Obesity subtypes, related biomarkers & heterogeneity

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Obesity is a serious medical condition worldwide, which needs new approaches and recognized international consensus in treating diseases leading to morbidity. The aim of this review was to examine heterogeneous links among the various phenotypes of obesity in adults. Proteins and associated genes in each group were analysed to differentiate between biomarkers. A variety of terms for classification and characterization within this pathology are currently in use; however, there is no clear consensus in terminology. The most significant groups reviewed include metabolically healthy obese, metabolically abnormal obese, metabolically abnormal normal weight and sarcopenic obese. These phenotypes do not define particular genotypes or epigenetic gene regulation, or proteins related to inflammation. There are many other genes linked to obesity, though the value of screening all of those for diagnosis has low predictive results, as there are no significant biomarkers. It is important to establish a consensus in the terminology used and the characteristics attributed to obesity subtypes. The identification of specific molecular biomarkers is also required for better diagnosis in subtypes of obesity.

Key words Adipose tissue - biomarkers - body fat - genome-wide association studies - heterogeneity - HOMA - obesity - subtypes

Introduction

Over the last few decades, obesity has become an increasing public health problem worldwide, and its related conditions differ by region. For example, in China, Russia and South Africa, obesity is associated with hypertension, angina, diabetes and arthritis, whereas in India, it is associated with hypertension. Obesity can also lead to a wide variety of other illnesses. Overall, obesity is defined as the excessive accumulation or abnormal distribution of body fat (BF),
affecting health. It is classified, primarily, by body mass index (BMI, kg/m²), which is a very limited criterion. Obesity is complicated by other diseases such as type 2 diabetes mellitus (T2DM), hepatic steatosis, cardiovascular diseases, stroke, dyslipidaemia, hypertension, gallbladder problems, osteoarthritis, sleep apnoea and other breathing problems and certain types of cancer (endometrial, breast, ovary, prostate, liver, gallbladder, kidney and colon), all of which can lead to an increased risk of mortality. Cases related to pituitary, thyroid and adrenal gland diseases are considered an independent pathology but may indicate obesity.

Multifactorial polygenic obesity involves several polymorphic genes. This subtype is caused by environmental factors such as diet, lack of physical exercise, ultra-processed foods, fast food, microbiome and the chemical contaminants, which can alter gene expression. This review was aimed to make a thorough investigation of the heterogeneous links and differences among various phenotypes for diagnosis and treatment of polygenic obesity in adults and in the relationship between genes and proteins as possible biomarkers. Table I shows the definitions for the different obesity subtypes.

A selective search of two databases (PubMed and the Cochrane Library) between 1998 and 2017 resulted in the selection of the most commonly reported subtypes of obesity and heterogeneity in adults. The terminology used for searches was as follows: (i) metabolically obese (MO), metabolically unhealthy obese (MUO), metabolically abnormal obese (MAO); (ii) metabolically healthy obese (MHO); (iii) metabolically unhealthy normal weight, metabolically abnormal normal-weight, normal weight obese; (iv) sarcopenic obese (SO); and (v) metabolically healthy normal-weight. All these terms were cross-checked with the words, genes, epigenetic, genome-wide association studies (GWAS), biomarkers and receiver operating characteristic (ROC) analysis. The four most common obesity phenotypes are shown in Table II.

### Heterogeneity in obese individuals

Among overweight and obese individuals, significant heterogeneity of phenotypes occurs, which is directly related to the participation of molecules, genes and cells, in addition to environmental, social and economic factors. For example, central obesity (also known as visceral obesity) is evident from an apple or android-shaped body, and confers a greater risk of developing metabolic complications. On the other hand, peripheral obesity, or peripheral fat accumulation in the gluteofemoral region, gives a pear-shaped body and has a gynecoid phenotype associated with reduced metabolic risk.

