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Differences in the vascular and metabolic profiles between metabolically healthy and unhealthy obesity

Eleonora Candi[a], Michela Campanelli[b], Giuseppe Sica[b], Francesca Schinzari[e], Valentina Rovella[c], Nicola Di Daniele[c], Jerry Melino[a,d,f], Manfredi Tesauro[c,*]

[a] Department of Experimental Medicine, University of Rome "Tor Vergata", 00133 Rome, Italy
[b] Department of Surgery, University of Rome "Tor Vergata", 00133 Rome, Italy
[c] Department of Systems Medicine, University of Rome "Tor Vergata", 00133 Rome, Italy
[d] Biochemistry Laboratory, Istituto Dermopatico Immacolata (IDI-IRCCS), 00100 Rome, Italy
[e] Department of Internal Medicine at Policlinico A. Gemelli IRCCS, 00168 Rome, Italy
[f] Medical Research Council, University of Cambridge, UK

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ABSTRACT

Individuals suffering from severe obesity but not presenting the typical metabolic alterations, are included in a subclass of obesity defined Metabolically Healthy Obesity (MHO). The physiological factors underlying what seems a protective and favourable metabolic profile remain unclear. MHO individuals are more insulin-sensitive, have relatively lower visceral/ectopic fat accumulation and reduced levels of chronic low-grade inflammation, compared to obese subjects with co-morbidities. The study of MHO subjects represents a great opportunity for the recognition of the mechanisms that lead to the vascular and metabolic complications in obesity. Finding the differences among the metabolic profile of visceral adipose tissue between metabolically healthy and unhealthy obesity may lead to future personalized and stratified therapies.This review article summarizes the pathomechanisms and metabolic changes in MHO and metabolically unhealthy obesity (MUO), reviews clinical studies on the subject, and discusses preventive and therapeutic options.

Introduction

Obesity is classified by body mass index (BMI, kg/m^2) and is defined as the excessive accumulation or abnormal distribution of body fat (BF) which affects health (Bray, 2003, Tesauro et al., 2011). Obesity has become a worldwide increasing public health problem, with numbers almost tripled compared to 1975 (WHO 2020). It has been established that abdominal obesity, assessed by waist circumference (WC), can help to evaluate obesity-related health risk (Clinical guidelines on the identification 1998 Nov, Zhu et al., 2002 Oct). Important evidence suggests that WC coupled with BMI predicts cardiovascular and metabolic risk better than BMI alone (Rexrode et al., 1998, Janssen et al., 2002). In the last 20 years our research group has demonstrated the presence of endothelial dysfunction, accelerated atherosclerosis and increase in cardiovascular disease, in patients with obesity and metabolic disorders related thereof (Tesauro et al., 2007, Tesauro et al., 2008, Tesauro et al., 2010, Tesauro et al., 2013, Schinzari et al., 2017, Schinzari et al., 2017). Apart from vascular calcification, hypertension and stroke, obesity is often complicated by other medical condition such as dyslipidemia, type 2 diabetes mellitus (T2DM), hepatic steatosis, gallstone formation, osteoarthritis, sleep apnea and various forms of solid cancers (endometrial, breast, ovary, prostate, liver, gallbladder, kidney and colon cancer) (Purnamasari et al., 2011, Sileri et al., 2004, Marafini et al., 2015, Tesauro et al., 2017, Schinzari et al., 2019, Schinzari et al., 2020, Iyengar et al., 2016).

