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Review

The sexual dimorphism of obesity

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ABSTRACT

The NIH has recently highlighted the importance of sexual dimorphisms and has mandated inclusion of both sexes in clinical trials and basic research. In this review we highlight new and novel ways sex hormones influence body adiposity and the metabolic syndrome. Understanding how and why metabolic processes differ by sex will enable clinicians to target and personalize therapies based on gender. Adipose tissue function and deposition differ by sex. Females differ with respect to distribution of adipose tissues, males tend to accrue more visceral fat, leading to the classic android body shape which has been highly correlated to increased cardiovascular risk; whereas females accrue more fat in the subcutaneous depot prior to menopause, a feature which affords protection from the negative consequences associated with obesity and the metabolic syndrome. After menopause, fat deposition and accrual shift to favor the visceral depot. This shift is accompanied by a parallel increase in metabolic risk reminiscent to that seen in men. A full understanding of the physiology behind why, and by what mechanisms, adipose tissues accumulate in specific depots and how these depots differ metabolically by sex is important in efforts of prevention of obesity and chronic disease. Estrogens, directly or through activation of their receptors on adipocytes and in adipose tissues, facilitate adipose tissue deposition and function. Evidence suggests that estrogens augment the sympathetic tone differentially to the adipose tissue depots favoring lipid accumulation in the subcutaneous depot in women and visceral fat deposition in men. At the level of adipocyte function, estrogens and their receptors influence the expandability of fat cells enhancing the expandability in the subcutaneous depot and inhibiting it in the visceral depot. Sex hormones clearly influence adipose tissue function and deposition, determining how to capture and utilize their function in a time of caloric surfeit, requires more information. The key will be harnessing the beneficial effects of sex hormones in such a way as to provide 'healthy' adiposity.

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1. Introduction

Over the past 20 years, adult and childhood obesity rates have doubled, while adolescent obesity has tripled (Ford et al., 2014). Two-thirds of Americans are currently at-risk for obesity related mortality or morbidity however this differs by sex. While the connection between obesity and risk of heart disease, hypertension, cancer, stroke, and diabetes is well established in men, it is less so for women

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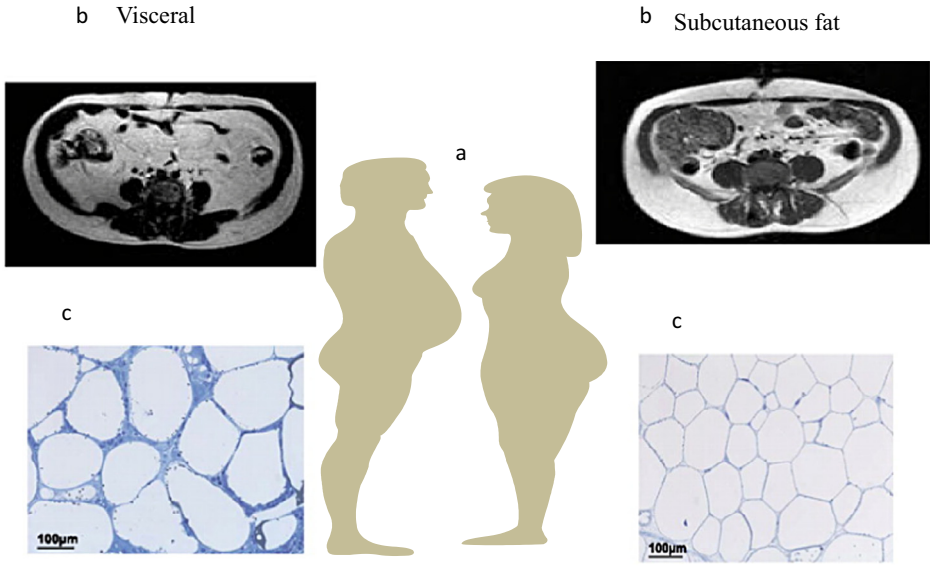

