Obesity and Metabolic Syndrome: Impact and Relationship with Menopausal Transition

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16.1 Introduction

The World Health Organization defines obesity as a chronic condition, characterized by excessive weight gain due to extreme fat mass deposition that negatively affects health and quality of life. Obesity has a multifactorial etiology, with an increased incidence in the overall population, in particular during childhood and adolescence, and its prevalence will further increase over the next few decades.

In the Italian population, one third of women are overweight or obese [1]. It is well known that there are two different kinds of obesity: visceral or central obesity (android) and peripheral obesity (gynoid). Central obesity, typical of men and postmenopausal women, is characterized by an increase in waist circumference, as measured using a waist/hip ratio (WHR) of more than 0.80. In gynoid obesity, which is typical in fertile women, fat is mainly localized in the thighs and buttocks. This different fat distribution reflects the different body structure of males and females, because of the ancestral role of the two genders: the man's abdominal obesity permits hunting and escaping, while gynoid fat distribution protects pregnancy in both mechanical and metabolic ways [2]. Moreover, around menopausal transition, many women experience weight gain and an increase in central adiposity. Central/visceral obesity is associated with important changes in lipid and glucose profiles, insulin resistance and/or diabetes mellitus, with an increase in metabolic and cardiovascular risk. The central and the peripheral fat mass also present structural differences in the fat cell: the adipocytes of gynoid obesity have few sides, a higher insulin sensibility, and greater density of estrogenic receptors, thus promoting higher fat mass deposition than in the android fat cells. On the contrary, the latter are more

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responsive to androgenic stimulation and produce and release a greater amount of pro-inflammatory adipocytokines in the portal circulation. The different estrogenic or androgenic responsiveness of the fat mass cells, depending on the site of fat deposition, may explain the reason for the different obesity localization in the two genders and during a woman's life [3].

A positive relationship exists between the waist girth increase and the worsening of the cardiovascular profile, even in people of normal weight, especially women [4]. In fact, more than body mass index (BMI), the main positive predictive factor of the negative impact of obesity on health is abdominal fat. According to the International Diabetes Federation (IDF) criteria, the waist circumference is the main diagnostic element of metabolic syndrome, which inextricably links the visceral adiposity with the worsening of the metabolic profile (Table 16.1).

The metabolic syndrome represents a whole heterogeneous disorder that correlates with high mortality and morbidity rates and high economic and social costs. The syndrome affects 20–25 % of the general population with an increased prevalence with aging, in particular among older people 50–60 years of age. The characteristics of the syndrome are visceral obesity, abnormal lipid and glucose metabolisms and high blood pressure: the specific pathophysiological feature is represented by insulin resistance, which may explain each of the metabolic impairments: the insulin resistance promotes the storage of fat tissue at a visceral level, less sensitive to insulin action, and as a consequence a higher lipolytic function may increase the release of non-esterified fatty acids (NEFAs) into the liver circulation. These NEFAs cause abnormal synthesis of glucose and triglycerides that in turn compromises hepatic insulin clearance. Furthermore, the fat mass is not considered to be simply an energetic store but an active endocrine tissue that releases a large number of adipocytokines, some of which have pro-inflammatory and pro-atherogenic functions (TNF α, IL-6, leptin, adiponectin, etc.) with an active role in modulating insulin sensitivity: for example, the reduced secretion of adiponectin plays a crucial role in inducing insulin resistance, but also in determining the clustering of elevated triglycerides and small, dense LDL particles. Increased leptin secretion may be responsible for sympathetic nervous system overactivity and hypertension, while reduced omentin may play an important role in the development of atherogenic processes [5].

Insulin resistance promotes sodium retention at the kidney level, with a consequently negative impact on blood pressure homeostasis. Finally, when the pancreatic compensatory mechanisms for insulin resistance become inadequate, the fasting glucose increases and, because of the reduced glucose cell intake, diabetes progresses: the metabolic syndrome is taking place (Fig. 16.1).

Insulin resistance, in turn, may be dependent on different problems: an intrinsic/structural cell disorder, owing to receptoral or post-receptoral function defects, or an acquired disorder, such as excessive weight (overweight or obesity), which increases the amount of fat and induces a change in the receptor binding ability of hormones. Insulin resistance is also dependent on familial predisposition, especially when there are diabetic relatives and often with the combination of many of the elements described above.