Nevertheless, it has been noted that some severely obese individuals, do not present the typical metabolic alterations of the so-called metabolic syndrome and they seems not to be affected by the same high level of comorbidity. To distinguish this type of obesity, it was coined "metabolically healthy obesity (MHO) (Candi et al., 2018, Schinzari et al., 2017). Data relating to the real difference in cardiovascular events and mortality of this population compared to lean and metabolically healthy individuals are controversial. Unlike in earlier studies, in recent studies, the absence of metabolic syndrome was not associated with a reduced risk of cardiovascular disease, (Kramer et al., 2013, Bell et al., 2014, Chang et al., 2014, Arnlöv et al., 2010, Hamer and Stamatakis, 2012). For this review article, A selective search of two databases (PubMed and the Cochrane Library) between 2000 and 2020

* Corresponding author at: Manfredi Tesauro, MD, Associate Professor of Internal Medicine, Department of Systems Medicine, University of Rome "Tor Vergata", Viale Oxford 81, 00133 Rome, Italy.
E-mail address: mtesauro@tiscali.it (M. Tesauro).

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Table 1
Determinants of MHO and MUO.

Metabolic Unhealthy Obese (MUO)	Metabolic Healthy Obese (MHO)
Men	Women
Insulin Resistance	Preserved Insulin Sensitivity
Arterial Hypertension	Normotension
Dyslipidemia	Normal Lipid Profile
Chronic Low-Grade Inflammation	Lower Inflammatory Activity
Altered Liver Function	Normal Liver Function
Older	Younger
Higher Visceral/Ectopic Fat Accumulation	Lower Visceral/Ectopic Fat Accumulation
Poor Nutritional Status	Physically Active

was conducted to investigate the heterogeneous links and differences among the metabolic profile of visceral adipose tissue between metabolically healthy and unhealthy obesity, resulting in the selection of the most commonly reported subtypes of obesity.

In general, MHO individuals are more insulin-sensitive and have relatively less abdominal fat (both visceral and subcutaneous) than their disease-prone counterparts (Karelis, 2008, Samocha-Bonet et al., 2012). Diet and exercise can decrease both insulin resistance and inflammation in such obese patients. Environmental factors such as unhealthy diet, lack of physical exercise, ultra-processed foods or fast food, microbiome and chemical contaminants, seems to alters gene expression and lead to a shift toward metabolically unhealthy obese (MUO). Long-term studies have indeed shown that the prevalence of MHO in a population of obese subjects gradually decreased over time (Soriguer et al., 2013) and that both severity and duration of obesity were associated with the incidence of the metabolic syndrome during the observation period (Hwang et al., 2015, Mongraw-Chaffin et al., 2016).

Definition of MHO and MUO

More than 30 different definitions of MHO have been used in clinical studies. MHO could be defined by the absence of any metabolic disorder and cardiovascular disease, including type 2 diabetes, dyslipidaemia, arterial hypertension, and atherosclerotic cardiovascular disease (ASCVD) such as coronary artery disease in a person with obesity (BMI ≥30 kg/m$^{2)}$ (Rey-López et al., 2014, Iacobini et al., 2019). MHO is more often observed in young, physically active persons with a better nutritional status and low levels of ectopic and visceral fat storage. Recently, Lavie and colleagues (Lavie et al., 2018) proposed a definition of MHO in obese adults meeting all of the following criteria: serum triglycerides ≤1.7 mmol/l (≤150 mg/dl), HDL-cholesterol serum concentrations >1.0 (>40 mg/dl) (in men) or >1.3 mmol/l (>50 mg/dl) (in women), systolic blood pressure (SBP) ≤130 mmHg, diastolic blood pressure ≤85 mmHg, no antihypertensive treatment as an alternative indicator, fasting blood glucose ≤ 5.6 mmol/l (≤100 mg/dl), and no drug treatment with glucose lowering agents. Conversely, MUO is characterized by the presence of high liver fat content, less adipose tissue on the lower extremities, lower cardiorespiratory fitness and physical activity, insulin resistance, higher markers of inflammation, and adipose tissue dysfunction (Table 1). A proinflammatory, diabetogenic and atherogenic secretion pattern may contribute to the development of MUO. So far, data supports models for the development of MUO (Blüher, 2009, Ghaben and Scherer, 2019) in which ectopic fat and impaired adipose tissue function may lead to systemic insulin resistance, lipotoxicity, and a proinflammatory state. Theoretically, this condition might play a causal role in the transition from MHO to MUO, but whether circulating parameters can predict the conversions, it is still a matter of debate and it remains an open question that needs to be addressed in prospective epidemiological studies.

