



2016 Laparoscopic Surgery: Global view

New obesity classification criteria as a tool for bariatric surgery indication

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Abstract

Obesity plays relevant pathophysiological role in the development of health problems, arising as result of complex interaction of genetic, nutritional, and metabolic factors. Due to the role of adipose tissue in lipid and glucose metabolism, and low grade inflammation, it is necessary to classify obesity on the basis of body fat composition and distribution, rather than the simply increase of body weight, and the Body Mass Index. The new term of adiposopathy ("sick fat") clearly defines the pathogenic role of adipose tissue. Four phenotypes of obese individuals have been described: (1) normal weight obese (NWO); (2) metabolically obese normal weight; (3) metabolically healthy obese; and (4) metabolically unhealthy obese or "at risk" obese. Moreover, sarcopenic obesity has been related to all the phenotypes. The category of normal weight lean, represented by metabolically healthy normal weight has been classified to distinguish from NWO. It is crucial to recommend a bariatric surgery taking into account adiposopathy and sick fat that occurs with the expansion of fat mass, changing the inflammatory and metabolic profile of the patient. Body fat percentage and genetic polymorphism have to be evaluated to personalize the best bariatric surgery intervention.

Key words: Obesity; Adiposopathy; Normal weight lean; Normal weight obese; Metabolically obese normal weight; Metabolically healthy obese; Metabolically unhealthy normal weight; Metabolically unhealthy obese;

Laparoscopic gastric banding; Fat mass

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Core tip: Obesity is a global public health problem due to its association with several diseases and reduced lifespan, as result of complex interaction of genetic, nutritional, and metabolic factors. The term of adiposopathy clearly defines the pathogenic role of adipose tissue. Four phenotypes of obesity have been described, based on body fat composition and distribution: (1) normal weight obese; (2) metabolically obese normal weight; (3) metabolically healthy obese; and (4) metabolically unhealthy obese. Sarcopenic obesity has been characterized, related to all the described phenotypes. Body fat percentage and genetic polymorphism have to be evaluated to personalize the best bariatric surgery intervention.

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BODY COMPOSITION STUDY AS A NEW WAY TO CLASSIFY SUBJECT

The American Medical Association's Council on Science and Public Health Report 4, has identified the following common criteria to define a disease as: (1) an impairment of the normal functioning of some aspect of the body; (2) characteristic signs or symptoms; and (3) harm or morbidity^[1].

The World Health Organization (WHO) defines obesity as "a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired, and, due to the alarming prevalence increase, declared it as a "global epidemic"^[2].

The high prevalence of obesity is a global public health problem due to its association with several diseases^[3,4], and reduced lifespan^[5]. It arise as a result of complex interaction of genetic, life style, dietary habitus, energy expenditure, nutritional and metabolic factors, as the adipocyte metabolism^[6,7].

The shared definition that the adipose tissue and skeletal muscle are an energy storage has been replaced by the notion that these tissues have a role in lipid and glucose metabolism due to the large number of bioactive proteins, termed adipokines and myokines produced^[8], that are related to some cardiovascular risk factors influences of obesity^[9].

Moreover, obesity and glucose metabolism are intimately related to low grade systemic inflammation, involving a number of pro-inflammatory cytokines produced by many cell types that also appear to be

major regulators of adipose tissue metabolism^[10].

Therefore, the greatest limitation of any measure that relegates the diagnosis of obesity to the mere quantity of weight and circumference gain, without taking into account the body composition, in terms of body fat increase and body lean decrease, is the failure to consider the impact of adiposity on physiological and metabolic processes that result in increased morbidity and mortality^[11].

Due to the endocrine and inflammatory role of the adipose tissue it is necessary to classify obesity condition on the basis of body fat composition and distribution, rather than simply on the increase of body weight (Figure 1). Therefore, the body mass index (BMI), a ratio between weight to the squared height (kg/m²) of a subject, used to easily approximate body fat percentage and stratify people into categories, leads to a large error and misclassification.

According to BMI, general population is classified in five categories: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5-24.9 kg/m²), class I obesity - overweight (BMI 25.0-29.9 kg/m²), class II obesity - obesity (BMI 30.0-39.9 kg/m²), class III obesity - extreme obesity (BMI > 40 kg/m²).

The currently used BMI cut-off values for pre-obesity and obesity are based on morbidity and mortality studies in relation to Caucasian population^[8-10].

However, there is a controversy in the literature, termed the "obesity paradox", which associates better survival and fewer cardiovascular events in patients with mildly elevated BMI afflicted with chronic diseases^[11].

In fact, the outdated BMI formula developed nearly 200 years ago by Quetelet, is not a measurement of adiposity, but merely an imprecise mathematical estimate^[12-14].

Its popularity stems in part from its convenience, safety, and minimal cost, and its use is widespread, despite the fact, BMI ignores several important factors affecting adiposity. Moreover, the error in the diagnosis of obesity generates important effects on health care costs.

BMI formula is only an arithmetic approximation for the relative quantity of adiposity and is used to predict and evaluate disease risk in epidemiological studies, thereby acting only as a population-level indicator of obesity.

Because BMI does not measure PBF directly and poorly distinguishes between total body fat and total body lean, or bone mass, the use of BMI as an index of PBF for a person may be inaccurate and not useful as a cardiovascular risk factor^[15-17].

However, according to a WHO expert committee, "there is no agreement about cut-off points for the PBF that constitutes obesity"^[10].

Current research suggests that the obesity cut-off points of PBF are in the 23%-25% range in men and 30%-35% range in women^[18].

The clinical use of WHO BMI cut-off values when

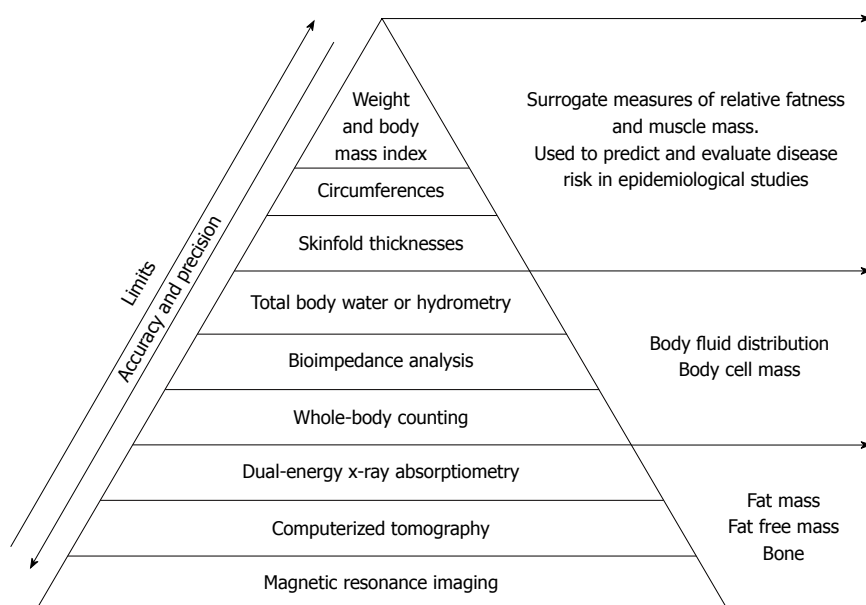


Figure 1 Techniques in body composition.

applied to the Italian population cause misclassifications, and a considerable number of subjects, both males and females, will not be classified as obese based on their BMI alone^[19].

The disagreement became impressive in the classification of obese women: in the class of age 30-40 the proportion of obese women according to BMI is 30% reaching about 82% if the classification is based on PBF. Notably, among women that were classified as normal according to their observed PBF, the median BMI was 20.1, ranging from 15.6 to 26.7.

For the Italian population, the percentage of obese women according to PBF classification increases as age increases, ranging from 63.17% in women younger than 20 years to 87.39% in women older than 60^[20].

Moreover, values corresponding to normal weight, overweight, and various subgroups of obesity are confounded by body frame and muscularity, fluid retention, sarcopenia in aging or disease, spinal deformities, physical disabilities, and transcultural differences. A person with the same BMI, may have a large proportion of total body fat mass and be obese, or may have a considerable muscle mass and be a weight-lifter. Moreover, PBF at a given BMI will tend to vary across gender, age, and race-ethnicity^[21-23].

Moreover, it is recommended to measure waist circumference (WC) in adults with BMIs below 35 kg/m², to further assess disease risk^[24].

Anyway, obese individuals differ not only in the amount of excess fat mass, but also in the regional distribution of the fat within the body. The fat distribution affects the risk associated with obesity. It is useful therefore, to be able to distinguish between those at increased risk as a result of abnormal fat distribution or android obesity from those with the less serious gynoid fat distribution, in which fat is more

evenly and peripherally distributed around the body^[2].

On the hand even if there are some obese people are prone to develop alterations in fat distribution and metabolic disease, others are protected from the adverse metabolic effects of weight gain and increased adiposity^[25].

Some studies suggested that the main issue to explain the metabolic abnormalities in normal weight individuals was fat distribution.

