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Review Article

The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function

Gijs H. Goossens

Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands

Keywords
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Abstract
The current obesity epidemic poses a major public health issue since obesity predisposes towards several chronic diseases. BMI and total adiposity are positively correlated with cardiometabolic disease risk at the population level. However, body fat distribution and an impaired adipose tissue function, rather than total fat mass, better predict insulin resistance and related complications at the individual level. Adipose tissue dysfunction is determined by an impaired adipose tissue expandability, adipocyte hypertrophy, altered lipid metabolism, and local inflammation. Recent human studies suggest that adipose tissue oxygenation may be a key factor herein. A subgroup of obese individuals – the 'metabolically healthy obese' (MHO) – have a better adipose tissue function, less ectopic fat storage, and are more insulin sensitive than obese metabolically unhealthy persons, emphasizing the central role of adipose tissue function in metabolic health. However, controversy has surrounded the idea that metabolically healthy obesity may be considered really healthy since MHO individuals are at increased (cardio)metabolic disease risk and may have a lower quality of life than normal weight subjects due to other comorbidities. Detailed metabolic phenotyping of obese persons will be invaluable in understanding the pathophysiology of metabolic disturbances, and is needed to identify high-risk individuals or subgroups, thereby paving the way for optimization of prevention and treatment strategies to combat cardiometabolic diseases.

Gijs H. Goossens, PhD
Department of Human Biology
NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center
PO Box 616, 6200 MD, Maastricht, The Netherlands
G.Goossens@maastrichtuniversity.nl

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Introduction

Obesity is currently one of the main public health concerns since it is a major contributor to the global burden of chronic diseases, including cardiovascular disease, non-alcoholic fatty liver disease, type 2 diabetes mellitus, and certain types of cancer [1]. Insulin resistance in peripheral tissues and pancreatic beta-cell dysfunction are key factors in the development of type 2 diabetes. Although the relative contributions of these parameters to the pathophysiology of type 2 diabetes have been debated extensively, it is well established that a feedback loop exists between insulin sensitive peripheral organs and the pancreatic beta-cell [2]. The hyperbolic relationship between insulin sensitivity and insulin secretion explains the markedly increased insulin response in insulin resistant as compared to insulin sensitive subjects [3]. Normoglycemia is maintained in situations where the compensatory increase in insulin secretion is sufficient to overcome peripheral insulin resistance. However, failure of this compensatory insulin response will lead to impaired glucose metabolism and may eventually result in overt type 2 diabetes [2, 3]. Therefore, it is of utmost importance to better understand the pathophysiological basis for both insulin resistance and beta-cell dysfunction in humans. The aim of the present review is to provide an adipocentric view on the pathophysiology of insulin resistance in humans. More specific, the importance of total fat mass, body fat distribution, and adipose tissue function in the metabolic phenotype of obese individuals will be highlighted, and the clinical relevance thereof will be addressed. In addition, the putative role of adipose tissue oxygenation in adipose tissue biology and metabolic health will be discussed.

Detailed Metabolic Phenotyping in Obesity: Paving the Way Forward

BMI

The BMI, which is an anthropometric index that is used as a surrogate marker for fat mass and for classifying obesity, is positively associated with risk factors for cardiovascular and metabolic diseases when BMI is above 18.5 kg/m^2. Importantly, the relationship between BMI and body fat mass is not sufficiently strong to accurately estimate adiposity in a particular individual since BMI does not take body composition (i.e., skeletal muscle mass) into account. Therefore, if the amount of fat mass is the true risk factor for cardiometabolic health and longevity, then the use of BMI is only an approximation and is therefore inadequate [4]. The use of BMI as an indicator of metabolic health is even more problematic in older obese persons with decreased muscle mass and strength, i.e. sarcopenic obese patients, who are at special risk for adverse outcomes [5]. Based on the most recent prospective data from the Global BMI Mortality Collaboration, a BMI of 20.0–25.0 kg/m^2 is associated with the lowest mortality rate [6]. Noteworthy, the latter analysis limited confounding and reverse causality by restricting analyses to never-smokers, excluding subjects with known pre-existing chronic disease and omitting the initial 5 years of follow-up. The use of universal BMI cut-off points to classify subjects as normal weight, overweight and obese, however, do not consistently reflect adiposity in different ethnic populations. This may be particularly problematic for South Asian populations, displaying a greater proportion of body fat for a given BMI than Caucasians [7]. The latter is in agreement with the higher susceptibility to develop type 2 diabetes and coronary artery disease in South Asians in spite of lower BMI [8]. The value of BMI as a marker for obesity and indicator of metabolic health has been extensively debated and is discussed in more detail elsewhere [4]. Currently, more sensitive techniques to determine body composition are available, and phenotyping beyond BMI is clearly needed to accurately assess metabolic health at an individual level.