Prevalence of MHO and MUO

The prevalence of MHO is not very reliable and show a large variation due to lack of standardized definitions of this phenotype. MHO has been shown to range between 4.2% and 13.6% in a random sample from a Chinese adult population (Liu et al., 2019). A recent meta-analysis from 12 cohort and 7 intervention studies, found a 35% prevalence of MHO with significant regional differences (Lin et al., 2017). In general, MHO seems to be more prevalent in women than in men and decreases with age (Table 1) . The greatest gender difference has been found in the United Kingdom National Child Development Study (NCDS), with MHO prevalence of 9% in men compared to 28.4% in women, whereas MHO prevalence was similar in men (19%) and women (21.1%) in a cohort from Italy (Van Vliet-Ostaptchouk et al., 2014). MHO has also been found in Asian and African populations (depending on diagnostic criteria and based on a BMI ≥25 kg/m2 cutoff for obesity), ranging from 4.2% in a cohort from China with an obesity prevalence of 24.3%, to 13.3% among Asian Indians with a 28.1% obesity prevalence, and 28.5% in African Americans (Geetha et al., 2011, Cherqaoui et al., 2012). MHO may be a more frequently observed condition in children and adolescents. In a cross-sectional study from Canada, which included girls and boys aged 8–17 years with a BMI ≥ 85th percentile, prevalence of MHO was 21.5% when cardiometabolic risk factors were considered, and 31.5% if insulin resistance parameters were applied to define MHO. In children and adolescents of the Korea National Health and Nutrition Examination Survey, MHO prevalence was between 36.8% and 68.8% (Prince et al., 2014, Yoon et al., 2017). The risk of transitioning from MHO to MUO is greater in those with a higher BMI, older age, evidence of more severe metabolic dysfunction (i.e., number of abnormal metabolic criteria and values that are closer to the upper limit of the normal range, and the presence of hepatic steatosis), a poor lifestyle index (a composite of type of diet, leisure time and physical activity) and weight gain during the observation period (Chen et al., 2019, Lallukka and Yki-Järvinen, 2016).

Hamer et al. (Hamer et al., 2015 Nov) have characterized MHO as possibly transitional stage before the onset of metabolic dysfunction. He examined the behavioral and biological characteristics of healthy obese adults that progressed to an unhealthy state over 8 years follow-up. They analyzed 2422 men and women (44.2% men) from the English Longitudinal Study of Ageing and over 8 years follow-up, 44.5% of healthy obese subjects had transitioned into an unhealthy state, compared to only 16.6 and 26.2% of healthy normal-weight and overweight adults respectively. The Authors concluded that MHO is a relatively unstable phenotype that was not attributable to self-reported lifestyle behaviors, but they observed greater increases in waist circumference that is likely to be reflective of adverse changes in visceral adiposity. Important features of instability were also development of low-grade systemic inflammation, impaired glycemic control, and reduction in HDL-cholesterol. It is also known that estrogens are important regulators of fat distribution, body weight, inflammation, and metabolic risk. The upper body fat accumulation, decreased peripheral fat deposition, and ectopic fat accumulation are examples of altered body composition during the transition to menopause; these alterations could be considered the main mediator of cardiometabolic related morbidity and mortality, and are likely menopause-related. The menopausal status is one of the factors contributing to the conversion of MHO status to MUO status in the women. The findings that the degree of conver-

