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Obesity and gender differences

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Summary. The metabolic syndrome is characterized by the association of cardiometabolic risk factors, leading to increased morbidity and decreased life expectancy, and is closely related to abdominal obesity. Obesity is a major risk factor for several chronic diseases, such as cardiovascular diseases, type 2 diabetes, chronic liver and gallbladder disease, some forms of cancer, osteoarthritis, musculoskeletal disorders, and psychosocial problems. The worldwide prevalence of obesity nearly tripled over the last forty years. Overall, about 13% of the world's adult population were obese in 2016.
In most populations, the prevalence of obesity in adults is greater in women than men, but men are more likely to develop obesity-complicating diseases. Obesity induces a state of chronic, low-grade inflammation, that has been implicated in the development of metabolic syndrome and its associated pathophysiological consequences, such as insulin resistance, cardiovascular disease, and many non-metabolic obesity-related sequelae.
A 5% weight loss improves obesity-related risk factors, and its benefits can persist as long as such weight loss is maintained. Weight loss can be achieved via different strategies, including lifestyle interventions, drugs or bariatric surgery. Gender differences in the various therapeutic strategies exist worldwide: men prefer to exercise, while women are more likely to join weight-loss programs, take prescription diet pills, and follow special diets. Intensive lifestyle interventions are difficult to achieve and maintain over a long period of time. Pharmacotherapy is the second-line treatment for obesity, but in Europe only orlistat, liraglutide and the fixed combination of naltrexone and bupropion are available. Weight loss obtained by bariatric surgery significantly impacted the number of hospitalizations due to obesity-associated risk factors and reduced the incidence of diabetes, hypertriglyceridemia and hyperuricemia, as well as cancer and overall mortality. Gender differences in the prevalence of obesity and its complicating diseases do exist, but the exact mechanisms are yet to be fully clarified.

Key words. Metabolic syndrome, obesity, obesity-complicating diseases, gender differences, chronic low-grade inflammation, diabetes, steatosis, obstructive sleep apnea, cancer, weight loss strategies.

Obesità e differenze di genere

Riassunto. La sindrome metabolica è caratterizzata dall'associazione di fattori di rischio cardiometabolico che portano a un aumento della morbilità e a una riduzione della spettanza di vita, ed è strettamente legata all'obesità addominale. L'obesità è uno dei più importanti fattori di rischio per molte malattie croniche, quali malattie cardiovascolari, diabete mellito tipo 2, malattie di fegato e colecisti, alcune forme di cancro, malattie osteoarticolari e problemi psicologici. Nel mondo la prevalenza dell'obesità è triplicata negli ultimi 40 anni e nel 2016 circa il 13% della popolazione adulta era obesa.
Nella maggior parte del mondo la prevalenza dell'obesità negli adulti è maggiore nelle donne rispetto agli uomini, ma gli uomini tendono a sviluppare con più facilità le complicanze dell'obesità. L'obesità induce uno stato di infiammazione cronica di basso grado responsabile dello sviluppo della sindrome metabolica e delle sue conseguenze fisiopatologiche, quali l'insulinoresistenza, le malattie cardiovascolari e le altre complicanze non metaboliche dell'obesità.
Il calo di peso di almeno il 5% riduce tutti i fattori di rischio legati all'obesità e i suoi benefici persistono finché il calo ponderale viene mantenuto. Il calo di peso può essere raggiunto con differenti interventi terapeutici, quali le modifiche dello stile di vita, i farmaci e la chirurgia bariatrica. Esistono alcune differenze di genere nella scelta delle diverse opzioni terapeutiche, gli uomini preferiscono l'attività fisica, mentre le donne prediligono programmi di calo ponderale con farmaci e diete specifiche. I programmi intensivi di cambiamento dello stile di vita sono difficili da raggiungere e seguire nel lungo periodo. La terapia farmacologica è considerata la seconda linea di trattamento nell'obesità, ma in Europa sono in commercio solo l'orlistat, la liraglutide e l'associazione naltrexone-bupropione. Il calo ponderale più significativo e duraturo nel tempo nella maggior parte dei casi si ottiene con la chirurgia bariatrica, che porta a una significativa riduzione dei fattori di rischio associati all'obesità e dell'incidenza di diabete, ipertrigliceridemia, iperuricemia, cancro e mortalità per tutte le cause. Esistono sicuramente delle differenze di genere nella prevalenza dell'obesità e nelle malattie a essa associate, ma i meccanismi sottostanti necessitano di ulteriori approfondimenti e chiarimenti.