Certain attributes of visceral fat, the adipose tissue surrounding abdominal organs, make its accumulation more worrisome than the accumulation of subcutaneous fat, which resides below the skin^[26-28].

Other markers for excess body fat evaluation have to be used in clinical practice and investigation (*e.g.*, WC, skin fold thickness, waist-to-hip ratio, waist-to-height ratio).

WC or waist-to-hip ratio has been used as a proxy measure for body fat distribution when investigating the health risk increased with an increasing ratio. Some studies have suggested that WC, either singly or in combination with BMI, may have a stronger relation to some health outcomes than BMI alone^[29]. Moreover, progressively higher values of BMI and WC are associated with a progressive elevation in metabolic markers of cardiovascular disease (CVD) risk such as total serum cholesterol, triglycerides, blood glucose and a progressive reduction of HDL-cholesterol, with a clear-cut increase in the incidence of all-cause and cardiovascular deaths as well as of cardiovascular morbid and fatal events^[30]. In post-menopausal women, it was reported that both BMI and WC were associated with mortality, but WC may be more important than BMI^[31], as it reflects abdominal fat levels. In the Nurses' Health Study, waist-to-hip ratio and WC were also independently strongly associated with increased

risk of coronary heart disease among women with a BMI of $< 25 \text{ kg/m}^2$ ^[32]. WC reflects abdominal or intra-abdominal fat, and hip circumference reflects different aspects of body composition in the gluteo-femoral region, *i.e.*, muscle mass, bone, and fat mass. The importance of waist and hip measurements, and the waist to hip ratio, lies in the apparently different physical and metabolic characteristics of these two regions, and therefore the diverse clinical outcomes in subjects with a gynoid (low waist to hip ratio, lower body obesity) or android (high waist to hip ratio, upper body obesity) body conformation. This may be due to the tendency for abdominal adipocytes to enlarge (hypertrophy) whereas subcutaneous femoral adipocytes increase in number (hyperplasia), perhaps due to increased levels of the adipogenic transcription factors CCAAT/enhancer-binding protein α (C/EBP α ; GeneBank accession No: NC_000019) and peroxisome proliferator-activated receptor- γ 2 (PPAR γ 2; GeneBank accession No: NC_000003) in hypertrophic adipocytes^[33]. Hypertrophic adipocytes tend to be associated with dyslipidemia and insulin resistance^[34]. It has been suggested that the composition of gluteal fat deposits correspond more closely with that of visceral deposits rather than femoral deposits^[35].

In conclusion, diagnosis, therapy and follow up of all subtypes of obesity must not be based on "body weight" parameter, but body composition parameters and energetic expenditure are required.

To overcome misclassifications, direct measurements of PBF, by magnetic resonance imaging (MRI), computerized tomography (CT), dual energy X-ray absorptiometry (DXA), bioimpedance analysis, total body water or hydrometry, and skinfold thickness would be a better tool for diagnosing the obese phenotypes (Figure 1).

OBESITY AS DISEASE: SICK FAT OR FAT MASS DISEASE

Bays *et al.*^[36] have coined a new term that well defines the concept of "sick fat", the adiposopathy, in order to highlight the pathogenic role of adipose tissue. The adiposopathy is caused by positive caloric balance, that occurred in hypercaloric diet and sedentary lifestyle in genetically predisposed and environmentally sensitive individual^[36]. Impaired adipocyte proliferation or differentiation (adipogenesis), visceral adiposity, growth of adipose tissue beyond adequate vascular supply and ectopic fat deposition are anatomical manifestations of adiposopathy that are associated with adverse endocrine and immune responses leading to metabolic disease^[37,38].

In order to understand the importance of the role of adipose tissue in the onset of a pathological condition and distinguish the degree and type of disease, we agree with the definition proposed by Bays of adiposopathy, as "sick fat disease", and obesity

as "fat mass disease"^[38]. Different adverse physical and metabolic health consequences could occur as directed or undirected consequences of adipose tissue mass spread and dysfunction^[39], such as metabolic syndrome (MS), respiratory disorders, joint pain, diabetic retinopathy, low self-esteem, cardiovascular, neurologic, pulmonary, musculoskeletal, dermatologic, gastrointestinal, genitourinary, renal and psychological diseases and cancer^[3,4,40-42]. Moreover, also a slight rise of body weight may represent a risk factor for the onset of metabolic abnormalities that lead to development metabolic disease^[43].

According to Patel and Abate^[44], the subcutaneous adipose tissue (SAT) can be a major contributor of systemic free fatty acid flux, more than visceral or retroperitoneal fat, able to determine the insulin resistance development.

Apovian *et al.*^[45] explained the insulin resistance and vascular endothelial dysfunction in obese subjects with the phenomenon of adipose tissue macrophage (ATM) infiltration, in the form of crown-like structures, associated with and elevated plasma high sensitivity C-reactive protein (hs-CRP) levels.

Because of the complexity of the obesity condition, it is clear that we need a new and more adequate model, possibly based on findings at the physiopathological level and a new method to correctly identify all the affected subjects for an efficient and successful treatment.

If Bays *et al.*^[39] affirmed that to deny the adiposopathy, also in mildly overweight patients, represents denying the opportunity of cure to this individuals, and perhaps to entire populations, we added the importance to evaluate PBF in normal weight individuals to predict in advance the risk of adiposopathy, and to verify the real state of health.

ECTOPIC FAT DISTRIBUTION AND ORGAN FUNCTION

The association between visceral fat and metabolic and cardiovascular disorders is also related to accumulation of ectopic fat that accompanies visceral adiposity^[46]. Moreover, the hepatic fat observed in patients with insulin resistance could be independent from the visceral fat content^[47].

Healthy expansion of subcutaneous fat in response to obesity is accompanied by enlargement of fat mass through enhanced recruitment of preadipocytes along with adequate vascularization of expanding adipose tissue and minimal fibrosis and minimal infiltration of inflammatory ATMs. In contrast, pathologic expansion is associated with rapid growth of fat tissue through the enlargement of existing adipocytes and inadequate vascularization leading to fibrosis and inflammatory ATM infiltration that secrete high levels of inflammatory cytokines^[48].

This pathologic expansion is associated with adipose

tissue accumulation in ectopic locations such as liver, skeletal muscle, and pancreas as well as visceral adiposity^[49].

The existence of “metabolically healthy obese (MHO)”^[50,51] further supports this concept as these individuals have less ectopic fat despite high amount of subcutaneous fat in gluteal depot and are insulin sensitive^[51].

Therefore, adipose tissue distribution is a more significant predictor of metabolic and cardiovascular risk than overall adiposity. Inability to expand subcutaneous depots in response to positive energy balance^[52] results in metabolic and cardiovascular complications.

IMPACT OF CROSS TALK

Adipose tissue, found in several locations throughout the body and long thought to be primarily a repository for triglycerides, is also important for regulating metabolism and body’s physiologic. Fat is an endocrine tissue and, indeed, may constitute the largest endocrine organ in the body^[53,54].

If in the past, adipose tissue was considered to be a metabolically inactive fat depot, the current view of adipose tissue is that of an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism, and inflammation and immunity^[55].

Expansion of the adipose tissue is accompanied by an increased infiltration of immune cells, in particular macrophages and T-cells^[56], with a pro-inflammatory phenotype. The “cross-talk” between the infiltrating cells and the tissue-resident adipocytes leads to secretion of adipokines, cytokines, chemokines, and lipids with a predominant proinflammatory character^[57].

Several indirect lines of evidence suggest that fatty acids can modulate the immune response. One of these is that levels of several fatty acids are associated with levels of inflammatory markers in healthy individuals^[58].

More directly, the type of fatty acids contained in the diet has been suggested to influence the risk of development of inflammatory diseases in which the immune system plays an important role.

This cross-talk has also been shown to affect the function of adipocytes, such as lipolysis, which will most likely result in altered concentration of circulating free fatty acids.

Some of obesity phenotypes are associated with a high risk of developing diabetes type 2 (T2DM) however for a given adiposity, there is a large heterogeneity in the metabolic risk mainly linked to the location of excessive adipose tissue.

The cause of glucose, lipid, or atherogenic disorders can be found in the visceral adipose tissue (VAT), representing a predictive factor for those disorders^[59].

The role of visceral fat in the development of peripheral insulin resistance in T2DM is related to the insulin-mediated glucose uptake^[60], that can be

directly affected by inflammatory cytokines, like tumor necrosis factor alpha (TNF- α), transforming growth factor beta (TGF- β), and interleukin 6 (IL-6) secreted by visceral fat depot.

Moreover, it has been demonstrated that both hepatic fat accumulation than hepatic insulin resistance are related to visceral fat depots, representing approximately 20% of total body fat mass in men and 6% in women^[61], as approximately 80% of hepatic blood supply is derived from the portal vein^[62].

Due to the interactions within adipose tissue and muscle, involved in the endocrine bi-directional “cross-talk” between these tissues^[63], it was observed a loss of muscle strength, that depends on both decrease in muscle mass and accumulation of inter-muscular adipose tissue, contributing to the decline of muscle quality^[64]. Therefore, the evaluation of body lean mass, together with body fat mass analysis and body force assessment, could contribute to predict sarcopenic obesity risk.