sion from MHO to MUO in women with higher visceral adipose tissue was less pronounced than in men may be due to this substantial effect of menopause on body fat distribution (Mongraw-Chaffin et al., 2018). Kaba (Kabat et al., 2017 Jan) and colleagues, in a multivariable analysis, demonstrated several predictor variables, showing significant associations with specific transitions: these investigators enrolled 3512 women, followed-up for an average of 6 years to examine the frequency of different metabolic obesity phenotypes at baseline, the 6-year transition probabilities to other states, and predictors of the risk of different transitions. Six phenotypes were defined by cross-tabulating BMI (18.5– o 25.0, 25.0– o 30.0, ⩾ 30.0 kg m2) by "metabolic syndrome". A continuous-time Markov model was used to estimate 6-year transition probabilities from one state to another. Over the 6 years of follow-up, one-third of women with the healthy obese phenotype transitioned to the metabolically unhealthy obese (MUO) phenotype. Overall, there was a marked tendency toward increased metabolic deterioration with increasing BMI and toward metabolic improvement with lower BMI. Among MHO women, the 6-year probability of becoming MUO was 34%, whereas among unhealthy normal-weight women, the probability of 'regressing' to the metabolically healthy normal- weight phenotype was 52% (Kabat et al., 2017 Jan). These results indicate that metabolic obesity phenotypes are susceptible to change and that there is a strong interplay between body weight and metabolic health. Metabolically unhealthy normal weight (MUNW) women had the highest rates of metabolic improvement, whereas MHO women had the highest rates of metabolic deterioration (Kabat et al., 2017 Jan).

Main Clinical Differences between MHO and MUO

The heterogeneous definitions of MHO represent an important limitation for the interpretation of studies reporting a wide range of associations between MHO, cardiovascular disease, overall mortality, and the risk for metabolic diseases (Mongraw-Chaffin et al., 2018). MHO is characterized by three main clinical features: a reduced accumulation of visceral adipose tissue (VAT) and ectopic fat for equal total adiposity, preserved insulin sensitivity, and a lower degree of systemic and adipose tissue inflammation (Iacobini et al., 2019). How much and where fat is stored, is controlled by a number of factors. The main predictors of body fat distribution are age, sex, and total body fat content. However, substantial evidence indicates that fat distribution for a given BMI is regulated also by genetic factors, Moreover, in a large BMI-stratified cohort, Stefan and al (Stefan et al., 2018), linked high liver fat content and predominantly abdominal and visceral adiposity to MUO, whereas greater insulin sensitivity, better insulin secretion, cardiorespiratory fitness, and lower body subcutaneous fat mass, were associated with an MHO phenotype. Moreover, epidemiological studies have demonstrated that, for a given amount of total fat, greater fat accumulation in the lower body's subcutaneous adipose tissue (SAT) is a determinant of MHO and is associated with lower risk of cardiovascular disease (CVD). Conversely, in equally obese individuals, prevalent fat accumulation in VAT, as determined by computed tomography, is associated with a MUO phenotype, characterized by hyperinsulinemia, glucose intolerance and atherogenic dyslipidemia (Iacobini et al., 2019) (Fig. 1). Among these features, multiorgan insulin resistance is considered the most important factor responsible for the development of CVD. Insulin sensitivity is greater in people with MHO than in those with MUO, and many individuals diagnosed with MHO are more insulin resistant than those who are metabolically healthy and lean (MHL), manifested by higher fasting plasma insulin concentrations and blood glucose concentrations following an oral glucose tolerance test (Bell et al., 2015). The factors responsible for the greater preservation of insulin action in people with MHO than in those with MUO are not clear, but could be related to differences in potentially modifiable lifestyle factors and alterations in adipose tissue biology (Sun et al., 2011).