Fig. 1. Approximately 80% of all body fat is in the subcutaneous depot and lies just under the skin primarily around the waist, in the subscapular area, and in the gluteal and femoral (thigh) areas. Visceral fat, accounting for 10–20% of total fat, is in the abdomen primarily in the omentum and mesentery but also in perirenal, gonadal, epicardial, and retroperitoneal depots. Visceral fat accounts for a higher percentage of total fat in men than in women. In men adipose tissue preferentially accumulates in the visceral depot while fat accumulation is primarily in the subcutaneous depot in women. The magnitude of this difference is amplified from late puberty to early adulthood as men develop the typical android body shape while women a more gynoid shape. Menopause is followed by redistribution of adipose tissue to the visceral depots leading to a more central or android shape in post-menopausal women who are not hormone replaced. The timing of these changes implicates involvement of sex hormones. Up to the transition through menopause, women tend to accrue adipose tissue preferentially in the subcutaneous depot due to its greater storage capacity, and the expandability of subcutaneous fat can be traced to a greater degree of hyperplasia of fat cells. Men accrue adipose tissue preferentially in the visceral depot, and the accumulation of excess fat in the visceral depot is primarily achieved by hypertrophy of fat cells. Once storage capacity is exceeded, visceral adipose tissue is characterized by fibrotic and inflamed adipose tissue which is highly correlated with the metabolic syndrome. (a) A cartoon depicting android and gynoid deposition of adipose tissue in males and females. (b) Representative coronal midsection MRI images of a BMI-matched male and female demonstrating fat distribution with the white matter depicting adipose tissues. (c) Representative histologic adipose tissue sections from subcutaneous or visceral adipose tissues. The subcutaneous adipose tissue has smaller more 'plastic' adipocytes whereas the visceral adipose tissue is characterized by larger adipocytes encased in fibrotic tissues.

and the mechanisms underlying these sexually dimorphic influences remain poorly understood. Over the past decade adipose tissues have been determined to be more than a storage vessel for triglycerides, rather, these tissues actively contribute to metabolic homeostasis by secreting a wide variety of signaling molecules and hormones. An often underappreciated finding is that adipose tissue function and deposition differ by sex. Females have an overall higher total body fat content when compared to men. Importantly, females differ with respect to distribution of adipose tissues, males tend to accrue more visceral fat, leading to the classic android body shape which has been highly correlated to increased cardiovascular risk; whereas females accrue more fat in the subcutaneous depot prior to menopause, a feature associated with protection from the negative consequences associated with obesity and the metabolic syndrome (Fig. 1). After menopause, fat deposition and accrual shift to favor the visceral depot. This shift is accompanied by a parallel increase in metabolic risk reminiscent to that seen in men. A full understanding of the physiology behind why, and by what mechanisms, adipose tissues accumulate in specific depots and how these depots differ metabolically by sex is important in efforts of prevention of obesity and chronic disease. A review of sex differences in obesity/adipose tissue distribution is timely given that obesity has recently been classified as a disease, and that the National Institutes of Health has made it mandatory to explore gender differences in disease states.

2. Estrogens and adiposity

Obesity is influenced by a number of variables such as ethnicity, socioeconomic status and education which makes it difficult in humans to determine whether a *biological* difference *per se* exists regarding the propensity to gain weight between men and women. By contrast, in animal models where non-biological factors are excluded, studies suggest the propensity toward development of obesity differs between the sexes and this is directly due to sex hormones. For example, female rats gain less weight compared to males when presented with a metabolic challenge such as a high fat diet, a difference no longer seen following ovariectomy (Stubbins et al., 2012). Estrogens protect against increased body adiposity/obesity through their effects to suppress appetite and increase energy expenditure. Estradiol suppresses feeding by enhancing the potency of other anorectic signals, such as cholecystokinin, apolipoprotein A-IV, leptin, brain derived neurotrophic factor (BDNF), and by decreasing the potency of orexigenic signals such as melanin-concentrating hormone and ghrelin (Clegg et al., 2006, 2007; Geary, 2001; Messina et al., 2006; Shen et al., 2010; Zhu et al., 2013).

In women, caloric intake varies across the menstrual cycle. Women tend to eat less during the 4-day periovulatory phase of the menstrual cycle when estradiol reaches its peak and these cyclic changes in feeding are absent in women with anovulatory cycles (Barr et al., 1995; Buffenstein et al., 1995; Davidsen et al., 2007; Lissner et al., 1988). Consistently, cycling female rodents consume different amounts of food across their 4-day ovarian cycles, consuming the least during diestrus, which occurs right after preovulatory rise in estradiol secretion, and consuming the most during estrus when estradiol levels are lower indicating physiologic estradiol levels are negatively correlated with food intake (Asarian and Geary, 2013; Tarttelin and Gorski, 1971).

Estrogens also protect against weight gain by increasing energy expenditure. Many postmenopausal women gain body weight due the natural decrease in endogenous estradiol levels during menopause and reductions in energy expenditure can be prevented by estrogen replacement therapy (Gambacciani et al., 1997). Additionally, postmenopausal women have a lower fat oxidation and energy