Parole chiave. Sindrome metabolica, obesità, malattie correlate all'obesità, differenze di genere, infiammazioni croniche di basso grado, diabete, steatosi, apnea ostruttiva del sonno, cancro, strategie di perdita di peso.

Introduction

The metabolic syndrome is a condition characterized by the association of cardiometabolic risk factors, including obesity, dyslipidemia, hypertension, impaired fasting glucose, proinflammatory and prothrombotic state.[1] First described by Reaven,[2] the metabolic syndrome is believed to be the pathophysiological background for chronic diseases, including cardiovascular disease[3] and type 2 diabetes mellitus, leading to increased morbidity and decreased life expectancy.[4] The metabolic syndrome defining criteria have been established by multiple agencies over time, but the most frequently used are those published by the National Cholesterol Education Program (NCEP)/Adult Treatment Panel[5] and the International Diabetes Foundation[6] (Table 1). In 2009 IDF and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to reconcile the different clinical criteria, thus leading to a 'harmonized' definition of the metabolic syndrome[7] (Table 1 and 2). All criteria consider the metabolic syndrome closely associated with abdominal obesity. Moreover, the rise in the metabolic syndrome prevalence is mainly due to a rise in obesity rates among adults.

Obesity is defined as an abnormal or excessive fat accumulation, which is classified on the basis of the Body Mass Index (BMI). Obesity is defined as a BMI 30 kg/m^2 or greater, while the range 25-30 identify overweight.[8] Excess body weight is an important risk factor for mortality and morbidity. In a large, pooled analysis of prospective studies, both overweight and obesity were associated with an increase in all-cause mortality in subjects who never smoked and had not been diagnosed with cancer or heart disease.[9] Since several studies described a U-shaped association between BMI and all-cause mortality,[9,10] it had been suggested that overweight might be protective.[11] However, a recent population cohort study observed a J-shaped association between BMI and mortality, with an increase of risk above 21-25 kg/m^2 for most outcomes, including all-cause mortality, cardiovascular disease, and cancer. This association was stronger at a younger age versus older, with a BMI associated with a lowest mortality risk being higher in older individuals, and in men versus women.[12]

Obesity is a major risk factor for several non-communicable chronic diseases, such as cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012, type 2 diabetes, chronic liver and gallbladder disease, some forms of cancer, osteoarthritis, musculoskeletal disorders, and psychosocial problems (Figure 1), causing each year nearly three million deaths worldwide.[13-15] After high blood pressure, smoking, high blood glucose, and physical inactivity, overweight and obesity are the fifth leading global risk factor for mortality worldwide,[14] with large decreases in life expectancy and increases in early mortality. The extent of life expectancy loss is similar to that associated with smoking.[16] At global level, overweight and obesity cause more deaths than underweight; the combined burden of these diet-related risks and physical inactivity in low- and middle-income countries is similar to that caused by HIV/AIDS and tuberculosis. Combining the

Table 1. Diagnostic criteria for the metabolic syndrome according to NCEP/ATPIII, IDF and the IDF/NHLBI/AHA/WHF/IAS/IASO Joint Interim Statement (from Ahmed A et al,[120] and Alberti KGMM et al,[7] modified)

	NCEP/ATP III **Any three or more of the five components**	**IDF** **Central obesity (prerequisite) plus any two of the four other criteria**	**'Harmonized' criteria** **Any three or more of the five components**
Central obesity Increased waist circumference	Men: ≥102 cm Women: ≥88 cm (*Ethnicity specific cut-off. For South Asians ≥90 cm in men, ≥80 cm in women)	Men: ≥94 cm Women: ≥80 cm (*Ethnicity specific cut-off. For South Asians ≥90 cm in men, ≥80 cm in women)	Population- and country-specific definitions (see Table 2)
Raised triglycerides	>150 mg/dL or drug treatment for elevated triglycerides	>150 mg/dL or drug treatment for elevated triglycerides	>150 mg/dL or drug treatment for elevated triglycerides
Reduced HDL cholesterol	Men: <40 mg/dL Women: <50 mg/dL	Men: <40 mg/dL Women: <50 mg/dL	Men: <40 mg/dL Women: <50 mg/dL
Raised fasting plasma glucose	≥100 mg/dL or previously diagnosed type 2 diabetes	≥100 mg/dL or previously diagnosed type 2 diabetes	≥100 mg/dL or drug treatment of elevated glucose
Hypertension	≥130/85 mm Hg or drug treatment for elevated blood pressure	≥130/85 mm Hg or drug treatment for elevated blood pressure	≥130/85 mm Hg or drug treatment for elevated blood pressure