The study of MHO subjects can represent an important model for the recognition of the mechanisms underlying vascular and metabolic damage in obesity. In fact, obesity alone is capable of leading to vascular dysfunctions even in the absence of other metabolic alterations. Already in 2006, Van Guilder and colleagues, demonstrated the presence of endothelial dependent dysfunction in obese subjects who did not have arterial hypertension and type 2 diabetes (Van Guilder et al., 2006). In addition, it was demonstrated that NO-mediated, endothelium-dependent vasodilation is altered in overweight / obese subjects compared to healthy lean people (Weil et al., 2011). In a study carried out by our research group we have shown that obese subjects – in addition to presenting an altered endothelium-dependent vasodilation mediated by nitric oxide, also have NO-independent response due to an altered responsiveness of vascular smooth muscle cells to the action of nitric oxide (Schinzari et al., 2015 Nov 1). We could further characterize obese subjects as MUO as they presented at least an alteration of the lipid and carbohydrate parameters typical of the metabolic syndrome (Schinzari et al., 2015 Nov 1). Our results demonstrated a reduction in the endothelium-dependent but not endothelium-independent responsees compared to MHO subjects, suggesting that metabolic alterations tend to worsen the reduced endothelium-dependent vascular function already present in obesity (Schinzari et al., 2015 Nov 1, Mather et al., 2004). This observation suggests that coexistence of metabolic changes sums further endothelial impairment to the vascular dysfunction induced by obesity in itself. Another relevant feature of the obesity-related vasculopathy is the enhancement of the vasoconstrictor tone, related predominantly to increased activity of the endothelin (Campia et al., 2014, Schinzari et al., 2013, Schinzari et al., 2018). The first evidence in this regard reported the interactions between the ET-1 and NO systems in the vasculature of obese or type 2 diabetic individuals (Mather et al., 2004). The investigators observed that antagonism of ET-1 actiion by use of BQ-123, a selective blocker of ETA receptors, is able to correct the defect in endothelium-dependent vasodilation seen in these patients. Weil et al, who have observed improved endothelium-dependent vasodilation following blockade of ET-1 receptors in overweight / obese patients, have subsequently reported similar findings (Weil et al., 2011). We have confirmed these data and showed that ET-1-dependent vasoconstriction was greater in obese subjects with metabolic alterations compared to MHO (Schinzari et al., 2015 Nov 1). Furthermore, Kan et al. in a recent trial enrolled 2,204 Korean subjects with the MHO phenotype, and showed how MHO phenotype might be a transient state before their progression to MUO state, approximately a half of the MHO subjects converted to the MUO phenotype after the median follow-up of 41.1 months (Kang et al., 2017 Jun 23). The authors applied a novel mathematical model which estimates visceral adiposity based on anthropometric and lipid profiles. They found that a so-called "visceral adiposity index" (VAI) correlated well with the incidence of conversion to the MUO phenotype and multiple factors that might contribute to this "shift". The most frequently reported key characteristics of the MHO phenotype are reduced accumulation of visceral and ectopic fat and higher insulin sensitivity. Conversely, visceral fat accumulation with adipose tissue fibrosis and lower insulin sensitivity predicted the conversion of MHO subjects to MUO. Moreover, adipose tissue macrophage content is greater in visceral adipose tissue in people with MUO than in those with MHO, Moreover, plasma concentrations of markers of inflammation, primarily C-reactive protein, plasminogen activator inhibitor-1 (PAI-1), IL-6, and TNF-α, are higher in MUO compared to MHO. These data corroborate the hypothesis that the presence of metabolic alterations tends to worsen endothelial and adipose dysfunction.

The Risk of Adverse Outcomes in MHO versus MUO

The prognostic value of MHO has recently been challenged by a study showing that MHO individuals are still at higher risk of coronary heart disease, cerebrovascular disease, and heart failure compared to normal weight metabolically healthy individuals (Caleyachetty et al., 2017). In addition, in MHO, cardiovascular risks may be reduced fol-