INFLAMMATION AND THE ROLE OF GENETIC VARIATIONS OF INFLAMMATORY TRIAD CYTOKINES IN OBESITY RELATED CHRONIC-DEGENERATIVE DISEASES

The obese state is a low-grade systemic inflammation, characterized by abnormal adipokine production, and activation of some pro-inflammatory signalling pathways, resulting in the induction of several biological markers of inflammation. In fact, inflammatory markers, such as C-reactive protein (CRP), IL-6, IL-1 family [IL-1 α , IL-1 β and IL-1 receptor antagonist (IL-1Ra)] and TNF- α are increased in obese individuals compared with lean subjects, although not to the same extent observed in classic inflammatory conditions^[65].

Though all the functional consequences of the increase in inflammatory processes in obese are not yet known, is an established fact that cytokines have metabolic activities, as many “adipokines” can modulate of both the metabolic and vascular homeostasis^[66], acting not only as autocrine/paracrine regulators, but also reaching, from the perivascular fat depot, the surrounding target organs, through the systemic circulation (“outside-to-inside” cellular cross-talk)^[67-69].

This inflammatory mechanism is the basis of the increased risk of development of T2DM, acute heart attacks and Alzheimer’s disease^[70,71] in obesity.

Polymorphisms and allele variants of cytokines genes are presumed to be involved in obesity and related chronic-degenerative diseases, therefore an understanding of their food association could be useful for nutritional pre-emption.

The practical application of predictive and preventive

medicine requires early identification of the individuals who are on a path toward earlier development of disease, followed by the introduction of a targeted intervention. Ideally, one could use the identification of specific polymorphisms, an early marker of disease susceptibility, to prevent complications of disease by the use of nutritional agents that modulate the biology resulting from the genetic variation.

A high degree of sequence variation recently has been shown to exist in cytokine genes. These gene polymorphisms are relatively common in regulatory regions of the cytokine genes and therefore may be functionally significant in defining inter-individual differences in transcription or post-transcriptional processes. These genetic variations therefore provide a potential mechanism by which individuals may have different degrees of response to the same stimulus.

Among the first genes activated with any injurious challenge are the genes for IL-6, IL-1 and TNF- α . These molecules activate each other and both are critical components of the inflammatory process.

IL-6

Besides regulating the immune system, IL-6 also plays a role in the regulation of body fat and energy expenditure. Recent studies have shown that IL-6 deficient mice develop mature onset obesity with high leptin levels in the circulation^[28].

Moreover, intracerebroventricular IL-6 treatment decreases body fat and increases energy expenditure in rodents^[72].

In humans, high cytokine levels (including IL-6) and cytokine brain synthesis were found to increase resting energy expenditure and induce cachexia. Additionally, a subcutaneous injection of IL-6 increased resting metabolic rate and hypothalamic-pituitary-adrenal axis activity in a dose-dependent fashion, suggesting that hypothalamic corticotrophin-releasing hormone may mediate both of these actions in humans. A second possibility by which IL-6 may affect energy expenditure is enhanced adrenergic stimulation. In the other hand, high circulating IL-6 concentrations have been found to predict the development of type 2 diabetes^[73,74]. IL-6 has a central role in the mechanism of pro-inflammation pathway and there are some evidences suggesting the implication of a network of cytokines for the development of metabolic disorders, as type 2 diabetes, CVD, and sarcopenia.

Polymorphisms that affect the gene transcription and production of IL-6, like the gene promoter -174 G/C polymorphism, are examples of genetically determined-changes in metabolism and energy homeostasis. In fact, IL-6 gene promoter polymorphism -174 G/C is shown to influence IL-6 transcription as well as overweight and insulin sensitivity.

Data suggest that endogenous IL-6 has effects on energy expenditure but upper endogenous IL-6 production, *e.g.*, due to the presence of allele C of

-174G/C polymorphism, contributes to obesity in humans and related pathologies and is a disadvantage for longevity.

TNF- α

Macrophages, whose adipose tissue is composed, are the major source of TNF- α produced by the white adipose tissue and contribute approximately 50% of white adipose tissue-derived IL-6^[75].

TNF- α participates to inflammatory events but it's also an important autocrine/paracrine of fat cell function which limits adipose tissue and skeletal muscle expansion, by inducing lipolysis^[76], insulin resistance^[77], and muscle apoptosis^[78]. Its presence also results in an increase in circulating leptin concentrations^[79] and, finally, its overexpression, by exceeding fat, aimed at stopping the growth of tissues^[80].

Several population-based studies have suggested an association between TNF- α polymorphisms and obesity-related phenotypes^[81].

TNF- α has a direct (possibly paracrine) function in adipose tissue where it limits its mass by stimulating lipolysis and decreasing lipoprotein lipase expression and activity, that means it's involved in the adipostatic function^[76].

TNF- α can induce hyperlipidemia and insulin resistance, especially in presence of single nucleotide polymorphisms (SNPs) on the promoter (-308 G/A and -238 G/A)^[82].

In fact, TNF- α is an antagonist of insulin receptor and an overproduction could impair insulin signalling as well as down-regulate adipose lipase producing hyperlipidemia. Levels of TNF- α are high in an obese population and moreover experiments *in vitro* show that allele A alters binding of nuclear factors to the -308 region causing a general increase in transcriptional^[83]. Interestingly, cases with the -308 A allele of the TNF- α gene have significantly higher hip and WC, BMI and body fat mass values than obese individuals carrying the -308 G allele, but not the waist-to-hip ratio^[84].

An higher fasting insulin levels, higher Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), higher systolic blood pressure and lower HDL cholesterol were highlighted among -308 A allele TNF- α obese carriers than -308 G obese carriers, and overweight subjects with impaired glucose tolerance showing a genotype have higher risk of developing T2DM than subjects without this genotype^[85].

This observation is consistent with previous findings, suggesting that leptin secretion and insulin resistance are affected by TNF- α expression. Disturbances in circulating levels of leptin may be accompanied by a lower control of appetite and thermogenesis or may occur as a consequence of leptin resistance.

IL-1

Other intriguing molecules produced by adipose tissue and involved in metabolism are that belonging to

the class of IL-1. IL-1 biological activity involves two agonists, IL-1 α and IL-1 β , specific receptors, and a naturally occurring antagonist, IL-1Ra. Some of the most relevant properties of IL-1 biological activity are the ability to initiate cyclooxygenase type 2 and inducible nitric oxide, leading to substantial expression of prostaglandin E2 and nitric oxide by cells exposed to IL-1 β .

Moreover, IL-1 β is able to determine lipolysis, glucose transport, and adipocyte maturation in adipose tissue, to inhibit lipogenesis, *via* the IL-1 receptor type 1 and the IL-1 receptor accessory protein, like TNF- α .

In obese individuals the serum level of IL-1Ra is up-regulated for a feedback down-regulation, resulting in an acquired resistance to leptin, rising the high values as in inflammatory autoimmune diseases and sepsis^[86,87].

Polymorphisms affecting IL-1 production, like the SNP at IL-1 β (+3954), the SNP at IL-1 α (-889) and the SNP at IL-1 α (+4845) are associated with increased levels of inflammatory mediators, and also with increased severity of several chronic diseases, including Alzheimer's disease^[88], periodontal disease and others. This proinflammatory IL-1 genotype pattern recently has been associated with cardiovascular acute coronary events. For example, despite having total cholesterol levels below 200 mg/dL, individuals who carried two copies of IL-1 α (+4845) allele 2 were four times ($P < 0.01$) more likely to have a coronary heart disease event during an 11-y monitoring period than were individuals with the same level of cholesterol but who did not carry this IL-1 genotype (unpublished data, Interleukin Genetics, Waltham, MA, United States).

The IL-1Ra antagonizes the effects of IL-1 α and -1 β ^[89], and the anti-inflammatory cytokine interferon-beta and leptin can induce IL-1Ra production without increasing IL-1^[86,90]. In subjects with hyperleptinemic obese individuals the serum sIL-1Ra levels are higher as compared to non obese subjects^[91].

Furthermore, in subjects that underwent to intestinal bypass surgery, sIL-1Ra levels dropped after weight loss, correlating with BMI and the degree of insulin resistance better than with serum leptin levels, according to metabolic control unmediated by leptin.

GLUCOTOXICITY

The ability of the pancreatic alpha and beta cells to increase the uptake of glucose can be compromised by constant hyperglycemia, even mild. This mechanism, compromising the glucose transport mediated by insulin, prevents the possibility of self correction, and start a vicious cycle mechanism that leads to deterioration of the metabolic process^[92].

Continuous overstimulation of the beta-cell by glucose could eventually lead to depletion of insulin stores, worsening of hyperglycemia, and finally deterioration of beta-cell function.

The mechanisms responsible for changes of insulin sensitivity vs insulin resistance clearly vary and involve changes in both beta-cell function and beta-cell mass, although in most instances it appears that functional changes predominate. Moreover, the beta-cell must also alter its activity when this critical modulator changes for more prolonged periods^[60].