Table 16.1 The differences in the diagnostic criteria for metabolic syndrome

	WHO (1999)	ATP-III (2001)	IDF (2005)
Fasting glucose	Diabetes mellitus, impaired glucose tolerance	>110 mg/dl	>100 mg/dl or previously type-II diabetes
Blood pressure	≥140/90 mmHg or use of medication	>130/85 mmHg or use of medication	>130/85 mmHg or use of medication
Dyslipidemia (TG)	≥150 mg/dl	≥150 mg/dl	≥150 mg/dl
Dyslipidemia (HDL-CH)	<35 mg/dl for males	<40 mg/dl for males	<40 mg/dl for males
	<39 mg/dl for females	<50 mg/dl for females	<50 mg/dl for females
Central obesity	WHR >0.9 in males	Waist circumference	Waist circumference
	>0.85 for females and/or BMI >30	≥102 cm for males	>94 cm for males
		≥88 cm for females	>80 cm for females of Caucasian race
Microalbuminuria	Urinary albumin excretion ratio ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g		
Diagnostic criteria	MD type II or IGT and two criteria	Three or more criteria	Central obesity and two criteria

WHO World Health Organization, ATP-III National Cholesterol Education Program-Adult Treatment Panel III, IDF International Diabetes Federation, TG triglycerides, HDL-CH high-density lipoprotein cholesterol, WHR waist/hip ratio, BMI body mass index

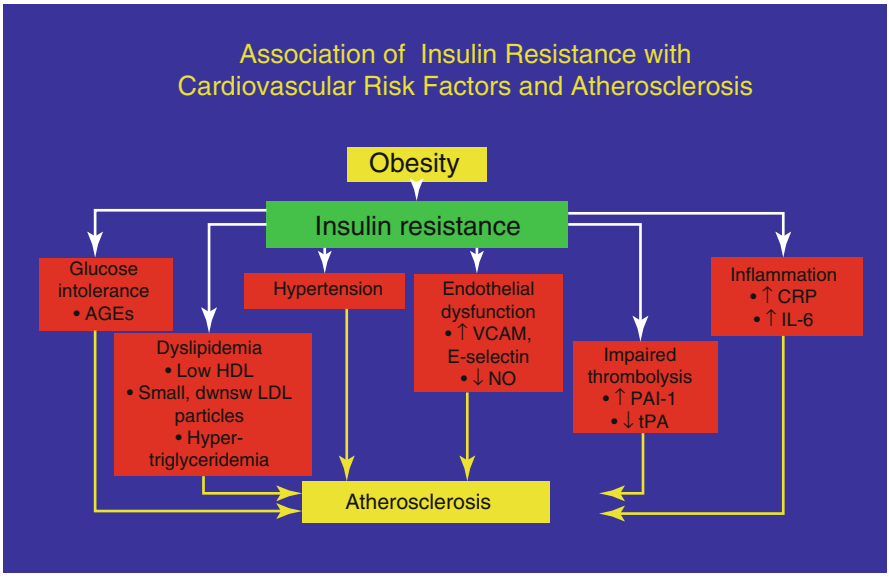

Fig. 16.1 The metabolic impact of the combination of obesity and insulin resistance and cardiovascular risks

16.2 Relationship Among Obesity, MS and Menopausal Transition

As we know, menopausal transition is characterized by an early (approximately 10 years before the start of the menopause) and a progressive increase in FSH levels, linked to a decrease in inhibin production by the ovaries; at the same time, the higher frequency of anovulatory cycles induces a decrease in progesterone during the luteal phase, resulting in relative hyperestrogenism, followed by a long period of hypoestrogenism when the menopause has actually taken place.

At present, although a large number of publications have been produced, the change in body weight during menopausal transition represents a important topic of discussion.

Usually, the modifications of weight are dependent on an increase in energetic impute and/or a decrease in energy consumption, mostly because of physical activity and resting energy expenditure. It is well known that women after the age of 45–50 years, in the absence of changes in their lifestyle (feeding and physical activity), show a progressive increase in bodyweight. What is the cause of this?

Whereas weight gain per se cannot be attributed to the menopause transition, the change in the hormonal milieu at menopause is associated with an increase in total body fat, and in particular there is an increase in abdominal fat [6]. Lovejoy et al. [7] showed that progressively, during perimenopause, there is an increase in abdominal fat mass, concomitant with climacteric hypoestrogenism, with a slow increase in weight despite the reduced trend in total calorie intake (Fig. 16.2).