Table 2. Current recommended waist circumference thresholds for abdominal obesity (from Yoon et al,[121] modified)

Population	Organization	Male, cm	Female, cm
Europid	IDF	≥94	≥80
Caucasian	WHO	≥94 (increased risk) ≥102 (higher risk)	≥80 (increased risk) ≥88 (higher risk)
United States	AHA/NHLBI (ATP III)	≥102	≥88
Canada	Health Canada	≥102	≥88
European	European Cardiovascular Societies	≥102	≥88
Asian	IDF/WHO	≥90	≥80
Korean	KSSO	≥90	≥85
Japanese	Japanese Obesity Society	≥85	≥90
China	Cooperative Task Force	≥85	≥80
Middle East, Mediterranean, Sub-Saharan African	IDF	≥94	≥80
Ethnic Central and South American	IDF	≥90	≥80

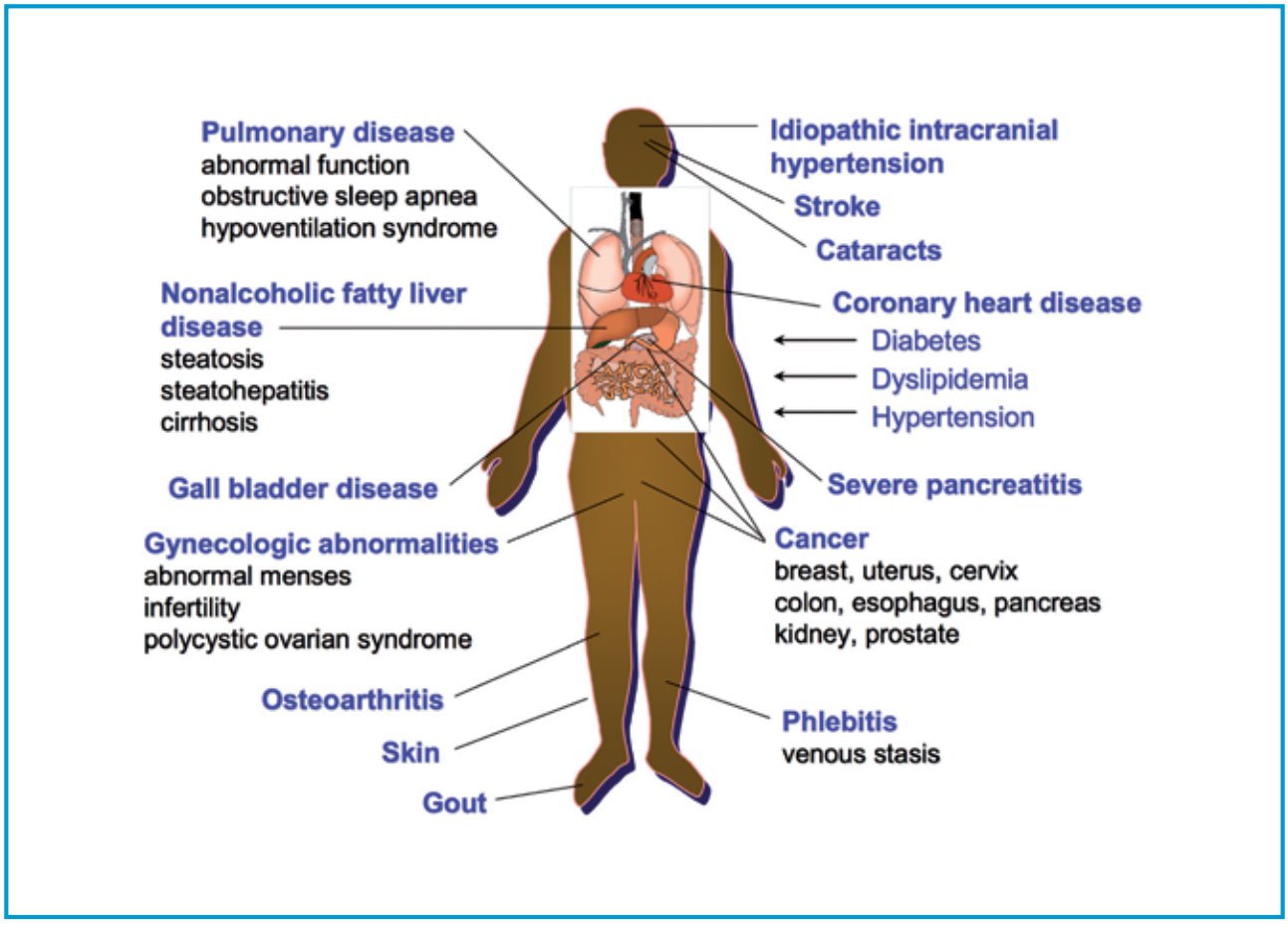

Figure 1. Medical complications of obesity (from Bhoyrul et al,[122] modified).