Several mechanisms might explain the glucotoxicity due to prolonged hyperglycemia^[93,94], such as beta-cell exhaustion, oxidative stress induced by free radical oxygen species, endoplasmic reticulum (ER) stress, inflammation caused by proinflammatory cytokines and chemokines, loss of neogenesis, proliferation of beta-cells, gradual loss of insulin gene expression and other beta-cell specific genes, changes in mitochondrial number, morphology and function, disruption in calcium homeostasis^[95].

In the presence of hyperglycemia, prolonged exposure to increased free fatty acids result in accumulation of toxic metabolites in the cells ("lipotoxicity"), finally causing decreased insulin gene expression and impairment of insulin secretion.

Chronic exposure to abnormally high blood glucose has detrimental effects on insulin synthesis/secretion, cell survival and insulin sensitivity through multiple mechanisms ("glucotoxicity"), which in turn lead to hyperglycemia and finally to the vicious circle of continuous deterioration of beta cell function^[96].

Beta cells exposed to an increased insulin secretory request place a high demand on ER for the synthesis of proinsulin, leading to cellular stress^[97].

Due to chronic ER stress and strong unfolded protein response, beta cell death through apoptosis (mediated by stress kinases and transcription factors) may be initiated. In addition to glucose, free fatty acids (FFA) and islet amyloid polypeptide are triggers of beta cell ER stress^[98]. Moreover, reactive oxygen species (ROS), free radicals that are intermediate metabolites derived from oxygen metabolism in mitochondria, primarily due to hyperglycemia, causes oxidative stress in various tissues, playing an important role in both physiology and pathology in beta-cells. ROS are continuously produced by the mitochondrial electron transport system as a byproduct of the oxidative phosphorylation pathway; however, normal cells have antioxidant defenses to rapidly neutralize ROS and maintain an optimal redox potential for appropriate biological cell function^[99]. This optimal redox balance is impaired because of increased ROS production and insufficient endogenous anti-oxidant defenses of the β -cells.

Chronic hyperglycemia leads to decreased number of mitochondria and changes of their morphology^[99] in the β -cells. This is associated with impaired oxidative phosphorylation, decreased mitochondrial Ca²⁺ capacity and decline in ATP generation^[100]. In addition, disruption in Ca²⁺ homeostasis (*e.g.*, changes in glucose-induced Ca²⁺ influx, ER Ca²⁺ depletion) negatively impacts on beta cell growth/function and on

the insulin secretion pathway^[101].

LIPOTOXICITY

When adipose tissue cannot meet the demand of storing excessive energy, triglyceride is accumulated in non-adipose tissues as ectopic fat, which may lead to insulin resistance in the liver and skeletal muscle and insufficient insulin secretion in the pancreas^[48,102,103].

High plasma FFA and triglyceride levels lead to increased import of FFAs into non-adipose tissues (*i.e.*, liver, muscle, pancreas), contributing to intracellular lipid accumulation. This phenomenon, known as lipotoxicity, may play an important role in the pathogenesis of diabetes and heart failure in humans^[104].

Adverse consequences of lipid overload have been observed in many organ systems, mainly in the heart, skeletal muscle, pancreas, liver, and kidney^[104].

In addition to primary hyperlipidemias, serum triglycerides^[105,106] and FFAs^[107] are elevated in type 1 and type 2 diabetics and plasma FFA levels are elevated in obese individuals^[108].

The cross-talk has been shown to affect the function of adipocytes, such as lipolysis, which will most likely result in an altered concentration of circulating free fatty acids. Indeed, obese persons have higher levels of free fatty acids in plasma compared to lean subjects^[109-111].

Several indirect lines of evidence suggest that fatty acids, contained in the diet, can modulate the immune response. One of these is that levels of several fatty acids are associated with levels of inflammatory markers in healthy individuals^[58].

The overall data suggest that low concentrations of fatty acids can influence the proliferation of T-cells, whereas higher concentrations induce apoptosis in a dose-dependent manner, through the induction of several pathways^[112-117].

In addition, the concentration at which apoptosis occurs is also determined by the degree of saturation and the length of the fatty acid. While short-chain fatty acids are not toxic even at a concentration of 800 mmol/L or higher^[113], longer, and more unsaturated fatty acids can already be toxic in low concentrations (*e.g.*, linoleic acids) is toxic at 100 mmol/L^[114,115]. In contrast to the apoptotic effects, the modulatory effects of low, non-toxic concentrations of fatty acids on proliferation do not seem to correlate with length of the fatty acids tested.

de Jong *et al.*^[59] conclude that, free fatty acids induce proliferation of resting T-cells in low concentrations, while higher concentrations induce apoptosis.

BODY FAT DISTRIBUTION ACROSS GENDER AND ETHNICITY

Etiological contributing factors to VAT depot and distribution are represented by age, gender, genetics,

and ethnicity^[118].

Substantial anatomical differences between males, that accumulate adipose tissue in the upper body (trunk, abdomen), and females, with a usual accumulation of adipose tissue in the lower body (hips, thighs), are practically unique in human^[119-121].

Vague^[122] identified two different body shapes, proposing the two terms "android obesity", to refer to adipose tissue accumulated preferentially in the trunk/upper body area closely related to hypertension, CVD, gout, and diabetes, and the term "gynoid obesity" to refer to adipose tissue accumulation in the hips and thighs, with less associated complications^[123,124].

Visceral fat depot, evaluated by MRI and computed tomography (CT), was found to be specifically associated with the metabolic alterations related to obesity, both in men and women^[125-127]; subcutaneous fat in general define a positive effect on insulin sensitivity^[128].

Genetic predisposition could explain the fact that females, although high BMI, are protected against insulin resistance more than males^[118]. Furthermore, the capacity to increase the fat depots depends on the ease with which local preadipocytes can be readily activated toward differentiation process^[129].

Although ethnicity is a factor that determines the different adipose tissue distribution and responses to the cardiometabolic risks^[118,130,131], as highlighted by Deurenberg *et al.*^[132], that observed ethnic differences in BMI at similar levels of PBF, in Chinese, Indonesian, and Thai populations respect to Caucasians (American, Australian, and European Whites analyzed as one group). Moreover, Asian Indians have more abdominal fat than Caucasians^[133,134], and Caucasians have more VAT than African Americans^[135-137]. On the other hand, in Asians and Indian Asians the accumulation of fat is mainly in the visceral area^[131,138,139].

Genetic and epigenetic programming is one of the most credible explanations for the observed differences in the storage of lipid depot^[118,139,140].

OBESITY: BODY COMPOSITION PHENOTYPES

Nowadays four phenotypes of obese individuals have been widely described (Table 1): (1) normal weight obese (NWO)^[141]; (2) metabolically obese normal weight (MONW)^[142,143]; (3) MHO; and (4) metabolically unhealthy obese (MUO) or "at risk" obese with MS^[144].

The characteristic of the four obese phenotypes are depicted in Figure 2.

Moreover, the sarcopenic obesity has been characterized, and related to all the described phenotypes^[145]. Moreover the category of normal weight lean (NWL), represented by metabolically healthy normal weight (MHNW) has been classified to distinguish from NWO.

According to the causality and anatomic, pathophysiological, and clinical manifestations of obese phenotypes, we can define NWO and MHO belonging