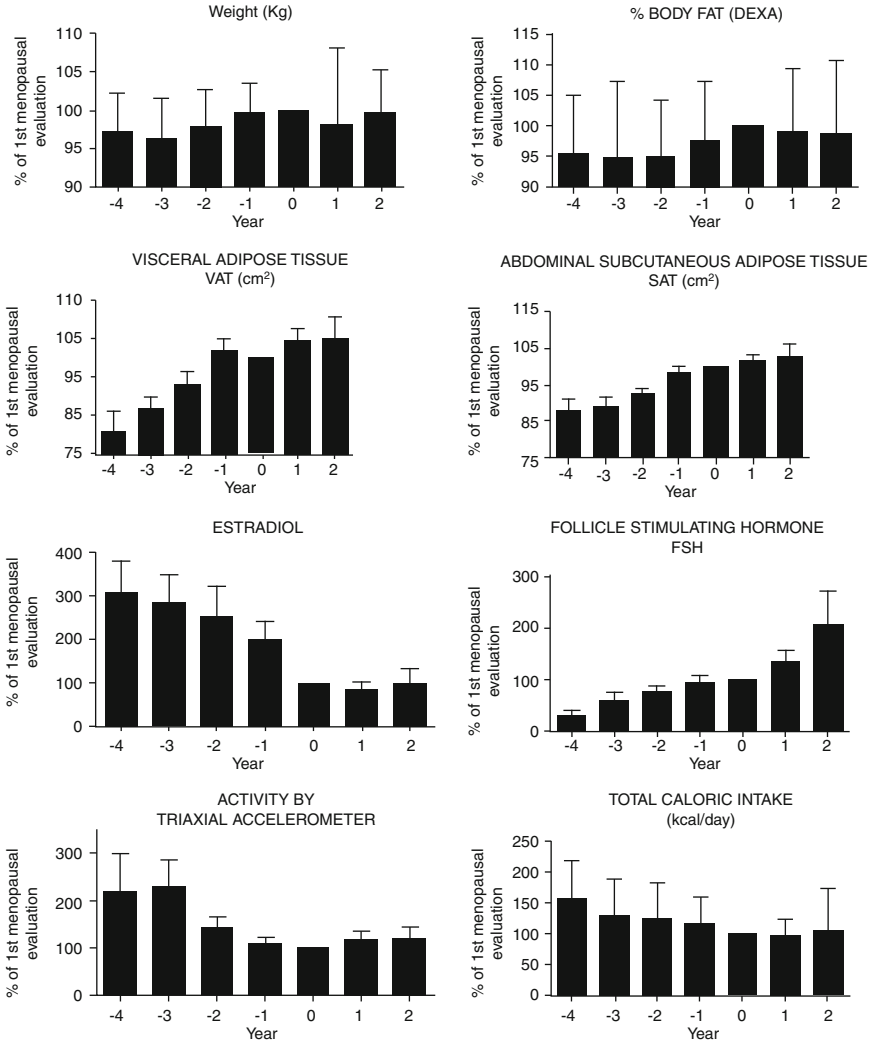

Fig. 16.2 Despite weight that remains the same, there is an increase in body fat mass and in visceral adipose tissue (Modified from Lovejoy et al. [7])

From the clinical point of view, it is important to know the metabolic condition of our patients: during reproductive life, they may have suffered from some metabolic disorders, including thyroid dysfunction or mellitus diabetes and/or insulin resistance, as in the case of polycystic ovary syndrome (PCOS) or a history of being overweight/having obesity. The exposure to environmental factors, until the beginning of childhood, can affect the normal weight and worsens it: in general, personal health history affects the metabolic change that occurs during menopausal transition.

The gonadal steroid hormones have specific metabolic effects during perimenopausal transition. As mentioned before, menopausal transition is characterized by

alternating hypoestrogenic and/or hyperestrogenic periods with low progesterone levels. Indeed, during the luteal phase of the menstrual cycle, the typical increase in P/E2 ratio induces an increase in body temperature of about 0.4 °C [8]: this temperature rise causes an elevation of basal metabolism of about 200 kJ (50 kcal) per day [9]. On the contrary, the absence of a progesterone increase during menopausal transition determines the lack of energy consumption under resting conditions typical of the luteal phase (about 50 kcal a day, for 12–14 days: approximately 600–700 kcal every month). This event is at the basis of the increase in fat mass deposition during the perimenopause [10] and does not induce the physiological burning of calories during the luteal phase.