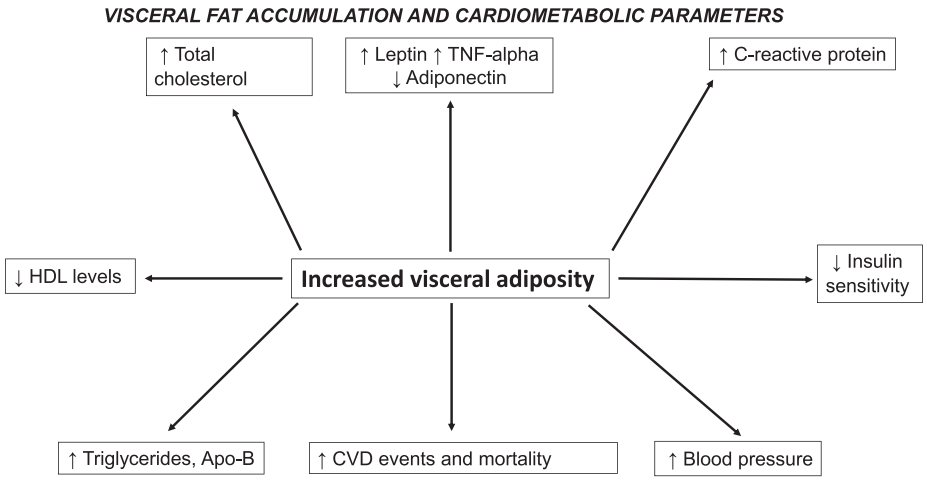

Fig. 1. Expantion of visceral adipose tissue leading to cardiometabolic abnormalities and increased cardiovascular events and mortality.
HDL: High density lipoprotein, CVD: cardiovascular disease, Apo-B: Apolipotprotein B, TNF: tumor necrosis factor alpha.

lowing weight loss intervention; therefore the clinical priority should be to encourage and facilitate weight loss. However, metabolic and cardiovascular complications are not the solely detrimental aspects of obesity as respiratory problems, sleep apnea and musculoskeletal disorders (especially osteoarthritis), as well as several types of cancers, are all established obesity-related disease complications (Iacobini et al., 2019). The normal decline in metabolic health associated with increasing age, the metabolic insult of prolonged excess adiposity, and the tendency to gain weight throughout middle age, likely influence the stability of MHO. The data from longitudinal studies suggest that approximately 30% to 50% of people with MHO convert to MUO after 4 up to 20 years of follow-up (Kang et al., 2017 Jun 23, Bell et al., 2015). The major factors determining the conversion of MHO to MUO are a decline in insulin sensitivity and an increase in fasting blood glucose (Bell et al., 2015). The risk of transitioning from MHO to MUO is greater in those with a high BMI, older age, evidence of more severe metabolic dysfunction (i.e., number of abnormal metabolic criteria and values that are closer to the upper limit of the normal range, and the presence of hepatic steatosis) (Moussa et al., 2019), a poor lifestyle index (a composite of diet composition, leisure time physical activity, and cigarette smoking) (Schröder et al., 2014), and weight gain during the observational period (Cui et al., 2015, Espinosa De Ycaza et al., 2018). In general, the risks of type 2 diabetes (T2D), CVD, and all-cause mortality are greater in people with MUO than in those with MHO and greater in those with MHO than in those who are metabolically healthy and lean (MHL) (Zheng et al., 2016, Hamer and Stamatakis, 2012). Moreover, the risks of these adverse outcomes are directly related to the number and severity of metabolic abnormalities (Caleyachetty et al., 2017, Kuk et al., 2018). The risk of developing T2D is much lower in those with MHO than MUO, but the risk is still about 4-fold greater than in those who are MHL and is directly related to the number of metabolic abnormalities at baseline (Twig et al., 2014, Guo and Garvey, 2015). The risk of CVD events is lower in people with MHO than in those with MUO, but is still higher in people with MHO than in those who are MHL (Eckel et al., 2016). A meta-analysis that used pooled data from 18 studies followed over a median of 10 years found that the risk of CVD events was about 50% greater in people with MHO at baseline than in people who were MHL (Zheng et al., 2016). The risk of all-cause mortality in people with MHO relative to those who are MHL depends on the number and severity of metabolic abnormalities and the stability of metabolic health. The combined data from five large cohort studies that followed participants for an average of 13 years found that people with MHO and no metabolic syndrome components (excluding waist circumference) did not have an increased risk of all-cause mortality compared with the MHL group; however, the risk of all-cause mortality was greater in participants with MHO versus MHL, when participants with one abnormal metabolic risk factor (excluding waist circumference) were included in the MHO group (Kuk et al., 2018).