Table 1 Obesity classification

Publication	Year	Definition
Normal weight obesity - NWO		
De Lorenzo <i>et al</i> ^[141]	2005	Normal weight (by BMI) + PBF > 30 (dual X-ray absorptiometry) + ↓ lean body composition of the left leg. Do not have metabolic syndrome
Di Renzo <i>et al</i> ^[162]	2006	NWO syndrome is characterized by wild type homozygotes genotypes regarding IL-15 R-α and MTHFR 677C/T polymorphism
De Lorenzo <i>et al</i> ^[147]	2007	↑ concentrations of pro-inflammatory cytokines IL-1α, IL-1β, IL-6, IL-8, TNF-α in NWO respect to non obese group
Di Renzo <i>et al</i> ^[160]	2007	The allele 2 (A2) of IL-1 receptor antagonist (Ra) in NWO subjects was associated with ↑ of IL-1β plasma amount
Marques-Vidal <i>et al</i> ^[151]	2008	Normal weight (by BMI) + ↑PBF (Bioelectrical impedance) or fat mass index ≥ 8.3 kg/m ² (men) or ≥ 11.8 kg/m ² (women)
Di Renzo <i>et al</i> ^[161]	2008	Genotyping of -175 G/C IL-6 polymorphism: in G/G the serum IL-6 level of NWO (10.70 ± 2.52 pg/mL) and obese (10.67 ± 1.09 pg/mL) was significantly higher compared with NWL women (5.54 ± 1.51 pg/mL). Positive correlation between PBF and plasma IL-6 and between HOMA-IR and plasma IL-6 only in NWO e obese G/G carrier
Marques-Vidal <i>et al</i> ^[149]	2010	↑ blood pressure, ↑ lipid levels and ↑ prevalence of dyslipidaemia [OR = 1.90 (1.34-2.68)] and fasting hyperglycaemia [OR = 1.63 (1.10-2.42)] respect to lean women, whereas no differences were found between NWO and overweight women.
Di Renzo <i>et al</i> ^[159]	2010	↓ glutathione and nitric oxide metabolites were significantly lower in pre-obese-obese and NWO compared to normal weight individuals. Lipid peroxide levels negatively correlated to FFM% and positively correlated to PBF, IL-15, TNF-α, insulin, total cholesterol, LDL, and triglycerides
Romero-Corral <i>et al</i> ^[157]	2010	NWO not manifest the metabolic syndrome, despite a cluster of metabolic and genetic features such as the higher prevalence of dyslipidemia, hypertension (men), CVD (women), and a 2.2-fold increased risk of CVD mortality (women) compared with those with low PBF
Kim <i>et al</i> ^[156]	2013	Normal weight (by BMI) + ↑ PBF
Madeira <i>et al</i> ^[155]	2013	Normal weight (by BMI < 25) + Sum of triceps and subscapular skinfolds > 90 th percentiles
Di Renzo <i>et al</i> ^[164]	2013	G/A -308 TNF-α polymorphism contributes to sarcopenic obesity susceptibility in NWO
Di Renzo <i>et al</i> ^[165]	2014	TP53 codon 72 in exon 4 polymorphism was associated to the reduction of appendicular skeletal muscle mass index in NWO, leading to increase of sarcopenia risk
Oliveros <i>et al</i> ^[146]	2014	Normal BMI, ↑ PBF content and at increased risk for metabolic dysregulation, systemic inflammation and mortality
Jean <i>et al</i> ^[158]	2014	Highlight the importance of PBF correct assessment and body fat distribution in the clinical setting to identify NWO phenotype
Metabolically healthy obese - MHO		
Bonora <i>et al</i> ^[178]	1998	Subgroup of obese individuals with a normal metabolic response
Sims ^[179]	2001	The MHO subset include family members with uncomplicated obesity, early onset of the obesity, fasting plasma insulin within normal range, and normal distribution of the excess fat
Karelis <i>et al</i> ^[190]	2004	↑ Fat mass + Normal Metabolic profile + ↑ insulin sensitivity
Karelis <i>et al</i> ^[143]	2005	Favorable inflammation profile: ↓ hsCRP, ↓ α-1 antitrypsin levels compared with insulin-resistant women, suggesting that lower inflammation state could play a role in the protection of this phenotype
Succurro <i>et al</i> ^[171]	2008	Respect to MONW, MHO have a healthier metabolic risk profile and ↑ disposition index (insulin sensitivity x insulin secretion)
Wildman <i>et al</i> ^[50]	2008	In NHANES sample, it was found a prevalence of 32% among obese adults over the age of 20
Arnlov <i>et al</i> ^[192]	2010	MHO individuals were at an increased risk of major CVD events as compared to MHNW individuals in follow-up periods (> 15 yr)
Eshtiaghi <i>et al</i> ^[194]	2014	MHO phenotype over a 10 yr period progressed to frank metabolic syndrome
Achilike <i>et al</i> ^[196]	2015	Among subjects classified as MHO at baseline, almost half (47.6%) of them progressed to metabolically unhealthy obese (MUO) within the 7.8-yr follow-up period
Shaharyar <i>et al</i> ^[195]	2015	Both MHO individuals and MONW phenotypes were associated with ↑ high hsCRP, and hepatic steatosis
Metabolically obese but normal weight - MONW		
Ruderman <i>et al</i> ^[166]	1981	Subtle increase in adiposity and/or hyperinsulinism creating obese associated diseases in normal weight (by standard weight tables)
Ruderman <i>et al</i> ^[167]	1998	CHD, T2DM and other disorders associated with obesity + normal weight (< 115% of ideal body weight or BMI < 28 kg/m ²)
Dvorak <i>et al</i> ^[168]	1999	Impaired insulin sensitivity, BMI < 26.3 kg/m ² ↑ total fat mass (+20%), ↑ PBF (+16%) (dual x-ray absorptiometry), ↑ subcutaneous fat (+33%), ↑ visceral fat (+26%)
Esposito <i>et al</i> ^[176]	2004	↑ inflammation biomarkers, TNF-α and IL-6, in as a result of the larger visceral fat areas in this group
Conus <i>et al</i> ^[169]	2004	Insulin sensitivity determined by HOMA > 1.69 with normal weight (by BMI < 25 kg/m ²), ↑PBF (dual X-ray absorptiometry), ↓ FFM, ↓ physical activity energy expenditure, ↓ peak oxygen uptake
Meigs <i>et al</i> ^[170]	2006	BMI < 25 kg/m ² + Metabolic Syndrome criteria/insulin resistance
Succurro <i>et al</i> ^[171]	2008	Normal weight (by BMI) + Impaired insulin sensitivity, ↑ visceral adiposity, ↓ HDL, ↑ fasting glucose, ↑ triglycerides, hypertension
Thomas <i>et al</i> ^[175]	2012	According magnetic resonance imaging, they refined MONW phenotype and renaming this sub-phenotype as "thin-on-the-outside fat-on-the-inside" (TOFI), with a higher ratio of visceral:subcutaneous abdominal adipose tissue

Eckel <i>et al</i> ^[172]	2015	↑ waist circumference (women: 75.5 cm vs 73.1 cm; men: 88.0 cm vs 85.1 cm), ↑ HbA1c (6.1% vs 5.3%), ↑ triglycerides (1.47 mmol/L vs 1.11 mmol/L), and ↑ hsCRP (0.81 mg/L vs 0.51 mg/L), ↓ HDL (1.28 mmol/L vs 1.49 mmol/L) and ↓ adiponectin (6.32 μg/L vs 8.25 μg/mL)
Du <i>et al</i> ^[173]	2015	Lipid accumulation product and visceral adiposity index, two markers of visceral obesity, identify the MONW phenotype
Metabolically unhealthy obese - MUO		
Alberti <i>et al</i> ^[201]	2005	MUO subjects are characterized by a BMI ≥ 30 kg/m ² , a PBF > 30% and high visceral fat mass, closely linked to the development of the metabolic syndrome, T2DM, and atherosclerotic cardiovascular disease
Fabbrini <i>et al</i> ^[47]	2009	In MAO subjects, but not MNO subjects, moderate weight exacerbated several metabolic risk factors for CVD: ↑ blood pressure, ↑ plasma triglyceride, ↑ in intra hepatic triglyceride, ↑ VLDL apoB100 and ↓ plasma adiponectin concentrations and insulin sensitivity in the liver, skeletal muscle, and adipose tissues, ↓ adipose tissue expression of genes involved in glucose uptake and lipogenesis
O'Connell <i>et al</i> ^[210]	2010	MUO and obese with T2DM subjects had a omental adipocyte size greater than MHO, moreover MUO group had an intermediate degree of steatosis (43%) respect to MHO (3%) and obese with T2DM (74%).
Di Daniele <i>et al</i> ^[202]	2013	6 mo of dietary intervention based on Italian Mediterranean Diet in "at risk" obese subjects, determined a reduction (-52%) in the prevalence of the metabolic syndrome and a reduction in terms of waist circumference, BMI and total body weight.
Calanna <i>et al</i> ^[211]	2013	At-risk obese individuals showed ↑ plasma glucose dependent insulinotropic polypeptide, ↓ post-glucose load glucagone-like-peptide-1, and ↑ levels at baseline and after glucose load, indicating inappropriate glucagone suppression

BMI: Body mass index; PBF: Percentage of total body fat; NWO: Normal weight obesity; NWL: Normal weight lean; FFM: Fat free mass; HOMA: Homeostatic model assessment; LDL: Low density lipoprotein; HDL: High density lipoprotein; CVD: Cardiovascular disease; MHO: Metabolically healthy obese; HbA1c: Glycated haemoglobin; hsCRP: High sensitive C-reactive protein; MHNW: Metabolically healthy normal weight; MONW: Metabolically obese normal weight; MUO: Metabolically unhealthy obese; CHD: Chronic heart disease; T2DM: Type 2 diabetes mellitus; MAO: Metabolic abnormal obese; MNO: Metabolically normal obese.

to the category of "fat mass disease", and MONW and at risk obesity to "sick fat disease". Moreover, NWO women are quite different from MHO women and may also be distinguished from MONW women, according to fat distribution, inflammatory and metabolic parameters, and genetic variants.

NWO

The new concept of NWO had been proposed^[141,146]. NWO subjects have normal BMI (18.5-24.9 kg/m²), and highest body fat percentage (BF%) (men, ≥ 23.5%, women, ≥ 29.2%), associated at a higher degree of subclinical vascular inflammation and risk for cardiometabolic disease, of which body fat is a major contributing factor^[147-149].

Worldwide prevalence of NWO is near to 10%, and the prevalence is higher in women than in men^[150-152]. In women, prevalence of NWO increased considerably with age, and virtually all women aged over 55 with a BMI < 25 kg/m² were actually considered as NWO. Even if the proportion of PBF changes with age and sex^[23,153], using sex and age-specific thresholds for PBF led to a much lower prevalence of NWO in women, whereas little differences were found for men^[15,20].