This decline in energy consumption seems to be not exclusively dependent on progesterone deficiency but also on other factors, such as the amount of lean mass, the activity of the sympathetic nervous system (SNS), the endocrine status and the ageing-mediated physiological changes. In fact, the decline in basal metabolism observed in post-menopausal women may also depend on aging [11]. However, the basal metabolism decreases more during menopausal transition than could be attributed to the aging process [12]. Oestrogen depletion probably contributes to the acceleration of this decline. As the perimenopause becomes the menopause, the progressive reduction of oestrogen levels induces a progressive worsening of the insulin resistance, which is also increased owing to the concomitant cortisol increase (typical of aging and the menopause). This latter event induces gluconeogenesis and further promotes insulin resistance. The hypoestrogenism also partly induces a fall in GH levels, which produces an increase in the storage of abdominal fat mass with a decrease in lipid metabolism [13, 14].

Further confirmation of the role of oestrogen in fat mass control comes from experimental studies on animal models where in ovariectomized mice, the oestrogen treatment reduces the fat mass and the adipocyte cell size, independently of the energy intake. In particular, oestradiol seems to accelerate the fat oxidation pathways in the muscles and adipocyte lipolysis [15].

In summary, the decrease in basal metabolism induces the gain in fat mass which, in turn, may contribute to improving the incidence of obesity-related diseases, such as worsening of the cardiovascular profile and type II diabetes. The increase in visceral adiposity further worsens insulin sensitivity, in particular at the liver level, so that higher amounts of insulin are needed to control glucose intake at tissue levels. All these changes determine the increase in the rate of incidence of the metabolic syndrome in overweight/obese women during the menopausal transition.

Recently, it has been suggested that another possible link between menopausal hypoestrogenism and appetite control/weight gain is the increase in levels of orexin-A plasma [16]. This recently discovered hypothalamic neuropeptide is involved in the regulation of feeding behavior, of the sleep–wake rhythm and of neuroendocrine homeostasis [17, 18]. In post-menopausal women, while estrogens are at low levels, plasma orexin-A levels are significantly higher, being part of the induction for some cardiovascular risk factors, such as blood glucose, lipid profile, blood pressure and body mass index [19].

16.3 The Approach to Obesity and Metabolic Syndrome During Perimenopause

The approach to overweight/obese pre-menopausal women has to consider and evaluate a careful anamnesis and medical investigation, especially with regard to the age at obesity onset, any recent relevant weight change and if there are any members of the family with diabetes or other endocrinological diseases and/or obesity The purpose of this check is to exclude any clinical cause that might require specific therapeutic approaches, such as any uncommon secondary obesities, due to genetics, neurological or psychiatric conditions.

It is important to know if the patient has suffered in the past with PCOS and/or premenstrual syndrome and premenstrual dysphoric disease (PMS-PMDD). It is well recognized that insulin resistance is a frequent feature of the PCOS, especially for 50–60 % of the patients who are overweight/obese [20]. Moreover, we recently demonstrated [21] that people with PCOS and insulin resistance have a double chance of suffering from PMS-PMDD and mood disorders up to depression, during their reproductive life, mostly during menopausal transition. This condition seems to be due to reduced production of neurosteroids, in particular allopregnanolone, which is the most powerful endogenous anxiolytic and anti-depressant substance derived from progesterone catabolism [22]. These PCOS and hyperinsulinemic patients, during menopausal transition, are at a higher risk of suffering from more intense climacteric symptoms, in particular those due to neurosteroid deficiency (allopregnanolone), such as mood disorders, depression and anxiety, if they did not undergo a specific treatment to reduce insulin resistance and weight gain [23].

In addition to the clinical investigation, it is therefore necessary to assess the presence of insulin resistance, even in non-obese women; in fact, these patients may have a normal weight thanks to their lifestyle even though they have a predisposition to insulin resistance that is only disclosed by undergoing an oral glucose tolerance test (OGTT). This test is usually carried out over 4 h, but a positive response to this test can equally be achieved with just two blood samples, at time 0 (i.e. before drinking the glucose) and 60 or 90 min after a glucose load of 75 g of sugar: an insulinemic state is diagnosed when the insulin response is higher than 60 μU/ml [24, 25]. In women with a history of PCOS, insulin resistance has been demonstrated frequently during both pre- and post-menopause (Fig. 16.3) [26].

The therapeutical approaches for women during menopausal transition have to consider the body weight at the moment of the perimenopausal transition: women of normal weight and overweight/obese women should be treated differently. In the first case, the approach targets the prevention of weight gain, while in the latter group it is important to avoid a further weight increase, and/or to treat the metabolic abnormalities. In both cases, the first recommendation is a modification of lifestyle through the combination of a hypocaloric diet with physical activity.

