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Review

Management of obesity in menopause: Diet, exercise, pharmacotherapy and bariatric surgery

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ABSTRACT

Menopause is characterized by the progressive reduction of estrogens resulting to cessation of menses. It is associated with an increase of cardiovascular risk factors such as hyperglycemia, hypertension, dyslipidemia and of abdominal and/or selective visceral fat mass deposition. Obesity, a modern day epidemic, is promoted by an obesogenic environment that interacts with the genetic background. The result is a positive energy balance materialized by the accumulation of the adipose tissue. This process is marked by great individual variation. Obesity is also associated with the presence of cardiovascular risk factors. In this review, the main pathophysiologic processes for the increase of obesity in menopause and the possible effects of pre-menopausal obesity regarding the cessation of ovarian function are described. The interactions among the hypothalamic-pituitary-gonadal and -adrenal (stress system) axes and the environment are explored. Furthermore, the therapeutic means that a clinician can employ to help menopausal women to overcome the menopause-associated increase of their weight are developed.

Contents

1. Introduction

Menopause is defined as a transition period, characterized by the progressive reduction of estrogens and the classically described signs and symptoms. The severity of certain menopausal symptoms worsens from various individual co-factors such as age of onset and overall duration of menopause while weight increase might contribute to decrease of quality of life and self-esteem. The appearance and development of menopausal symptoms as well as the way they affect quality of life can be quantified by the use of a quality of life index such as MENQOL [1].

Obesity, a modern day epidemic, is the clinical result of positive energy balance, reflecting the difference between the caloric

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Table 1
Cardiovascular risk factors including those related to the definition of the metabolic syndrome.

Cardiovascular risk factors		
Non-modifiable	Modifiable	
		Component of the metabolic syndrome
Ageing	Hypertension	Yes
Heredity	Dyslipidemia	Yes
	Obesity	Yes
	Glucose intolerance	Yes
	Smoking	No
	Diabetes mellitus	No
	Sedentarism	No

content of the nutrients ingested through diet and the energy consumed by the body. This positive energy balance is materialized in the form of stored adipose tissue. The amount but also the pattern of adipose tissue storage showcases great individual variation depending on the genetic background of the individual and environmental factors. It depends also on the gender and the age of the individual [2]. The intervention on the obesogenic environment, which favors restricted mobility and high caloric intake, is considered as the key factor for controlling obesity in population scale, especially in developed countries. A factor of special importance is the stress response which influences and it is influenced by the aforementioned factors. Obesity is associated with insulin resistance, diabetes mellitus 2 (DM2), dyslipidemia, hypertension, cholelithiasis, some forms of cancer, steatosis hepatis, gastroesophageal reflux, obstructive sleep apnea, degenerative joint disease, gout, lower back pain and polycystic ovary syndrome. To refine knowledge on pathophysiology as well as to measure these interactions for eventual interventional purposes several biochemical and hormonal substances have been proposed as markers [3].

Post-menopausal women showcase an increase of incidence of cardiovascular heart disease (CHD) risk factors such as hyperglycemia, hypertension and dyslipidemias (Table 1) [4,5]. In addition, during menopause there is an increased deposition of abdominal fat as compared to peripheral fat [6,7]. Furthermore, recent studies, described elsewhere in the text, reveal various effects of pre-menopausal body mass index (BMI) on cycle length, FSH and E2 concentrations depending on menopausal status and individual factors such as age and ethnicity. This information stresses the importance of preexisting increased abdominal fat deposition on the timing of the cessation of ovarian function [8,9]. Because obesity epidemic spreads and life expectancy increases the coexistence of obesity and menopause is expected to further aggravate the individual's CHD risk.

In this review the main pathophysiologic processes for the increase of obesity in menopause are described evoking interactions of the hypothalamic-pituitary-gonadal and -adrenal (HPA) axes between them and the environment as well. In addition, the therapeutic means that a clinician can employ to help menopausal women to overcome the menopause-associated increase of their weight are developed.

2. Epidemiology of obesity in menopause

Obesity is rising throughout Europe and at least 135 million EU citizens are affected. More than half of European population is overweight (BMI greater than 25 kg/m^2) and obese (BMI greater than 30 kg/m^2) and almost a third are estimated to be obese. During the past 25 years, the incidence of obesity in Europe increased in different proportions from country to country [10]. In several countries obesity is more common in women [11,12]. On the other hand, the gradual ageing of the European population leads to a subsequent gradual increase of the total number of post-menopausal women. With menopause body weight and specifically abdominal obesity increases selectively [13]. Consequently, the combined increase of obesity and menopause leads to an exponential increase of risk for CHD and diabetes, two conditions that affect seriously the cost-effectiveness of the health care system [14].

Studies suggest that the fluctuation of female sex hormones at menarche, pregnancy and menopause may contribute to obesity associated with these hormonal states [15]. The menopause-related decrease of estrogens has been directly associated with body weight and abdominal fat increase [15]. Further epidemiologic studies of post-menopausal women treated with hormone replacement therapy (HRT) confirm that while estrogen deficiency is associated with weight gain, replacement with HRT is associated with weight loss (or significantly smaller weight gain) [16]. However, a number of studies are inconclusive as to whether body weight gained in midlife of women is due *per se* to the hormonal changes occurring prior, during and after menopause [17–19].

3. Hormonal changes and obesity in menopause

3.1. Role of estrogens in the regulation of the adipose tissue mass-distribution and total cardiovascular risk during peri- and post-menopausal period

Adipose tissue distribution and metabolism is dimorphic in humans, with women exhibiting more extensive body fat mass, as well as greater percentage of subcutaneous adipose tissue compared to men [20]. Estrogens have an indirect role in the regulation of appetite and body fat by acting through other tissues that regulate appetite, energy expenditure or metabolism. Estrogen receptors are widely distributed in the hypothalamus, the primary site in the brain that regulates energy balance, and the effects of estrogens on both energy intake and expenditure are well known [20,21].

The increase of visceral adipose tissue, occurring in women 3–4 years prior to menopause, correlates with circulating decreasing E2 and with concurrent increasing serum FSH [6,7]. These changes have been related to the changes of adipose tissue metabolism [15]. Estrogens influence adipose tissue lipoprotein lipase activity and increase lipolysis [22]. Estradiol can indirectly affect lipolysis by inducing the lipolytic enzyme hormone-sensitive lipase or by increasing the lipolytic effects of epinephrine [23]. Interestingly, it has been shown that estradiol administration attenuates lipolytic response in subcutaneous abdominal adipocytes, but not in adipocytes isolated from the visceral fat depot [24]. On this line estrogens attenuate the lipolytic response through up-regulation of the antilipolytic alpha2A-adrenergic receptors only in subcutaneous and not in visceral fat depots an effect which disappears in the menopausal period [24]. On the other hand, a recent longitudinal study in a limited number of menopausal women showed an overall increase of total abdominal fat (both subcutaneous and visceral) without preponderance of visceral fat accumulation [25]. Evidence indicates that estrogens and adipose tissue estrogen receptors are involved in the regulation of energy metabolism pathways from glucose transport to glycolysis [26].

Abdominal accumulation of adipose tissue, and the concomitant insulin resistant dyslipidemic state are important components of a cluster of metabolic abnormalities that are strongly related to CHD (Table 1). Estrogens appear to play a direct role to the vascular endothelial function, causing vasodilation while also protecting from atherosclerosis *via* their anti-inflammatory and lipid lowering effects [27]. Lipids (total cholesterol, LDL, triglycerides, Lp(a)) peak