### Table I. Definitions used for heterogeneity subtypes in obese individuals

| Obese groups | Definition                                                                 | Other terminology for this group | Notes |
|--------------|---------------------------------------------------------------------------|----------------------------------|-------|
| MHO¹¹,¹²     | Absence of metabolic disorders, including type 2 diabetes mellitus, dyslipidaemia, and hypertension | Metabolically normal obese, metabolically benign obese, metabolically healthy overweight/obese | Definitions vary in different studies, mainly based on inflammatory markers and cut-off values |
| MAO¹¹,¹²     | Defined by 2 main factors, BMI and metabolic status, which is classified as having three or more points from the NCEP-ATP III, to define MetS | MUO | Several definitions of MetS have been published since 1999, the first was proposed by the WHO |
| MONW¹¹,¹³    | Individuals are characterized by a BMI <25 kg/m², hyperinsulinaemia and (or) insulin resistance, increase abdominal and visceral adiposity, atherogenic lipid profile, unfavourable adipokine profile, as well as hypertriglyceridaemia and hypertension, and higher levels of oxidative stress | Metabolically obese healthy | Some definitions consider other variables such as BMI, FFM, VAT, HOMA, ATP III |
| Sarcopenic obese⁴ | BMI <25 kg/m², low muscle mass and weak muscle strength lack physical exercise | Sarcopenic overweight | |

MHO, metabolically healthy obese; MAO, metabolically abnormal obese; MONW, metabolically obese, normal weight; MetS, metabolic syndrome; BMI, body mass index; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; FFM, fat-free mass; VAT, visceral adipose tissue; HOMA, homeostasis model assessment; ATP III, adult treatment program III; MUO, metabolically unhealthy obese
One of the most commonly accepted diagnoses for obesity in a caucasian population is evidence of a BMI equal to or >30 kg/m$^2$. However, BMIs differ with ethnicity. A study on Dual-energy X-ray absorptiometry (DEXA) indicates that a BMI of 28 kg/m$^2$ in men, and of 24 kg/m$^2$ in women correlates better with adiposity. It is generally acknowledged that BMI indicates general adiposity, and the waist:height ratio (WHtR) indicates abdominal adiposity. People with ≥0.5 WHtR are classified as having high abdominal adiposity, although it may vary in different populations. A discrepancy also exists, particularly in individuals who have higher muscle mass.

**Metabolically healthy obese (MHO)**

MHO group or metabolically normal obese, or metabolically benign obese has been studied extensively, and, depending on the method of classification, represents 6-40 per cent of the obese population. However, these terms are inconsistent with the pathology, leaving no clear consensus on phenotype. The metabolic spectrum is defined in numerous studies. The homeostatic model assessment (HOMA) index is also used in MHO classification to identify an increased risk of mortality. In all MHO individuals, insulin levels and insulin resistance indices for HOMA, quantitative insulin-sensitivity check index (QUICKI), and Mffm/l, high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) are similar to a healthy population. However, MHO individuals show increase in other biomarkers, such as, leptin.

MHO individuals have a higher risk of developing metabolic syndrome when compared to healthy individuals of normal weight. Over time, there has been a transition from a metabolically healthy...
overweight/obese phenotype to a metabolically abnormal overweight/obese phenotype. Wang et al. found that MHO, in particular, was associated with subclinical cardiovascular dysfunction, lower global longitudinal systolic strain, dysynchrony and early diastolic dysfunction. Chang et al. reported that MHO individuals had a higher prevalence of subclinical coronary atherosclerosis than metabolically healthy normal-weight individuals; however, later studies suggested that these problems of MHO individuals might be even higher than in the metabolically unhealthy group.

The inflammatory state is reduced in MHO and may be explained by the fatty acid profile of myristic, palmitic, stearic, oleic and linoleic acids. MHO is also associated with lower levels of proinflammatory proteins and higher levels of anti-inflammatory molecules, such as overexpression of fetuin-A (AHSG), histidine-rich glycoprotein (HRG) and retinol-binding histidine-rich protein 4 (RBP4), and downregulation of histamine releasing peptide (HRP), hsCRP, complement factor 4A (C4A), and inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4). Together, these opposing effects counteract each other creating a pro-/anti-inflammatory profile.

One particular feature of MHO is an abnormality in Bromodomain and extra terminal (BET) proteins. Wang et al. discovered a connection between Brd2 obesity and T2DM. The Brd2 isoform promotes pancreatic β-cell function and proliferation and is one of the protein factors regulating gene transcription. It binds with acetylated lysines in nucleosomal chromatin and plays a role in energy metabolism. In MHO, a disruption of the BRD2 gene in the promoter region results in a reduced level of activity. BRD2 knockdown in mice protects them from insulin resistance and pancreatic β-cell dysfunction. Inhibition of BET proteins may increase insulin production and improve pancreatic β-cell function.