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Fat Mass

Although total fat mass is a more accurate measure of the metabolic phenotype than BMI, the absolute amount of body fat does not unambiguously reflect metabolic health at an individual level. This is exemplified by the finding that abdominal liposuction, which is the surgical removal of subcutaneous adipose tissue in the abdominal region, does not significantly improve obesity-associated metabolic abnormalities such as insulin resistance in humans [9]. Furthermore, pharmacological treatment with thiazolidinediones (peroxisome proliferator-activated receptor gamma (*PPAR-γ*) agonists) improve insulin sensitivity in humans, despite significant fat mass gain [10]. Another condition in which the association between adipose tissue mass and metabolic health might seem paradoxical is lipodystrophy. A deficiency of adipose tissue, as in patients with (partial) lipodystrophy, is also associated with insulin resistance and a high incidence of type 2 diabetes [11]. Indeed, lipodystrophic mice are severely insulin resistant [12], and surgical implantation of adipose tissue from healthy mice into lipodystrophic animals reversed insulin resistance in a dose-dependent manner [13]. Taken together, excessive adipose tissue mass as well as a (partial) lack of adipose tissue are related to insulin resistance and predispose towards chronic cardiometabolic diseases. This implies that total adipose tissue mass is not the predominant factor that explains the increased metabolic risk in obese individuals. Rather, the location where the excessive calories are stored in combination with adipose tissue function seem to determine metabolic health.

Body Fat Distribution

Body fat distribution is a strong metabolic and cardiovascular risk factor. The mechanisms that underlie inter-individual differences in body fat distribution are complex and remain to be elucidated although evidence indicates that sex hormones [14], use of glucocorticoids [15], genetic make-up [16], and epigenetic mechanisms [17–19] determine where the excessive calories from the diet are stored. Accumulation of adipose tissue in the upper body (abdominal region) is associated with the development of obesity-related comorbidities and even all-cause mortality. In contrast, population studies have shown that accumulation of fat in the lower body (gluteofemoral region) is associated with a protective lipid and glucose profile as well as a decrease in cardiovascular and metabolic disease prevalence after adjustment for total body fat mass [20, 21]. These differences in disease risk are due to strikingly divergent functional properties of these adipose tissue depots as will be discussed in the next section.

Adipose Tissue Function

Adipose tissue is the main lipid storage depot in our body and, as such, has a crucial role in buffering the daily influx of dietary fat entering the circulation [22, 23]. Thus, the ability of our body to adapt to (chronic) changes in caloric intake largely depends on the ability of adipose tissue to accommodate a potential excess of calories. In obesity, the subcutaneous adipose tissue may fail to appropriately expand to store the energy surplus. This in turn may lead to ectopic fat deposition in other tissues involved in metabolic homeostasis (i.e., skeletal muscle, the liver, and visceral adipose tissue) and, consequently, insulin resistance [22, 24, 25] (fig. 1). Therefore, the expandability of subcutaneous adipose tissue seems to be a critical factor in the development of insulin resistance [26] although this concept is mainly based on cross-sectional findings and has recently been challenged by an 8-week overfeeding study in humans [27]. Thus, lipids may be predominantly stored in subcutaneous adipose tissue before marked expansion of the visceral adipose tissue depot occurs although inter-individual differences in the fat storage pattern within a certain population may occur. The factors underlying impaired adipose tissue expandability are not yet fully understood, but the properties of its extracellular matrix and angiogenic capacity seem to be involved [28]. Interest-