information about morbidity and mortality and the numbers of healthy years lost by the DALY (Disability-Adjusted Life Year) approach, the loss due to high BMI is over 30 per-mil of the population in Europe.[14]

Considering the growing number of obesity-complicating diseases, this review will focus on type 2 diabetes mellitus, the condition most closely associated with obesity, as well as on some emerging issues, such as nonalcoholic fatty liver disease, obstructive sleep apnea and cancer, trying to highlight any gender differences in the epidemiology and pathophysiological mechanisms.

Epidemiology of obesity

Between 1980 and 2008, age-standardized mean BMI increased globally by 0.4 kg/m^2 per decade in men, and by 0.5 kg/m^2 per decade in women.[17] Among US adults, the mean weight increased more than 10 kg between 1960 and 2002.[18]

The global prevalence of obesity nearly tripled between 1975 and 2016;[8] also, the increasing rate accelerated. In fact, the global, age-standardized prevalence of obesity nearly doubled, from 6.4% in 1980 to 12.0% in 2008. Half of this increase occurred in the 20 years between 1980 and 2000, and half occurred over the 8 years between 2000 and 2008. The age-standardized prevalence of overweight increased from 24.6% to 34.4% during the same 28-year period. [19]

In 2016, 39% of adults aged 18 and older (39% of men and 40% of women) were overweight. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. In absolute numbers, more than 1.9 billion adults aged 18 and older were overweight. Of these, over 650 million were obese.[8]

In most populations, the prevalence of obesity in adults is greater in women than in men.[20] Although the women's reproductive role is implicated in the female excess of obesity,[21,22] this phenomenon is not distributed equally across countries, being rather more common in countries characterized by low gross domestic product, high income disparity and high gender inequality.[23] This observation suggests that, in addition to the biological and behavioral factors, socio-economic factors could also contribute to gender differences in the prevalence of obesity.

The prevalence of the metabolic syndrome varies depending on the defining criteria, but in the United States it has been reported to range from one-fourth to one-third of the adult population.[24] In recent decades, the prevalence of abdominal obesity in the US has increased more in women than in men[25] and today, in many countries around the world, the prevalence of visceral obesity associated with metabolic syndrome is two to ten times higher in women.[26,27] Like obesity, the metabolic syndrome appears to be on the rise, particularly in women and with age, with the greatest prevalence seen in adults aged 60 or older.[28] Some ethnic groups in the United States are at higher risk for the metabolic syndrome than others. In fact, African Americans and Mexican Americans are more likely to suffer from the metabolic syndrome; African-American women are about 60% more likely than their male counterparts to develop the syndrome.[29]

Complications of obesity: low-grade chronic inflammation and gender differences

While women present higher obesity rates than men, men are more likely to develop obesity-complicating diseases. Women have a lower prevalence of diabetes,[30] and for any given combination of risk factors, men with metabolic syndrome present a 2-fold risk of heart attack and stroke compared to women.[31] On the other hand, after menopause females exhibit an elevated risk of developing metabolic disorders, due to the decline of estrogen levels and to the higher proportion of testosterone,[32] that drives an increase in visceral adiposity.[33] However, menopausal hormone therapy has had little success in improving metabolic disorders.[34,35] So, while it is evident that they are involved in the onset of metabolic disorders, the exact role of sex hormones remains unclear.

Obesity – and visceral obesity in particular – is known to induce a state of chronic, low-grade inflammation, that has been implicated in the development of the metabolic syndrome and its pathophysiological consequences, such as insulin resistance, cardiovascular disease, and many non-metabolic obesity-related sequelae.[36] The relation between obesity and a pro-inflammatory state has largely been associated with adipose tissue inflammation, through the activation of leukocytes[37] and the production of several pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, tumor necrosis factor-α (TNF-α), and chemokines, such as monocyte chemoattractant protein-1 and its receptor, CCR2.[38] These signals originate in the visceral adipose tissue, and produce systemic effects. Sex steroid hormones modulate and affect gender-related adipose tissue distribution. Males preferentially expand adipocytes in the visceral adipose tissue, while females may expand adipocytes in both visceral and subcutaneous fat depots.[39] During menopause, estrogen levels decline, and the proportion of testosterone in women becomes higher, leading to a loss of subcutaneous tissue and a gain in visceral adipose tissue, the latter being associated with increased inflammation and systemic insulin resistance.[33, 40]