Metabolically abnormal obese (MAO)

A significant number of individuals in this group are overweight and have central obesity with metabolic syndrome, T2DM, cardiovascular or cerebrovascular disease and are likely to present diastolic or systolic high blood pressure and increased waist-hip circumference. This group differs significantly from the metabolic healthy obese subtype in levels of postprandial blood glucose, high-density lipoprotein cholesterol, triglycerides, insulin and adiponectin. Some of these are measured on the HOMA-IR despite variations. Certain biomarkers associated with metabolic syndrome, such as alanine aminotransferase, can increase greatly, but are still within the normal range of reference. In addition, the International Diabetes Federation (IDF), American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) have published a document on harmonizing the metabolic syndrome. The consensus criteria for a clinical diagnosis of metabolic syndrome is based on this document.

In the overweight and obese individuals, cardiometabolic risk is one of the main problems for which waist circumference (WC), and WHtR are used for identification. The other examples of heterogeneity expression are observed in the pro-inflammatory cytokines IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T cell expressed, and secreted (RANTES), macrophage inflammatory protein 1 alpha (MIP1α), and plasminogen activator inhibitor-1 (PAI 1) in visceral adipose tissue (VAT), whereas leptin and interferon inducible protein 10 are expressed mainly in subcutaneous AT (SAT). VAT is related to metabolic disorder and to upregulated activation and expression. Leucine rich repeat containing receptor family pyrin domain containing 3 (NLRP3) gene and IL1b are upregulated in VAT, which is infiltrated by proinflammatory macrophages in the MUO/MAO subgroup. Marques-Vidal et al. showed increased levels of hsCRP and also tumor necrosis factor-alpha (TNF-α) in a Swiss population based study which was associated with an increase in WC in men, and BMI in women.

It has been shown that high carbohydrate consumption and environmental factors among others modulate genotype interactions increases risk of obesity. Therefore, epigenetic mechanisms increase the number of changes in the genome, which may be related to the different phenotypes of obesity.

All gene variants are related to an increased risk of obesity; for example, the fat mass and obesity associated gene (FTO rs9999609) significantly predisposes an individual to diabetes and increased BMI and hip circumference. However, Veerman explained that the predictive power of this gene was attenuated significantly by its incomplete penetrance, suggesting that exploring gene expression in medical practice has limited relevance. Subgroups
or subtypes of heterogeneity have also been reported in other studies. A clinical subgroup of MAO is the hypertriglyceridaemic-waist phenotype (HTGW), which is classified by increased WC and increased fasting triglyceride levels, and a cluster of factors related to metabolic syndrome\(^5\). An epigenetic mechanism, known as DNA methylation, which is found in the HTGW phenotype in carnitine palmitoyltransferase 1A (CPT1A) and ATP binding cassette subfamily G member 1 (ABCG1) genes, may modify gene function through the addition of methyl to DNA. This process is strongly associated with HTGW in epigenome-wide analysis\(^56\).

A number of methylated CpG loci are also associated with obesity. Crujeiras et al\(^57\) showed that DNA methylation levels in obese insulin resistant or insulin sensitive patients could be classified by the clamp technique. Through genome-wide epigenetic analysis, 982 differentially methylated CpG sites (DMCPGs) were found in VAT. As proposed by Huang et al\(^58\), most of these DMCPGs could be related to the insulin pathway, and some could be used as markers. Pieliläinen et al\(^59\) studied SAT in monozygotic twins with different body masses and found 17 obesity-associated genes with differentially methylated 22 CpGs regions.

**Metabolically obese normal weight (MONW)**

The MONW is also known as metabolically abnormal with no obesity, metabolically abnormal individuals with no obesity (MANO), normal weight dyslipidaemia\(^60\), or pre-obesity\(^61\). As in other subtypes, MONW has multiple definitions\(^60\), most of which are inconsistent. Metabolically abnormal individuals with a normal BMI and no visual signs of obesity are also known as pre-obese individuals\(^61\). More than 23 per cent BF is evident in men and 30 per cent in women\(^62\) and both may have a visceral fat area (VFA) of ≥100 cm\(^2\), with a variable BMI cut off of <23, <25, or <26 kg/m\(^2\)\(^63\). The abnormal accumulation of BF in MONW\(^10,63\) accounts for only a small number of cases but takes into consideration VFA and BF percentage. These individuals may also develop prediabetes or borderline dyslipidaemia with upper-normal WC\(^64\).