Endurance training (aerobic exercise for 45 min a day, three sessions per week) has been shown to promote body weight and fat mass losses and to reduce waist girth and blood pressure in overweight/obese women. Moreover, these interventions

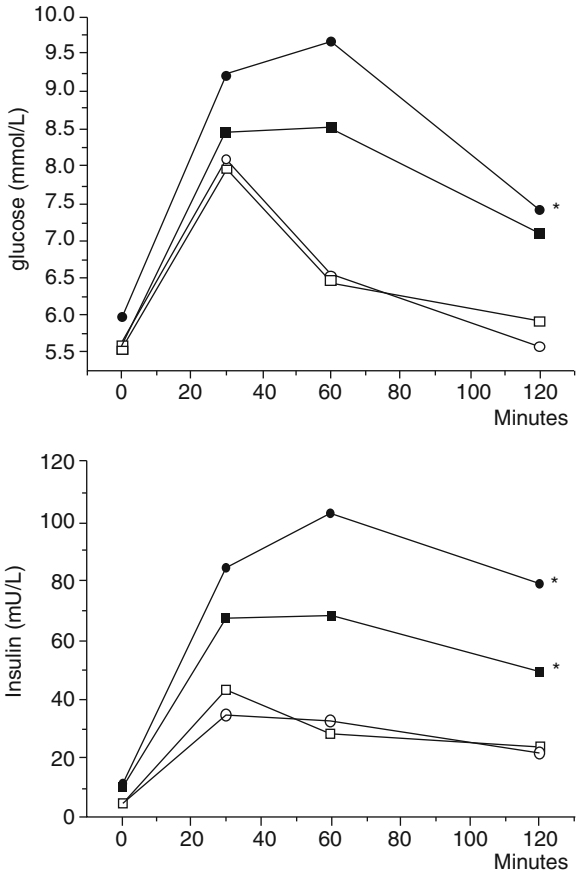

Fig. 16.3 The area under curve (AUC) is significantly higher in pre-/postmenopause groups of women with polycystic ovary syndrome (PCOS) than in control groups (Modified from Puurunen et al. [26]). □ pre-menopause control, ○ post-menopause control, ■ pre-menopause PCOS, ● post-menopause PCOS

decrease plasma triglyceride, cholesterol and low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol concentrations; the greatest improvement in metabolic risk profile has been observed in women with two or more determinants of the metabolic syndrome, but still with no coronary heart disease [27]. In addition, physical exercise amplifies triggers of an anorectic response, limiting the consumption of food [28]. Unfortunately, the association of diet and physical activity is effective in the short period, but is less valid for maintaining the weight loss in the long term.

In women of normal weight with climacteric symptoms, hormonal replacement therapy (HRT) has been successfully demonstrated to protect against perimenopausal changes in body composition [29, 30]. In these patients, no significant variations in weight, fat mass content and distribution have been observed, probably also thanks to the route of administration of HRT. In particular, transdermal estrogens seem to be more protective against fat mass increase and android fat distribution [31, 32]. Similar effects on body composition and on fat tissue have been observed when administering tibolone and raloxifene.

In obese women during menopausal transition, behavioral therapy is essential to achieve the weight control in the long term, but there are some medications such as metformin, inositol, orlistat, etc. that may help and facilitate weight loss. Metformin, a well-known anti-diabetes drug, reduces insulin levels, improving insulin sensitivity through an increase in glucose cell uptake, a treatment often administered to PCOS women during their fertile years. Also, myo-inositol in combination with chiro-inositol integrative administration may enhance insulin sensibility through an improvement in post-receptoral efficiency. Outside of the gynecologist's field of expertise, orlistat is a specific obesity treatment that reduces the absorption of dietary fats, promoting their fecal elimination.

In conclusion, overweight, obesity and metabolic syndrome are tightly linked with the changing of the hormonal pattern during menopausal transition. In fact, the progressively declining levels of estrogens and progesterone induce specific metabolic impairments, as the worsening of insulin resistance or the increasing of central fat mass storage. At the same time, obesity is an important factor that modulates hormone changes during menopausal transition, as women with higher BMI were more likely to enter the earliest transition stage, although they were slower to reach the post-menopausal stage than those with lower BMI [33]. Further, if during the fertile age the women had PCOS associated with overweight/obesity, it is more likely that insulin resistance led to a metabolic syndrome predisposition and to mood disorders, exacerbated by the arrival of the climacteric transition, which clinically happens in 45- to 50-year-old women.

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