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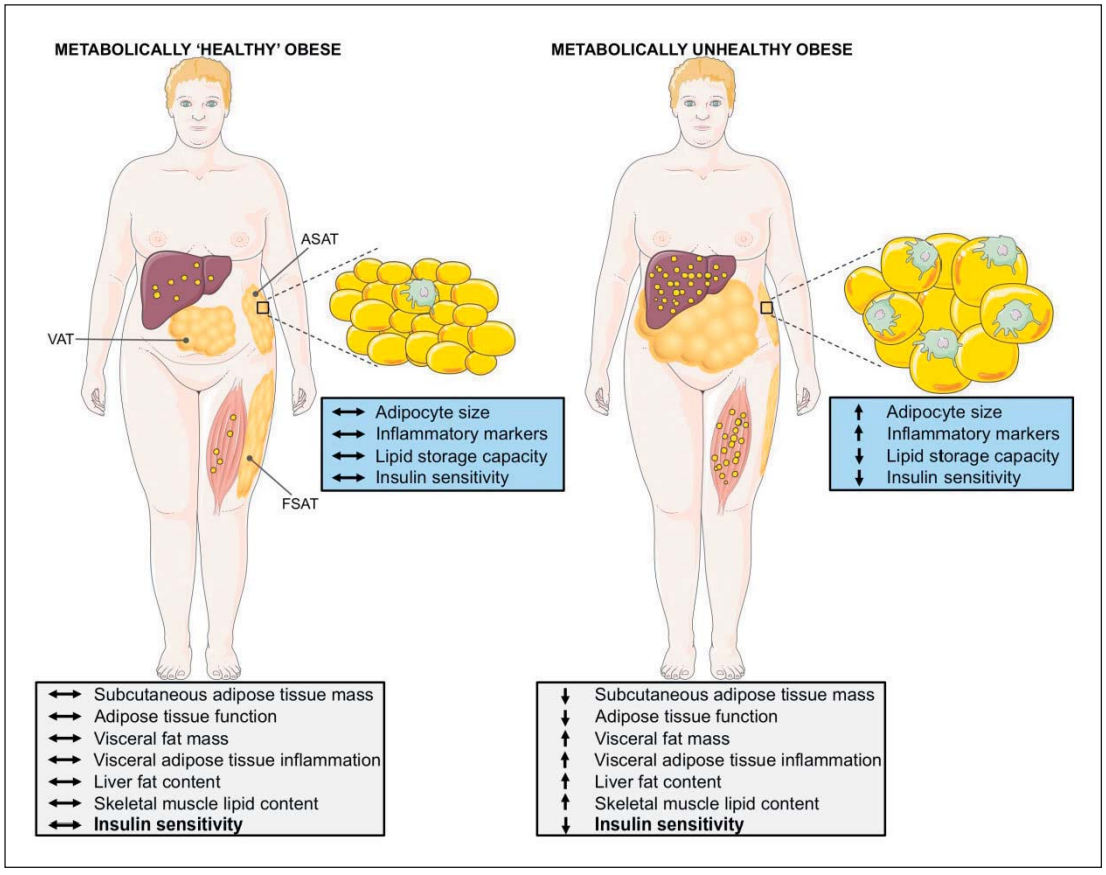

Fig. 1. Differences in adipose tissue function and body fat distribution between MHO and metabolically unhealthy obese individuals. Expansion of adipose tissue does not necessarily translate into metabolic abnormalities. A subgroup of individuals with obesity, referred to as MHO individuals, is relatively protected against the development of cardiometabolic diseases as compared to metabolically unhealthy obese subjects. Emerging evidence suggests that alterations in adipose tissue function and body fat distribution are key factors underlying the metabolically unhealthy obese phenotype. Metabolically unhealthy obese individuals are characterized by lower subcutaneous fat mass, adipocyte hypertrophy, a pro-inflammatory adipose tissue phenotype and an impaired fat storage capacity of adipose tissue, which may result in ectopic fat deposition (i.e., more visceral fat, lipid accumulation in the liver and skeletal muscle) and inflammation in visceral adipose tissue, thereby contributing to the development of insulin resistance and chronic cardiometabolic diseases. ASAT = abdominal subcutaneous adipose tissue; FSAT = femoral subcutaneous adipose tissue; VAT = visceral adipose tissue.

ingly, in contrast to the belief that inflammatory signals exert a fundamentally negative impact on metabolism, there is evidence in rodents that pro-inflammatory signaling in adipose tissue is required for proper adipose tissue remodeling and expansion [29]. It has been shown that adipose tissue-specific reduction in pro-inflammatory potential in mice reduced in vivo adipogenic capacity, which was associated with ectopic lipid accumulation, glucose intolerance, and systemic inflammation [29]. These data suggest that adipose tissue inflammation may be an adaptive response that enables safe storage of excess nutrients in adipose tissue, thereby protecting against metabolic and inflammatory perturbations.