In studies conducted in the USA, 24 per cent of adults of normal weight (BMI<25 kg/m\(^2\)) are considered metabolically abnormal and are at a high-risk of chronic diseases\(^11\) such as T2DM and cardiovascular disease. These individuals are physically inactive, have a BMI in the range of 20-27 kg/m\(^2\) and a fat mass of 2-10 kg, which is more than healthy controls of the same age\(^65\).

In MONW, some members of the same family may be hypertensive and have metabolic syndrome or cardiovascular disease, and a small number may be diabetic, although it is notable that the risk of developing diabetes mellitus is not dependent on central obesity, it depends on a number of factors in positive metabolic syndrome\(^66\). The adipose mass represents an important source of proinflammatory cytokines in obese individuals, and circulating concentrations of hsCRP, TNF-α, IL-1 α, IL-1β, IL-6 and IL-8 are elevated\(^67,68\). HsCRP in adults is strongly associated with a number of factors also seen in metabolic syndrome, central obesity and increased cardiovascular risk; however, it may not be specific to any obesity phenotype\(^69,70\). Yaghootkar et al\(^71\) reported on monogenic forms of insulin resistance in a subtype of MONW with a “lipodystrophy-like” phenotype linked to 11 genetic variants. It can lead to hypertension, coronary artery disease and diabetes mellitus.

**Sarcopenic obesity**

Sarcopenic obesity, or sarcopenically obese, is defined as a reduction in lean mass and is associated with predicting factors such as increased age, low socio-economic status, smoking, decreased physical activity, atherosclerosis and pulmonary disease\(^72\). These factors are related to an accumulation of BF and a decrease in skeletal muscle mass and muscle strength\(^24\). The prevalence of sarcopenic obesity in adults over 65 yr is higher in countries such as Mexico (10.2%), South Africa (10.3%) and Spain (11%)\(^72\).

For diagnosis, the under quintile of the skeletal muscle index (muscle skeletal/BMI) is commonly used, along with the measurement for grip strength (<30 kg for men and <20 kg for women)\(^73\). BF is measured by skinfold thickness, bioelectrical impedance analysis (BIA), DEXA, or calculation of predictive formulae, among other criteria\(^12\). DEXA not only detects adiposity but also shows osteopenia and osteoporosis\(^74\). BIA, is quick, inexpensive and non-invasive and is useful in clinical practice\(^75\). It measures body composition and is based on resistance and reactance\(^76\). Although there is no direct relation between resistance, reactance\(^77\) and adiposity, a different BIA prediction equation has been found which gives a positive predictive value for fat-free mass (FFM) in adults, for males and females\(^78\).
In particular, in sarcopenia studies with BIA, there are three main issues that need to be considered: (i) lack of standardization in the definition of sarcopenia, (ii) selection of adequate/appropriate equations to calculate FFM or appendicular lean soft tissue, and (iii) selection of population-specific cut-off points. Sarcopenic obesity can exist in individuals of different ages, not only in the older adult. Kim et al. showed the prevalence of non-sarcopenic non-obese (53%), sarcopenic non-obese (10%), non-sarcopenic obese (20%) and sarcopenic obese (15%) individuals. They found an increase in the systolic blood pressure in the sarcopenic groups.

Inflammatory markers, such as hsCRP, increase in males with sarcopenic obesity. Further, an increase in MCP-1 in serum marks the proinflammatory state. Several loci are associated with sarcopenic obesity, such as those located in PTPRD, CDK14 and IMMP2L genes. Similarly, single nucleotide polymorphism (SNPs), such as the TP53 polymorphism, predict the risk of sarcopenia, contrasting with other kinds of obesity. An association between −308 G/A TNF-α polymorphism and sarcopenic obesity was also established.

**Adipose tissue, biomarkers and heterogeneity**

There are three varieties of adipocytes: brown, white and beige. In humans, brown adipocytes are found in the neck, interscapular and supraclavicular areas. White adipocytes are found in subcutaneous and visceral regions, while beige are found in the supraclavicular region, inguinal canal and near the carotid sheath and the long muscle of the neck. The adipocytes produce a number of cytokines including adiponectin, leptin, interleukin (IL-6), PAI-1, adipin, TNF-α, resistin, angiotensinogen, aromatase and CRP. These are related to obesity, hypertension, atherosclerosis, diabetes and thrombosis, and some have a strong association with eating behaviours, chronic inflammation and metabolic disease.