The role of sex hormones in the chronic, low-grade inflammation observed in the metabolic syndrome is

still a matter of debate. Men and women have several differences in innate immunity and hematopoiesis,[41] as suggested by the higher prevalence of autoimmune diseases in women, related to a lower expression of toll-like receptor 4 and a lower cytokine production.[42,43] Peripheral blood mononuclear cells (PBMCs) from men produce more pro-inflammatory TNF-α and less protective IL-10 than PBMCs from women, following lipopolysaccharide stimulation.[44] After menopause, women experience an increased production of pro-inflammatory cytokines, that are substantially decreased by the hormone therapy.[45] In addition, women with polycystic ovary syndrome, and who therefore have an excess of androgens, are at a much higher risk for metabolic syndrome.[46] Estrogens have been reported to have anti-inflammatory properties, which contribute to cardiovascular protection, through the upregulation of endothelium-derived nitric oxide.[47,48] On the other hand, the role of androgens in obesity-induced inflammation is less clear, with no direct human studies having been specifically conducted on the role of androgens on immune cells. While androgens may improve β-cell insulin production and muscle and liver insulin sensitivity,[49,50] their role in adipose tissue remains unclear.

Diabetes

Overweight and obesity account for 44% of diabetes cases, 23% of ischemic heart disease patients, and around 7-41% of established cancers.[51] Among these diseases, type 2 diabetes is the most closely associated with obesity. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014[52] – with a more rapid increase in middle- and low-income countries[53] – and the prevalence of obesity-related diabetes is expected to double to 300 million by 2025.[54]

There are considerable gender differences in the response to an oral glucose challenge (OGTT). Women have lower fasting plasma glucose and higher plasma glucose 2 h following an OGTT.[55] This might be due to the smaller muscle mass and different gonadal hormones. In addition, a closer association between visceral adipose tissue and alterations in glucose homeostasis is observed for women versus men.[56] Consequently, the prevalence of pre-diabetic syndromes, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is sexually biased in all the populations studied, IFG being more prevalent in men, and IGT in women.[57-59] The prevalence of type 2 diabetes also differs between sexes, and it varies depending upon the stage of reproductive life.[60] There are more diabetic men before the age of puberty, while there are more diabetic women after menopause. Since the prevalence of diabetes increases with age and in most populations the number of elderly women is greater than that of men, the global prevalence of diabetes is higher in men, although there are more women with diabetes than men.[61]

Steatosis

Nonalcoholic Fatty Liver Disease (NAFLD) is defined as the fatty infiltration of the hepatocytes exceeding 5% of the liver weight in the absence of other causes, such as excessive alcohol intake or hepatitis.[62] NAFLD includes different conditions, from benign hepatic steatosis (Nonalcoholic Fatty Liver, NAFL) to steatosis with necro inflammatory changes and progressive fibrosis (Nonalcoholic Steatohepatitis, NASH), with cirrhosis, liver failure, hepatocellular carcinoma, and a high risk of mortality.[63] NAFLD is commonly associated with Metabolic Syndrome, obesity, diabetes, and hyperlipidemia. Nearly 80% of patients with Metabolic Syndrome have NAFLD.[64] The prevalence of NAFLD in the general population is 25%, but varies dramatically depending on the population being studied (in the United States it is estimated to be around 20%). By contrast, the prevalence of NASH is in the range of 2-3%. The prevalence is higher in white men than white women, but there are no differences between the Hispanic and the African-American population. Mean age at diagnosis is 50 years (range 16-80), and it is more common among Hispanics versus Whites and more common in Whites versus Blacks.[65]