Importantly, the inability to increase adipose tissue mass through adipocyte hyperplasia will evoke adipocyte hypertrophy during a prolonged positive energy balance. It is well estab-

lished that enlargement of adipocytes is a key characteristic of adipose tissue dysfunction [22, 24, 25]. Hypertrophic adipocytes have a markedly impaired capacity to rapidly store dietary fat, because they are already overloaded with stored lipids, which results in a redirection of lipids towards other metabolic organs. In addition, hypertrophic adipose tissue is characterized by infiltration of adaptive and innate immune cells and altered adipokine secretion. Together, these disturbances may lead to the development of peripheral insulin resistance [22, 24, 25].

One reason for the discrepancy in cardiometabolic disease risk between upper-body and lower-body obesity is that abdominal fat depots are characterized by rapid uptake and storage of energy from the diet and a high lipid turnover (i.e., lipolysis), whereas the lower-body fat stores have a reduced lipid turnover rate and sequester lipids that would otherwise be directed towards non-adipose tissues [30, 31]. In other words, the lower body fat seems to have a higher lipid buffering capacity and retains fatty acids well, thereby acting as a protective 'metabolic sink'. Differences in energy storage between subcutaneous and visceral adipose tissue following meal ingestion have not been examined directly since assessment of metabolite fluxes (arterio-venous concentrations gradients) across human visceral adipose tissue is unfortunately not feasible. Only few studies have investigated potential differences in the inflammatory phenotype of upper-body and lower-body adipose tissue, showing no major differences in gene expression of inflammatory markers between abdominal subcutaneous and gluteal adipose tissue [19, 32]. However, it has recently been demonstrated that in vivo IL-6 release from gluteofemoral adipose tissue was markedly lower than from the corresponding abdominal subcutaneous fat depot both in men and women [19], suggesting that lower-body fat may have a more beneficial inflammatory phenotype. Noteworthy, human abdominal subcutaneous adipose tissue is divided by the Scarpa's fascia into deep and superficial abdominal subcutaneous adipose tissue layers that have different structural and functional properties. It has been demonstrated that deep abdominal subcutaneous adipose tissue has a higher expression of pro-inflammatory, lipogenic and lipolytic genes, and contains higher proportions of saturated fatty acids and an increased proportion of small adipocytes [33, 34]. The latter finding is in line with greater adipogenic potential and lower *PPAR-γ* DNA methylation levels in abdominal superficial as compared to deep-layer adipocytes [35]. Moreover, deep abdominal subcutaneous adipose tissue seems to expand disproportionally more than the superficial fat depot with increasing obesity, which predisposed toward whole-body insulin resistance and increased cardiovascular risk independent of other adiposity measures in men [34].

Future studies are required to assess potential differences in the phenotype of upper-body and lower-body adipose tissue, and to unravel underlying mechanisms. To conclude, these findings emphasize the central role of adipose tissue function in cardiometabolic disease risk.

Adipose Tissue Oxygen Partial Pressure

Recent studies suggest that adipose tissue oxygenation, which is determined by the local balance between oxygen supply and oxygen consumption, may be a key factor determining the adipose tissue phenotype, as extensively reviewed elsewhere [36–39]. Although the number of studies in which adipose tissue oxygen partial pressure (AT PO_2) has been measured is very limited, several lines of evidence suggest that AT PO_2 is reduced in rodent models of obesity [40–42]. Importantly, the models used in these studies do not reflect human physiology, as discussed previously [36, 37]. The first study investigating abdominal subcutaneous adipose tissue oxygenation in obese and lean individuals supported the available data in rodents, showing lower AT PO_2 in obesity [43]. However, we have challenged the concept of adipose tissue 'hypoxia' in human obesity, demonstrating that AT PO_2 was *higher*

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rather than *lower* in obese compared to lean subjects, despite lower blood flow (oxygen supply), and was associated with adipose tissue inflammation and peripheral insulin resistance [44]. A diet-induced weight loss study that we have very recently performed in our laboratory substantiates the latter findings. Environmental hypoxia exposure decreases the partial pressure of arterial oxygen, and as such reduces oxygen supply to peripheral tissues, including adipose tissue [45]. Interestingly, exposure to moderate hypoxia for 10 subsequent nights increased whole-body insulin sensitivity in a small group of obese individuals [46] which may at least partly be explained by decreased AT PO_2 [44]. Future studies are required to establish the importance of the adipose tissue oxygenation in metabolic health.

Metabolically Healthy Obesity: A Misleading Concept?