As demonstrated by Kang *et al*^[154], NWO subjects highlighted a significantly higher blood pressure, fasting glucose level, and worse lipid profile compared to normal weight subjects, independently associated with elevated TBRmax values, that may determine and justify the metabolic and CVD occurring risks.

Due to the peculiarity of the relationship between lean mass distribution (lean of the right part of the body trunk and of the left leg), and CVD risk indexes, NWO could be considered an additional metabolic subset of obesity^[141,155,156].

They also do not manifest the MS, despite a cluster of metabolic and genetic features such as the higher prevalence of dyslipidemia, hypertension (men), CVD (women), and a 2.2-fold increased risk of CVD mortality (women) compared with those with low total body fat mass^[157].

Jean *et al*^[158] have provided three potential explanations for why normal-weight central obesity is linked to increased mortality include the following: (1) the accumulation of abdominal visceral fat as manifested by an increased girth: there is a very strong association between WC and visceral adiposity and the excess adipose tissue in the abdominal cavity organs, which are a source of inflammation and insulin resistance; (2) the reduced amounts of subcutaneous fat in the legs, hips, and buttocks, known to be protective for CVD and with a favorable metabolic function; and (3) the limited muscle mass, because like in NWO, people with normal-weight central obesity may also have sarcopenic obesity since, in order to have normal weight in the setting of large amounts of visceral fat, they likely have limited amounts of muscle mass.

De Lorenzo *et al*^[141] firstly described the NWO syndrome characterized by higher oxidative stress level^[159], early inflammatory status^[147] and few metabolic abnormalities.

The presence of SNPs of triad inflammatory genes, characterizes the NWO syndrome.

In NWO syndrome, the IL-1Ra allele 2 increases the risk of ovarian, pancreatic, cervical and gastric cancer, probably due to increased IL-1 production and inhibition of gastric acid secretion^[160].

According to the -174G/C promoter polymorphism of the IL-6 gene, G/G NWO showed a strong correlation between HOMA-IR and PBF^[161].

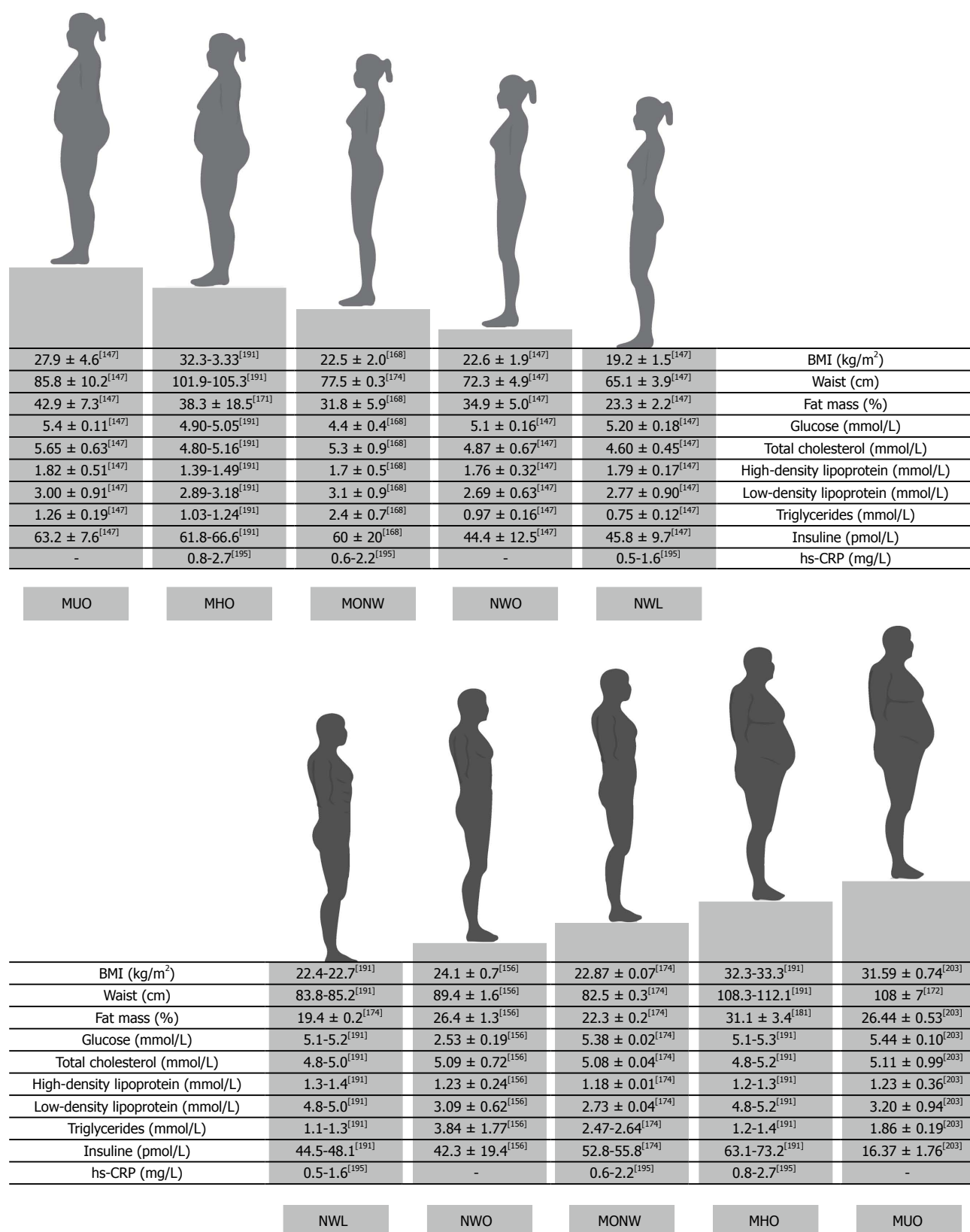


Figure 2 Characteristic of the four obese phenotypes. A: Women; B: Men. NWO: Normal weight obese; MONW: metabolically obese normal weight; MHO: metabolically healthy obese; MUO: metabolically unhealthy obese; BMI: body mass index; hsP: High-sensitive C-reactive protein. Data are expressed as average ± SD (a ± b), or as minimum-maximum (a-b), according to the references.

Moreover, NWO are characterized by a wild type homozygotes genotypes regarding IL-15 receptor-alpha and methylenetetrahydrofolate reductase (MTHFR)

enzyme^[162], suggesting a “conversion” between adipose tissue and skeletal muscle^[163].

The importance of the TNF-α gene polymorphism

to total body lean mass variation in NWO syndrome, demonstrating that G/A -308 TNF- α polymorphism contributes to sarcopenic obesity susceptibility^[164].

TP53 codon 72 in exon 4 polymorphism was associated to the reduction of appendicular skeletal muscle mass index (ASMMI) in NWO, leading to increase of sarcopenia risk^[165].

This finding gives much more support to the idea that a genetic approach could be predictive for finding a vulnerable category of people^[160-162,164].

MONW

MONW subjects, first described and revisited by Ruderman *et al.*^[166,167], represents a subset of persons who have a normal weight and normal BMI but have a cluster of metabolic characteristics that may increase the possibility of developing the MS.

MONW women, also defined as "metabolically unhealthy normal weight" (MUNW) have metabolic disturbances typical of obese persons and are characterized by having a high amount of visceral fat, a low BMI, a high fat mass, a low lean body mass, low insulin sensitivity, and high triacylglycerol concentrations, premature chronic degenerative disease and liver fat^[168-171].

In a recent paper Eckel *et al.*^[172] found that, MUNW individuals were characterized by known diabetes risk factors, *e.g.*, they were significantly more likely to be male, former smokers, hypertensive, and less physically active compared to normal weight individuals without incident diabetes. Higher WC (women: 75.5 cm vs 73.1 cm; men: 88.0 cm vs 85.1 cm), higher HbA_{1c} (6.1% vs 5.3%), higher triglycerides (1.47 mmol/L vs 1.11 mmol/L), and higher levels of high sensitive C-reactive protein (0.81 mg/L vs 0.51 mg/L) as well as lower levels of HDL-cholesterol (1.28 mmol/L vs 1.49 mmol/L) and adiponectin (6.32 μ g/mL vs 8.25 μ g/mL) characterized this phenotype.

Moreover, lipid accumulation product (LAP) and visceral adiposity index, two markers of visceral obesity, identify the MONW phenotype^[173].

Lee *et al.*^[174] recently found that in MONW individuals, the triglycerides index [(fasting triglycerides (mg/dL) \times fasting glucose (mg/dL)/2)] was higher respect to normal weight population, managing to clearly discriminate individuals at metabolic risk from NWL subjects.

Thomas *et al.*^[175] refined MONW phenotype using MRI, showing a disproportionate deposition of VAT respect to overweight or obese subjects; they called this sub-phenotype, "thin-on-the-outside fat-on-the-inside" (TOFI).