In a recent study conducted in patients with NAFLD, a correlation with a higher BMI and the presence of the metabolic syndrome was found, with no gender differences.[66] The NAFLD prevalence is also increasing in children (pediatric prevalence is 4.2-9.6%).[67] The 'multiple hit' hypothesis is currently the more accepted explanation of the pathogenesis of NAFLD. It considers multiple insults acting together on genetically predisposed subjects. Dietary and environmental factors, together with obesity, lead to raised serum levels of fatty acids (FFAs) and cholesterol, development of insulin resistance, adipocyte proliferation and dysfunction, and changes in the intestinal microbiome. Insulin resistance acts on the adipose tissue, worsening the adipocyte dysfunction, and induces lipolysis and the release of adipokines and proinflammatory cytokines, such as TNF-α and IL-6, which also contribute to maintain the state of insulin resistance. In the liver, insulin resistance amplifies *de novo* lipogenesis. The increased hepatic FFA flux deriving from the above processes, and from an altered activity of the gut microbiome, leads to two different situations: synthesis and accumulation of triglycerides, and 'toxic' levels of fatty acids, free cholesterol and other lipid metabolites, which cause mitochondrial dysfunction with oxidative stress and the production of reacting oxygen

species (ROS) and endoplasmic reticulum (ER) stress, with activation of an unfolded protein response, all leading to hepatic inflammation. Also, small bowel permeability can be enhanced, with a consequent increase in the circulating levels of molecules, which contributes to the activation of inflammasome and ER stress, such as lipopolysaccharide, and to the release of pro-inflammatory cytokines. Genetic factors or epigenetic modifications affect the hepatocyte fat content, the enzymatic processes and the liver inflammatory environment, thus influencing the risk of progression towards inflammation and fibrosis (NASH) or of persistence in a stable stage of disease (NAFLD).[68] Several studies show that, implementing an early intervention before the onset of fibrosis, the prognosis is excellent. However, if the treatment is delayed, and end-stage liver disease develops, the prognosis is poor.[69] At present, an aggressive multidisciplinary strategy for the management of obesity, diabetes, and the metabolic syndrome, with lifestyle modifications and weight loss, is the only effective treatment to reduce the morbidity of fatty liver.

Obstructive sleep apnea

Obstructive Sleep Apnea (OSA) is a clinical condition characterized by recurrent episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway, leading to increased negative intrathoracic pressure, sleep fragmentation, and intermittent hypoxia during sleep.[70] Among adults aged 30 to 70, approximately 13% of men and 6% of women have moderate to severe forms of OSA (apnea-hypopnea index >15 events per hour of sleep).[71] It is estimated that 50 to 60% of obese people and of patients with metabolic syndrome suffer from OSA.[72,73] The prevalence of OSA is even higher in obese patients with diabetes mellitus and morbid obesity.[74,75] Obesity is a major risk factor for OSA not only because it drives several anatomical and functional factors (such as the direct effects on the upper airway and the reduction of lung volume, through a combination of increased abdominal fat mass and recumbent posture), but also due to the obesity-related leptin resistance that may impair the neuroanatomic interactions necessary for a stable breathing.[76] In addition, the development of OSA and the consequent sleep fragmentation may contribute to accelerate weight gain, due to increases in commonly recognized appetite hormones, with subsequent alterations of the eating patterns, including a preference for calorie-dense foods.[77] There is a very strong evidence for OSA as an independent causative factor in the development of hypertension, with the risk increasing with OSA severity. Severe OSA has also been closely associated with an increased risk of stroke, ischemic heart disease, atrial fibrillation and excess mortality.[78] The treatment for OSA is CPAP (a device generating positive air pressure that pneumatically splints the upper airway open), combined with weight loss, which leads to a greater decrease in the cardiovascular risk.[79]

Cancer

Obesity represents a risk factor for a growing list of cancers and is frequently associated to poor clinical outcomes.[80] The hypothesis that the adipose tissue is involved in tumorigenesis is now called 'adiponcosis'.[81] Molecular mechanisms linking obesity and cancer are complex and not entirely clear. A low-grade chronic inflammation, the deregulation of growth signaling pathways, a chronic hyperinsulinemia and obesity-associated hypoxia are widely accepted as pivotal factors in cancer pathogenesis.[82] In particular, the reduction of adiponectin, the principal adipocytokine, in obese patients has been related to an increase in the risk of tumor onset. Adiponectin seems not only to be involved in metabolic responses such as energy metabolism regulation and insulin-sensitivity, but also to have an anti-inflammatory protective role, with anti-proliferative and pro-apoptotic effects, avoiding the development and progression of several malignancies, such as breast, colon, prostate, liver, lung, thyroid and endometrial cancer.[83,84] Breast cancer is a well-known obesity-related cancer.[85] Colorectal cancer is one of the most common obesity-related cancer.[86] Thyroid cancer has remarkably increased worldwide, becoming the second most commonly diagnosed cancer in young women, and is positively associated with an increased BMI and obesity.[87] A report from the World Cancer Research Fund (WCRF) established, more than a decade ago, ten obesity-related cancers, including postmenopausal breast, endometrial, ovarian, advanced prostate, colorectal, renal, pancreatic, liver, and gallbladder cancer, as well as esophageal adenocarcinoma.[88] Furthermore, there is a growing evidence base supporting a relation between diabetes – mainly type 2 diabetes mellitus – and certain types of cancer (breast, colon rectal, endometrial, non-Hodgkin lymphoma, bladder, liver and pancreatic),[89,90] probably due to the same predisposing conditions, such as obesity and insulin resistance.[91] Evidence from a large US prospective cohort has shown diabetes to be an independent predictor of mortality associated with colon rectal and pancreatic cancer both in men and women, with breast cancer in women, and with liver and bladder cancer in men.[92]