Abdominal obesity is associated with an increase in IL-6, while BMI and WC relate to TNF-α levels. Lim et al. found that BMI was a poor indicator of excess adiposity in the elderly and showed that WC was a better marker. They also associated MCP-1 with the proinflammatory state, in accordance with studies by Yang et al. in which they found an increase in hsCRP in elderly males with sarcopenic obesity.

**Accuracy and limitations in terminology and biomarkers**

When considering the main group classifications for, monogenic, polygenic, multifactorial obesity and mixed cases, monogenic is proved to be the most useful in confirming the specific type by molecular methods, and subsequently, implementing strategies for personalized medicine. In cases linked to multiple genes or polygenic phenotypes, the study of genetic markers is not beneficial in clinical diagnosis. This takes into consideration that genetic predisposition is not equal to inevitability of disease in wider concept. A wide spectrum of disease susceptibility may be evident from the genes found in polygenic obesity (for example, in genes LEPR, MC4R, PCK1, POMC and PPARγ), and is also significant in monogenic obesity. This indicates that highly penetrant rare variants may be related to severe obesity, and genes with common variants could be related to more common obesity. In addition, FTO, the gene most strongly associated with obesity, only explains 0.34 per cent of phenotypic variance, which increases to 1.45 per cent with 32 GWAS. Several of studies claimed that parental BMI, birth weight, maternal occupation, maternal gestational weight and gestational smoking gave a better predictive risk of obesity than GWAS. Therefore, genetic studies should be endorsed only in individuals with early-onset obesity if they have intellectual disabilities or exhibit developmental delays, or in syndromic types.

Without agreed terminology, at present, no research or clinical diagnoses define the different phenotypes sufficiently. Paradoxically, if the individual has normal biochemical blood parameters, they are considered
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accurate, but is useful if factors such as age, race, ethnicity and gender are taken into consideration. For examples, WC has a good correlation with DEXA measures of trunk fat mass percentage and metabolic syndrome\textsuperscript{102}. To predict estimated per cent BF in older Caucasian American females and males, use of Siri-Brozek equations is recommended\textsuperscript{26}. A simple index, which was evaluated in a cross-sectional study with 17,029 non-diabetic individuals from the Korea National Health and Nutrition Examination Survey, discriminated individuals with MONW from MHO is the triglyceride glucose (TyG) index\textsuperscript{21}. Others markers of visceral obesity: the visceral adiposity index and the lipid accumulation product (LAP) are good to identify MONW phenotype; these were evaluated in 3552 normal-weight individuals from the China Health and Nutrition Survey 2009 and identified people predisposed to develop metabolic diseases\textsuperscript{13}.

**Conclusion**

Although all obese individuals have excess BF, there are important heterogenic differences between the subtypes. After reviewing various clinical, biochemical and genetic reports it is found that important progress has been made by the different groups in identifying specific differences in types of obesity, and the present

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**Perspectives**

Despite a lack of clear definitions to classify obesity subgroups, there are markers or indexes that are useful to make basic differentiations such as VAT, and fat mass, that together with BMI, WC and WHtR, all related with intra-abdominal adiposity could help in the subgroups classification\textsuperscript{18} (Figure).

To differentiate the presence or absence of the metabolic component, VAT is useful because it is mechanistically related and strongest predictor to insulin resistance, T2DM, hypertension dyslipidaemia and cardiovascular disease\textsuperscript{101}. The drawback of measuring VAT is the high cost and difficulty in carrying out these procedures. It may not be not

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**Figure.** Differences between phenotypes of obesity. *Normal weight (NW) metabolically healthy and normal visceral adipose tissue (VAT) and normal BMI. *Metabolically healthy obese (MHO) individuals have high body mass index (BMI) and healthy metabolic profile, characterized by having excessive body fat, high insulin sensitivity, low VAT/total body fat mass index and low VAT. *Metabolically abnormal obese (MAO) individuals present high BMI, are associated with abnormal metabolic profile, high VAT and increased uric acid. *Sarcopenically obese (SO) are characterized by loss of skeletal muscle mass and function, increases risk of metabolic alterations mainly in older individuals and have high VAT with BMI between 25 and 30 kg/m\textsuperscript{2}. *Metabolically obese normal weight (MONW) individuals are characterized by high VAT and a normal BMI. Source: Ref. 17.
criteria can help in diagnosis and treatment of obesity. Ideally, we need progress in two ways, first, to find better markers to distinguish each subtype of obesity more accurately for improvements in treatment, and second, to have an international consensus on terminology.

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