in men of the same age.[15]

Several studies have shown that premenopausal women have a reduced risk of cardiovascular disease when compared with men,[18,19] but the risk of cardiovascular disease increases after menopause.[20] Studies have also suggested that the female myocardium is more resistant to ischemia/reperfusion injury than the male myocardium.[21-24] Recently, it was reported that some rare genes present on the X chromosome may be involved in the inflammatory cascade.[25-27] In females, some of the genes responsible for inflammation are overexpressed, and the reason for this could be incomplete silencing of any one of the X chromosomes.[28]

Males have increased oxidative stress markers and pro-inflammatory immune cells in both subcutaneous and gonadal fat tissue. Medrikova *et al*. have observed that when male mice were subjected to HFD, the macrophage infiltration was maximum in the gonadal and subcutaneous fat tissue although the levels of inflammatory markers in the gonadal fat tissue were similar between both the sexes.[29] Similar results were also reported by Pettersson *et al*., where males were found to be more susceptible to increased inflammatory response following HFD.[30] This differential inflammatory response in the adipose tissue may be the reason for males being more susceptible and females being less susceptible to develop diabetes and other obesity-related complications.[1] Intake of HFD also modifies the circulating sex steroid levels. The sex hormones, especially the estrogen plays an important role in sexual dimorphism. Estrogen enhances the subcutaneous fat accumulation and is a strong regulator of appetite and energy expenditure.[31-33] Serum testosterone levels were reduced in response to HFD in males,[34] whereas estrogen levels increased in response to HFD in females, which could be protective in females.[35,36] Thus, the adipose tissue modulates the circulating levels of sex steroids and circulating adipokines to exhibit the sexual dimorphism observed in obesity.

EFFECT OF GENDER ON CLINICAL RELEVANCE OF OBESITY

Overweight and obesity accelerate the process of atherosclerosis, hypertension, Type 2 diabetes, coronary heart disease, stroke, and breast cancer.[37] Obesity

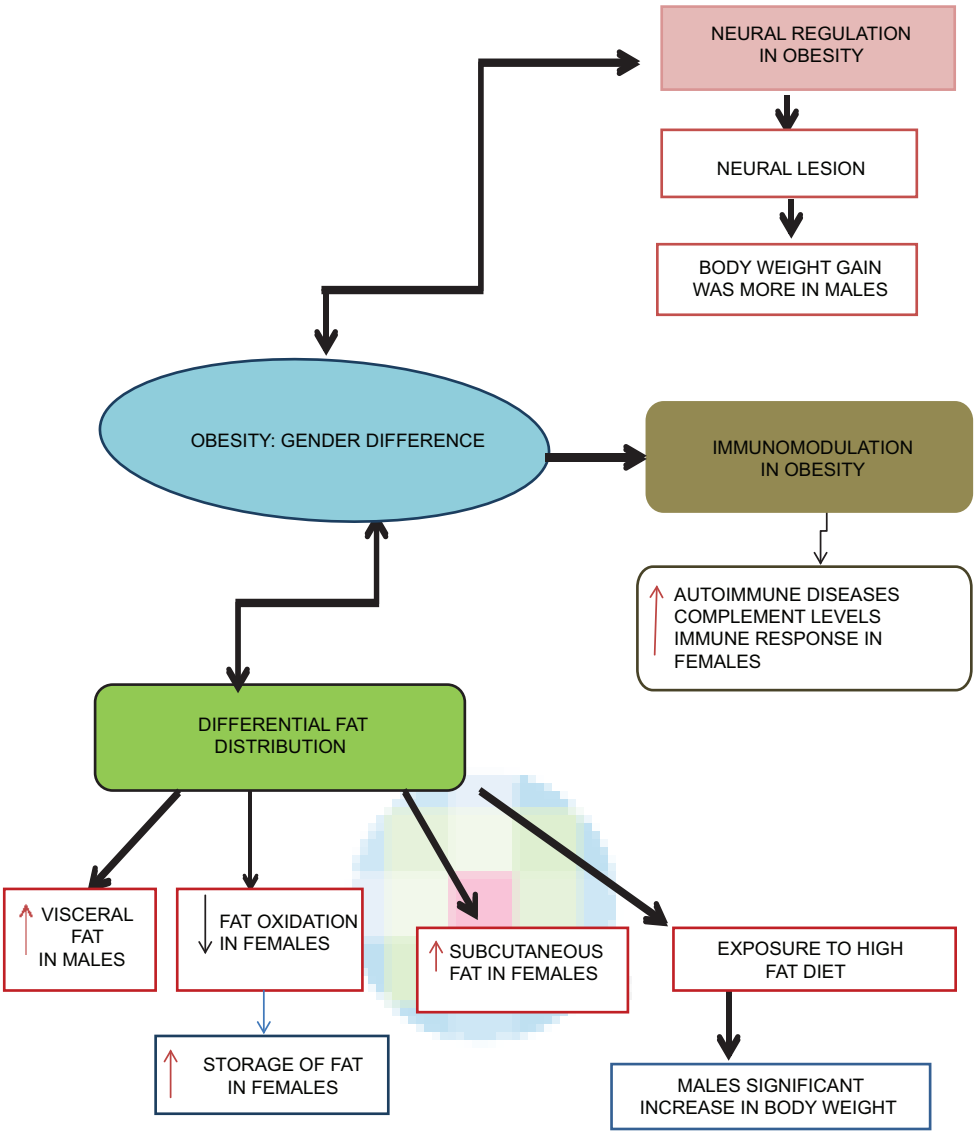

Figure 1: Schematic diagram of gender difference on neuroimmunomodulation in obesity

increases the risk of hypertension, and it has been reported that every one-kilogram reduction in the body weight decreases the blood pressure by 2 mmHg.[38] The excess of fat in obesity increases the risk of insulin resistance, which is one of the major trigger factors for the development of Type 2 diabetes.[39] The differential inflammatory response in adipose tissue makes males more susceptible to develop obesity-related complications.

CONCLUSION

Obesity and its associated complications pose a major public health threat in the present era. The gender difference in the amount and distribution of adipose tissue and the gender difference in the neural regulation and inflammation play a vital role in mediating the sexual dimorphisms observed in obesity and its associated comorbidities [Figure 1]. Hence, all these differences in the metabolic, neural, and immunological aspects of obesity should be considered while formulating the various treatment modules for obesity in both genders.

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Conflicts of interest

There are no conflicts of interest.

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