However, a number of historic studies and a growing number of recent studies observed that, among cancer patients, an elevated BMI is associated with improved survival, compared with normal-weight.[93] This surprising finding suggests the existence of an 'obesity paradox', well described in the cardiovascular and metabolic lit-

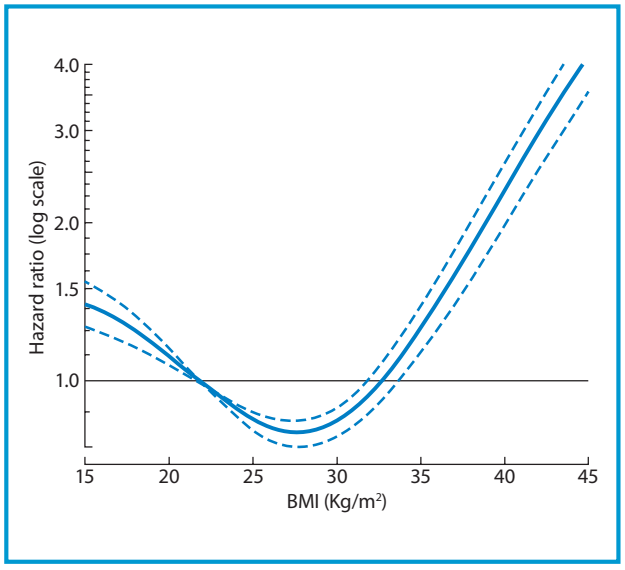

Figure 2. An illustration of the obesity paradox. The vertical axis represents the hazard ratio of mortality (log scale), compared with the baseline BMI of 22.5 kg/m^2. The plot represents a population in which the obesity paradox is observed, since the hazard ratio is below 1 in the overweight and obese range. The 95% confidence intervals are shown with dashed lines (from Lennon et al,[93]).

erature, but less so in oncology.[94,95]A BMI of 22.5 kg/m^2 has been widely accepted as a mid-reference point for normal weight. The obesity paradox occurs where the risk of outcome – typically mortality – is significantly reduced for BMI values above this reference, whereas an increased risk would be expected. At very high BMI values, risk either returns to unit or increases, as showed in Figure 2.[96] The obesity paradox has been observed in different cancer settings, for example, in colorectal and renal cancer undergoing surgery, colorectal metastases undergoing liver resection, and in elderly patients with acute myeloid leukemia and in patients with lymphoma undergoing autologous hematopoietic cell transplantation.[93] These conflicting findings may be partly explained by the heterogeneity of the cancer type and stage at diagnosis, the time of calculation of the BMI (pre, peri-, and post-diagnosis of cancer) and the unmeasured confounders, such as smoking, hormone replacement therapy or ethnicity.[93]

Treatment

Weight loss improves obese-related risk factors, and some evidence suggests that its benefits can persist as long as such weight loss is maintained.[97,98] This can be achieved via different weight loss strategies, including lifestyle interventions (diet and exercise), drugs, or bariatric surgery. Weight loss from various interventions was associated with a decreased risk of developing diabetes, and a reduction in low-density lipoprotein cholesterol, total cholesterol and blood pressure in the long term,[99,100] as well as reduced HbA1c levels, and a decrease in the use of antihyperglycemic, antihypertensive, and lipid-lowering drugs in diabetic patients after 1 year.[101] Furthermore, weight loss supported the reduction of the symptoms of depression and the remission – or reduced severity – of obstructive sleep apnea.[102,103] It should be noted that a >5% weight loss appears to be necessary for these beneficial effects.