TOFI subjects showed a higher ratio of visceral: subcutaneous abdominal adipose tissue, and it was been observed in both male and female subjects and it was accompanied by increased levels of both liver and muscle fat^[175].

Higher concentrations of inflammation biomarkers, TNF- α and IL-6, in the MONW group could be the result

of the larger visceral fat areas in this group, supporting the correlation between visceral fat and both insulin resistance and CVD^[176].

However, in different population, CRP levels were significantly higher in MONW women than in the control group, and serum IL-6, IL-18 levels in males and females did not differ in both groups^[177].

MHO

MHO is a new concept in which an individual may exhibit an obese phenotype in the absence of any metabolic abnormalities^[178,179].

MHO persons, despite having excess of body fat, have a metabolic profile characterized by high insulin sensitivity, a favorable lipid profile, and no sign of hypertension^[144].

However, there is no consensus as to how metabolic normality should be defined, so the reported prevalence of MHO ranges from 2% to 50%, depending on the specific criteria used and the population studied^[50,180-189].

MHO subjects when compared with obese insulin resistant adults have a healthier metabolic risk profile and higher disposition index (insulin sensitivity \times insulin secretion)^[171].

According to Karelis *et al.*^[190], the selection criteria for MHO individuals were partially based on the National Cholesterol Education Program's Adult Treatment Panel III report for lipid profiles [triglycerides: < 1.7 mmol/L, total cholesterol: < 5.2 mmol/L, HDL-cholesterol: > 1.3 mmol/L and low-density lipoprotein (LDL)-cholesterol: < 2.6 mmol/L] and from the study of Brochu *et al.*^[187] for insulin sensitivity (HOMA < 1.95); when 4 out of 5 criteria are met, the diagnosis of the MHO individual could be made. Intrahepatic triglyceride (IHTG) content and VAT volume were much higher in metabolically abnormal obese subjects than in MHO subjects.

In 2005 Karelis *et al.*^[143] indicated that postmenopausal women displaying the MHO phenotype also have a favorable inflammation profile, as shown by lower CRP and α -1 antitrypsin levels compared with insulin-resistant women, suggesting that lower inflammation state could play a role in the protection of this phenotype.

Manu *et al.*^[191] found that MHO was similar to NWL group regarding terms of age, fasting glucose and triglyceride levels, but with higher insulin resistance, C-reactive protein levels, LDL cholesterol levels levels and systolic blood pressure, and lower intake of dietary fiber and levels of physical activity.

However, studies with longer follow-up periods (> 15 years) have demonstrated that MHO individuals were at an increased risk of major CVD events as compared to MHNW individuals^[192,193].

Examining the natural history of the MHO phenotype it has been showed that over half of subjects progressed to frank MS over a 10 years period^[194].

Moreover, Shaharyar *et al.*^[195] demonstrated that both MHO individuals and MONW phenotypes were

associated with elevated hs-CRP, and hepatic steatosis.

In a recent paper, Achilike *et al.*^[196] showed that among subjects classified as MHO at baseline, almost half (47.6%) of them progressed to MUO within the 7.8-year follow-up period. MHO individuals who developed MUO were older and had more adiposity, higher 10-year CHD risk and lower HDL cholesterol than those who remained as MHO or become non-obese. They conclude that, MHO may not be a stable condition, because it confers markedly increased risk of developing multiple metabolic abnormalities in the future.

According to the editorial comment of Puri^[197], it must be simply accepted that obesity is a disease, and no level of obesity can be considered healthy. In fact, the studies by Chang *et al.*^[198], demonstrated that, on the basis of the coronary artery calcium scores, MHO had a significantly greater prevalence of coronary atherosclerosis than the metabolically-healthy but normal weight subjects. Moreover, Kramer *et al.*^[199] observed that compared with NWL subjects, MHO were at significantly greater risk for death and cardiovascular events.

All these data raised serious doubts on the concept of obese people maintaining a benign prognosis and highlight the fact that obesity per se is a genuine disease^[197].

Therefore, both MHO and MONW phenotypes, in the same manner of "at risk obese" phenotype, may not be benign and physicians should strive to treat individuals in these subgroups to reverse these conditions.

MUO

The MUO, also defined as "at risk" obese subjects are characterized by a BMI ≥ 30 kg/m², a PBF > 30% and high visceral fat mass, closely linked to the development of the MS, T2DM, and atherosclerotic CVD^[200-203].

Although a unifying definition of the MS does not exist^[204-206], there is a worldwide agreement about the role of insulin resistance and abdominal obesity as the main pathophysiological mechanisms for the development of metabolic disorders characterizing the MS^[207,208].

Hormonal differences after an oral glucose tolerance test may explain the propensity for impaired glucose homeostasis in then "at-risk" obese phenotype^[209].

O'Connell *et al.*^[210] divided the obese subjects in three class: MHO, MUO and obese with DM. They found that MUO and T2DM obese subjects had an omental adipocyte size greater than MHO, while subcutaneous adipocyte size, was related to metabolic health, and possibly progression from hepatic steatosis to fibrosis. Moreover, they showed that MUO group had an intermediate degree of steatosis (43%) respect to MHO (3%) and obese with T2DM (74%). Finally, they suggested that the size of the individual's adipocytes is more important than the size of the individual.

MUO individuals showed higher plasma glucose dependent insulinotropic polypeptide, lower post-glucose load glucagone-like-peptide-1, and higher levels at baseline and after glucose load, indicating inappropriate glucagone suppression^[211].

Many studies have demonstrated that increased IHTG content (*i.e.*, NAFLD) is a robust marker of metabolic dysfunction in obese people^[47,212,213], and the amount of IHTG is directly correlated with the degree of insulin resistance in the liver, skeletal muscle, and adipose tissue^[214].

However, not all obese persons develop NAFLD, insulin resistance, and cardiometabolic disease. A subgroup of obese people are those have increased IHTG content are the "Metabolic Abnormal Obese" (MAO)^[47].

Roberts *et al.*^[215] and others^[216-219] have found that, compared with Metabolic Normal Obese (MNO) subjects, MAO have decreased adipose tissue expression of genes involved in glucose uptake and lipogenesis^[47].

Moreover, Fabbrini *et al.*^[47] demonstrated distinct differences in the response to weight gain in MNO and MAO subjects. In MAO subjects, but not MNO subjects, moderate weight gain exacerbated several metabolic risk factors for CVD, including increased blood pressure, plasma triglyceride levels, VLDL apoB100 concentrations, and VLDL apoB100 secretion rates, and decreased plasma adiponectin concentrations and insulin sensitivity in the liver, skeletal muscle, and adipose tissues. Weight gain also caused a greater absolute, but not relative, increase in intra hepatic triglyceride content in MAO subjects compared with that seen in MNO subjects. Together, these data suggest that increased adipose tissue capacity for lipogenesis helps protect against the adverse metabolic effects of weight gain.

In general, metabolic disorders are associated more strongly with visceral adiposity, rather than with subcutaneous adiposity; also, the anatomic location of VAT means that fatty acids are released directly into the portal circulation and fat accumulation in the liver has been shown to be an important feature of the MS^[220,221].

SARCOPENIC OBESITY

Sarcopenia is defined as a loss of muscle mass leading to muscle weakness, limited mobility, and increased susceptibility to injury; an understanding of the underlying causes of muscle loss is critical for the development of strategies and therapies to preserve muscle mass and function^[222].

It is well known that muscle is a type of endocrine organ, and excess fat mass exerts harmful effects on vascular inflammation BMI can miscategorize a significant proportion of subjects who have lower muscle mass content and higher body fat levels as those having a same cardiovascular risk as healthy, non-obese subjects^[17].

Moreover, according to PBF cut-off classification, Di Renzo *et al.*^[165] found that 14.68% of individuals were affected by sarcopenic obesity (81.25% NWO and 18.75% MHO/at risk obese, respectively), and, according to the population attributable risk (PAR), the sarcopenia incidence could be reduced at least of 20%, by appropriate detection and treatment of obesity.

The combination of sarcopenia and obesity^[223,224], defined as sarcopenic obesity, is an important public health associated with functional limitations and increased mortality^[225,226].

The concept of sarcopenic obesity was firstly proposed by Roubenoff who suggested how the inflammatory cytokines, produced by adipose tissue, especially visceral fat, can accelerate muscle catabolism and thus contribute to the vicious cycle that initiates and sustains sarcopenic obesity^[145].

These cytokines have effects on the brain, liver, and pancreas that drive appetite, carbohydrate and fat metabolism, and energy balance. Thus, an increase in fat mass causes higher cytokines levels, which can affect protein metabolism both directly, *via* its effect on muscle amino acid balance, and indirectly, *via* insulin sensitivity.

Schrager *et al.*^[227], showed that components of sarcopenic obesity were associated with elevated levels of IL-6, C-reactive protein, IL-1 receptor antagonist, and soluble IL-6 receptor. They suggest that global obesity and, to a greater extent, central obesity directly affect inflammation, which in turn negatively affects muscle strength, contributing to the development and progression of sarcopenic obesity. These results suggest that proinflammatory cytokines may be critical in both the development and progression of sarcopenic obesity.