Intriguingly, expansion of adipose tissue does not necessarily translate into metabolic abnormalities. A subset of obese individuals (~10–30% of obese individuals) [47], often referred to as 'metabolically healthy obese' (MHO), seems to be relatively protected against worsening of metabolic health (fig. 1). Since the criteria to classify MHO as well as the cut-off values for these parameters have only recently been established [47], most studies performed thus far have defined MHO as the absence of metabolic disturbances, including dyslipidemia, insulin resistance, impaired glucose metabolism, and overt type 2 diabetes [47–50]. However, it can be debated whether MHO individuals are really healthy since several recently performed meta-analyses of prospective cohort studies have shown that the majority of MHO subjects have a markedly increased risk of developing type 2 diabetes [51] and cardiovascular disease [52, 53] over time as compared to healthy normal weight subjects. Strikingly, one of these meta-analyses has shown that metabolically healthy obesity was not associated with mortality and increased cardiovascular events compared with metabolically healthy normal weight when all studies were included. Notably, however, a 24% increased risk was found when only studies with follow-up periods longer than 10 years were included in the analysis [53]. In line, Appleton and colleagues [54] have demonstrated that MHO is a transient phenotype in about one-third of the MHO subjects. Interestingly, the latter study demonstrated that persistence of a MHO phenotype during 5.5–10.3 years of follow-up, which was related to younger age and lower central adiposity, was associated with comparable risks for diabetes and cardiovascular disease as seen in metabolically healthy normal weight subjects [54]. Therefore, it seems that the majority of MHO individuals is clearly on the way to becoming 'unhealthy' obese. Noteworthy, MHO individuals may also have a reduced quality of life due to an increased prevalence of other obesity-related comorbidities such as psychological abnormalities, osteoarthritis, respiratory diseases, gynecologic abnormalities, and skin problems. Indeed, a pooled analysis of 8 cross-sectional studies has demonstrated that MHO individuals have an increased risk of depressive symptoms [55]. These data indicate that major efforts should be made to prevent obesity and to maintain a metabolically healthy phenotype in subjects that already have developed obesity.

The key role of adipose tissue function in metabolic health becomes furthermore apparent when comparing obese insulin sensitive (MHO) and obese insulin resistant individuals. MHO subjects are characterized by more abdominal subcutaneous adipose tissue, lower visceral fat mass, less fat accumulation in liver and skeletal muscle, smaller (more insulin sensitive) adipocytes, less macrophage infiltration and inflammation in (visceral) adipose tissue, and a more favorable inflammatory profile as compared to metabolically unhealthy obese persons, matched for age, gender, BMI, and fat mass [48, 49, 56, 57] (fig. 1). In addition, it seems that the physical fitness level is an important determinant of the metabolic phenotype in obese individuals [58]. Together, these findings may imply that stratification of obese subjects

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based on metabolic health may be necessary to optimize prevention and treatment strategies, and it provides a tool to better understand the role of adipose tissue function and other potential biological mechanisms in obesity-related complications. Indeed, there is some evidence that risk stratification at baseline improves the effectiveness of a certain intervention in a particular subgroup of the population [59]. This is exemplified by a recent analysis of data from the TULIP study, demonstrating that stratification of subjects with prediabetes by phenotype (including impaired insulin secretion, insulin resistance, and non-alcoholic fatty liver) at baseline predicts the effectiveness of a lifestyle intervention to achieve normal glucose homeostasis. More specific, the latter study demonstrated that a high-risk phenotype at baseline was associated with reduced improvement in glycemia following lifestyle intervention [60].

Conclusions

BMI and body fat mass are important determinants of metabolic health at the population level. Body fat distribution and adipose tissue dysfunction, which may partly be explained by altered adipose tissue oxygenation, are key factors in the development of obesity-related insulin resistance and cardiometabolic diseases and better predict disease risk at the individual level. Although MHO individuals are relatively protected against chronic diseases as compared to metabolically unhealthy individuals, which is at least partly due to a better adipose tissue function and less ectopic fat storage, they do have a markedly increased risk of developing obesity-related diseases in comparison with normal weight individuals. Therefore, 'metabolically healthy' obesity should not be regarded as a harmless condition. Studies to further unravel the mechanisms underlying the protective properties of adipose tissue in MHO will be invaluable in obtaining a better understanding of the pathophysiology of insulin resistance and cardiometabolic diseases. Detailed metabolic phenotyping, including tissue-specific profiling, is essential to identify individuals or subgroups at increased risk of developing metabolic diseases, and to optimize prevention and treatment strategies.

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Disclosure Statement

The author has not declared any conflicts of interest.

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