Interestingly, gender differences in the various therapeutic strategies exist worldwide. While men prefer to exercise, women are more likely to join weight loss programs, take prescription diet pills, and follow special diets.[104,105] Although physical exercise is the key component of every lifestyle intervention, a thorough lifestyle intervention is crucial to achieve a significant and durable weight loss, since several studies reported additive effects on weight loss when it is combined with an energy-restricted diet. Several diet types have been proposed, from low-fat to low-carbohydrate, or the Mediterranean-style diet, but it has been shown that a sustained adherence to the diet, rather than the type of diet, determines the success of weight loss and the reduction of the cardiac risk factor.[106] However, intensive lifestyle interventions are difficult to achieve and to maintain over a long period of time, even if the patients are included in an optimal clinical trial setting, such as Look AHEAD (Action for Health in Diabetes),[107] and the weight regain following the weight lost through diet and exercise is estimated to be near 50% after only 1 year.[108]

The majority of guidelines recommend pharmacotherapy as the second-line treatment for obesity. Currently, the options for an effective obesity pharmacotherapy vary worldwide. While several new drugs for weight management are available in the US, so far only three of them – orlistat, liraglutide and the fixed combination of naltrexone and bupropion – have been licensed in Europe. Pharmacotherapy adjunctive to diet and exercise can result in clinically meaningful weight loss and help improve many obesity-complicating diseases.[109] It has been theorized that gender could be among the factors influencing the activity of the new obesity drugs, due to both pharmacokinetic and pharmacodynamic factors, but so far the data obtained in clinical studies do not support the need of dose adjustment by gender for any of these medicinal products.[110]

Bariatric surgery is an established and effective part of the weight loss management in morbidly obese patients, and actually produces sustained long-term weight loss, reducing co-morbidity burden and mortality in patients with severe obesity.[111] It is indicated in obese patients with a BMI ≥40 kg/m^2 or in individuals with a BMI >35 kg/m^2 in the presence of type 2 diabetes or other major comorbidities.[112]

Data from the Swedish Obese Subjects (SOS) study show that weight loss obtained by bariatric surgery significantly impacted the recovery rates from obesity-associated risk factors, such as diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension and hyperuricemia, and reduced the incidence rates of diabetes, hypertriglyceridemia and hyperuricemia versus the control group.[113] In addition, weight loss by bariatric surgery is associated with a significant reduction of overall mortality.[114] Bariatric surgery was also associated with a reduced incidence of cancer. Interestingly, the cancer-preventive effect of bariatric surgery was seen in women, whereas no effect was seen in men.[115,116] A recent study showed that weight loss following bariatric surgery is associated with a reduced risk of female-specific cancer (breast, endometrial, ovarian, and all other gynecological cancers), particularly in women with medium or high insulin levels at baseline, compared to those with low insulin levels.[117] Insulin is a growth factor with known metabolic and mitogenic effects, and hyperinsulinemia is one of the factors suggested to explain the link between obesity and cancer.[118] In addition, insulin is connected to endocrine risk factors for cancer, such as insulin-like growth factor 1, sex steroids and adipokines,[119] and it has been shown that insulin levels are reduced after bariatric surgery.[113]

Conclusions

Obesity and metabolic syndrome are life-threatening conditions, that can significantly increase morbidity and decrease life expectancy. They are a risk factor for several non-communicable chronic diseases, causing each year nearly three million deaths worldwide. Obesity and metabolic syndrome are on the rise in most countries, and represent now a global health problem. Gender differences in the prevalence of obesity and its complicating diseases do exist, but the exact mechanisms (biological, behavioral and socio-economic) are yet to be fully clarified. Weight loss improves obese-related risk factors, but its benefits persist only as long as such weight loss is maintained, and weight regain rate is high. The use of multidisciplinary treatment strategies that reduce diabetes, obesity and its complications will probably have a greater impact on mortality than addressing each disease individually. Primary prevention should target improvements in lifestyle factors, such as smoking cessation and weight management, to support the prevention of obesity-complicating diseases and extend life expectancy.

In addition, although data on gender differences in the response to the treatment of obesity are still lacking, there is an urgent need of new real-world data on gender-related difference, in order to optimize and tailor each treatment.

Key messages

- The metabolic syndrome is a combination of cardiometabolic risk factors, leading to increased morbidity and decreased life expectancy.
- The prevalence of obesity is increasing worldwide and obesity is a major risk factor for several chronic diseases.
- Obesity induces a state of chronic, low-grade inflammation, involved in the development of metabolic syndrome and obesity-complicating diseases.
- Weight loss (through lifestyle interventions, drugs or bariatric surgery) improves obese-related risk factors, and its benefits persist as long as such weight loss is maintained.
- Gender differences in the prevalence of obesity and its complicating diseases do exist, but the exact mechanisms are yet to be fully clarified.

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