The key problem for this disease is the diagnosis. For this reason, in order to avoid the risk of sarcopenic obesity, the diagnosis of obesity requires the utilization of various methods, including body composition evaluation, metabolic, functional and a genetic approach^[17,228,229].

The assessment of the physical status in association with genotype represents a very important information to evaluate both the health status and quality of life. Moreover, while a number of risk factors and diagnostic methodologies are available, it would be very useful to be able to develop additional predictive tools and risk indexes for this pathology.

Among various methods used to assess body composition, DXA-derived total body fat mass, total body lean mass and ASMMI measures can reflect both the PBF, than muscle mass and muscle strength, providing a reliable measure for assessment of sarcopenia and obesity^[15,19,230].

More significant deviations from normal healthy body composition trajectories configure the development of abnormal phenotypes such as high adiposity^[41], low muscle mass, or a combination of the two^[231].

For this reason, as highlighted by Prado *et al.*^[232], there is a need to detect the high adiposity with low

muscle mass phenotypes at younger ages in order to carry out timely personalized treatment interventions, in which weight loss strategies are aimed to increase or preserve muscle mass and reduce fat mass.

For this reason measurement of body composition are fundamental for individual risk stratification.

BODY COMPOSITION EVALUATION FOR BARIATRIC SURGERY

The success rates of suggested obesity prevention and treatment strategies including lifestyle modification, behavioral therapy, and pharmacotherapy are dissatisfactory and lack efficacy in the management of morbid obesity^[233].

Surgery for the treatment of severe obesity is gaining increasing favor, and surgical interventions are currently the most effective evidence-based approach towards clinically significant and sustainable weight loss along with reduction in mortality and obesity-related comorbidities^[234,235].

According to the different classification of obesity subtypes, it is important to choose as the selection criteria of the subjects that may be underwent to bariatric surgery both the PBF, the distribution of adipose tissue and the metabolic variables.

Bariatric surgery, including Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LB), duodenal switch, and sleeve gastrectomy^[236-238], has proven to be a treatment of choice for morbid obesity^[234,239], and it is recommended for patients with BMI above 40 kg/m² or higher than 35 kg/m² when associated with comorbidities which include the different components of MS and type 2 diabetes^[240].

As previously described, the expansion of adipose tissue lead to inflammation, hypoxia, insulin resistance, limitations on energy storage, net increase in circulating free fatty acids, lipotoxicity, adverse endocrine and immune responses.

For example, in order to reduce serious sleep apnea, immobility, CVD and other medical disorders, obese patients with pathological obesity may undergo surgical treatments interventions, to reduce the adipose tissue^[241].

Thus, a reduction in fat cell size and reduction in adipose tissue growth beyond its vascular supply are favorable effects that at least partially explain the observed reduction in inflammatory markers with a reduction in adiposity, occurs with bariatric surgery.

Reversion of the low-grade inflammation and of risk factors seem to occur when a reduction in BMI is achieved and loss of adipose tissue is observed in obese individuals, after LAGB^[241,242].

As previously described the different adipose tissue depots may contribute differently to obesity related comorbidities, most studies have focused on VAT and SAT findings from a single abdominal slice, as an appropriate surrogate measure of total VAT and total

SAT.

However, Weiss *et al.*^[243] reported that the ratio between VAT and SAT remains fairly constant 6 mo following bariatric. In fact, they observed a weight reduction of 47% in male and 42.6% in female subjects, with a reduction of VAT and total SAT of 35% and 32%, respectively, in both sexes.

Weight loss after bariatric surgery is usually associated with an improvement in insulin resistance^[244].

Most studies have demonstrated a strong association between VAT and insulin resistance^[245]. In one study, reduction in VAT was associated with improvement in oral glucose tolerance even after adjusting for overall weight loss^[246], even if it is unclear whether greater VAT is a marker of insulin resistance or plays a causal role^[247].

Moreover, insulin sensitivity correlated with generalized and regional adiposity, however, the magnitude of improvement in insulin sensitivity was predicted by the percent decrease in VAT, but not by other changes in body composition^[248].

Data from Carroll *et al.*^[249] indicated that 6 mo after LGBS there were significant improvements in many cardiovascular and metabolic risk markers, with a major decreasing in insulin resistance associated to VAT reduction. The calculated total VAT volume (by CT) from eight abdominal slices decreased by 22% at 6 mo post-LB surgery, and the reduction in VAT was significantly correlated with reductions in insulin, HOMA, and glucose.

Korner *et al.*^[250], using whole-body MRI in post-surgery weight-stable female patients (at 19-25 mo post-LB and RYGB surgery), found that in women post-surgery, VAT was 44% less than in control subjects, and the difference remained significant after adjustment for total adipose tissue (TAT) and menopausal status. After adjustment for TAT, SAT in women post-surgery was significantly greater than matched controls, and there was a significant negative correlation of VAT and the degree of weight loss in women but this relationship was not significant in men.

In fact, VAT was nearly identical in men post-surgery compared with matched controls even though the degree of weight reduction was not significantly different from women (27.4% vs 32.6%).

Interestingly Toro-Ramos *et al.*^[251] showed that bariatric surgery caused substantial and robust loss in total and regional adipose tissue at 12 and 24 mo postbariatric surgery, with continued losses between 12 and 24 mo in women, when body weight change was not significant. These results indicate that bariatric surgery has an important effect on reducing adipose tissue depots even after body weight has begun to stabilize. They found a remarkable 77% reduction in VAT at 12 mo postsurgery in both men and women.

Weight loss obtained after bariatric surgery is associated with a highly significant reduction in cardiovascular risk factors^[252,253]. Moreover, systematic review and meta-analysis reported complete resolution of

T2DM in high percentage of the cases^[239], and the rank order of increasing efficacy of the most common surgical procedures progresses from the purely restrictive to the mostly restrictive to the mostly malabsorptive.

Surgical treatment of massive obesity is being extended to adolescents, seemingly with similar success and risk rates as in adults^[254].

Pontiroli *et al.*^[237] have previously observed that, although LAGB induces a durable weight loss in morbidly obese patients, a significant proportion of these patients (25%) had a relatively modest weight loss.

It is not clear demonstrated whether genetic factors that play an important role in body weight homeostasis may account for the differences in the therapeutic effects of bariatric surgery. However, in literature there are some evidences that reported a relationship between -174G>C IL-6 polymorphism with diabetes, insulin resistance, MS, longevity and cardiovascular risk^[255-257].

Di Renzo *et al.*^[258] evaluated the efficacy of LAGB surgery and the effects on anthropometry, body composition, fluid distribution, some cardiometabolic parameters and IL-6 plasma levels of selected patients after 6 mo follow-up, according to 174G>C IL-6 polymorphism. The authors have shown that in obesity bariatric treatment, LAGB seemed to determine a weight loss, sparing muscle mass and causing only mild body fluid alterations. The loss of fat mass was significant, despite a slight proportional loss of lean mass. Moreover, for the first time, this study has provided evidence that, the promoter polymorphism of IL-6 (-174G>C) gene is associated both with body composition and fluid distribution, in obese subjects, at baseline and at 6-mo follow-up after LAGB. C (-) obese carrier showed a lower capability to lose weight and body fat mass after LAGB, and a higher LAGB induced detrimental effect on bone density. This implies that LAGB was less effective if the subjects were carrying risk genotypes (C-carriers) for obesity^[258].

In conclusion, it is possible suggest that an accurate and complete body composition evaluation together with genetic variations analysis would be a important tools for the selection of the type of the bariatric surgery, and for screening in order to predict therapeutic response of obese subjects, in terms of fat loss. Further studies of the court must be made to understand what is the best type of bariatric surgery, depending on the pathology.

Remains the undoubted value of the assessment of body composition in obese patient whose treatment of bariatric surgery is recommended, in the control of quality and effectiveness of the intervention, ensuring patient safety.

CONCLUSION

It is crucial, therefore, to recommend a bariatric surgery independently from BMI and body size, but taking into account adiposopathy and sick fat that

occurs with the expansion of body fat mass, changing the inflammatory and metabolic profile of the patient.

Interactions between genetic and environmental factors such as diet and lifestyle, particularly over-nutrition and sedentary behavior, promote the progression and pathogenesis of polygenic diet-related diseases.

In the different obese phenotype, it is of primary importance to highlight a potential connection between body composition (as weight, body lean mass, body fat mass), and genetic variants, to identify individuals, who were at increased risk of reduction of skeletal muscle mass, that could lead to sarcopenic obesity.

The highlighted findings underline that it is critical to assess body composition evaluation, looking to body fat mass and lean mass, and to identify a useful biomarker for selecting the population at risk for adipose tissue-associated inflammation, for preventive medicine purposes.

In this context, the mounting influx of global quantitative data from body composition, blood biomarkers, and genetic led to change the healthcare system, transforming of the concept of medicine, intended not only as a curative intervention but as a proactive P4 medicine, that is predictive, preventive, personalized, and participatory^[259].

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