A Pathophysiological Role for Visceral Adipose Tissue

Visceral adipose tissue is a hormonally active cellular compartment which possesses unique biochemical characteristics influencing several physiological and pathophysiological process (Fig. 1). White adipose tissue (WAT) is responsible for storage and release of the energy surplus and brown adipose tissue (BAT) is specialized in energy expenditure via beta-oxidation coupled to thermogenesis. WAT depots can be divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). The main factor that influences the storage of fat is the plasticity of SAT (Bala et al., 2016). Regarding the type of fat, while white adipose tissue is involved in the pathogenesis of obesity-related metabolic disorders, the energy-burning potential of brown adipose tissue confers to this type of fat a potential protective role for metabolic and cardiovascular health (Bartelt and Heeren, 2014). SAT may not be a risk factor for metabolic diseases, whereas VAT and ectopic fat accumulation in or around the liver, heart and muscles is causally related to insulin resistance, impaired glucose homeostasis and CVD (Gaggini et al., 2013). The role of adipose tissue in the up-take and the utilization of glucose is an important piece in the puzzle of metabolic abnormalities observed in obese patients. Insulin produces a postprandial disposal of glucose, increasing its up-take in adipocytes through GLUT4 mobilization, the main transporter of glucose into the adipose cell. Experimental studies on mice, showed that the mutation of GLUT4 gene decreases the expression of this transporter in adipose tissue and skeletal muscle. This decrease did not result in obesity, but led to hypertension and diabetes, thus being a good animal model for the study of diabetes without complications induced by obesity (Stenbit et al., 1997). The role of BAT and WAT in the storage and the utilization of energy is different. Mice with selective genetic deficiency of the insulin receptor in brown adipocytes show an age-dependent loss of interscapular brown fat and develop an insulin-secretion defect resulting in a progressive glucose intolerance, but do not developt insulin resistance. This model provides a direct evidence for the role of the insulin receptors in brown fat adipogenesis and suggests the role of brown adipose tissue in the regulation of insulin secretion and glucose homeostasis (Gaggini et al., 2013). The MHO phenotype is characterized by an improved insulin-sensitivity compared to their counterparts with MUO. The accumulation of abdominal, visceral and ectopic fat will induce insulin resistance and metabolic unhealthy profile (Blüher, 2010, Schinzari et al., 2010). A recently published study showed that individuals with either liver or muscle insulin-resistance exhibit an abdominal visceral fat area similar to the one of the insulin-sensitive individuals; those with insulin resistance at the both levels

had a significantly higher visceral fat area than those insulin- sensitive in both tissues (Chen et al., 2015). More SAT and less VAT, as well as lower fat accumulation in liver and skeletal muscle as compared to MUO subjects matched for BMI and fat mass characterize MHO individuals. Conversely, in equally obese individuals, prevalent fat accumulation in VAT, as determined by computed tomography, is associated with a MUO phenotype, characterized by hyperinsulinemia, glucose intolerance and atherogenic dyslipidemia (Tchernof and Després, 2013). Finally, it was demonstrated that obese individuals matched for VAT, had comparable glucose tolerance irrespective of the amount of abdominal SAT, whereas those matched for SAT had different glucose tolerance, depending on the magnitude of fat accumulation in VAT (Ross et al., 2002). Therefore, the reason why MHO subjects are relatively protected against cardiometabolic diseases may lie in part in the divergent regulatory functions of VAT and SAT depots. Consistently, previous studies have shown that, in the presence of positive calorie balance, SAT expansion prevents the risk of lipid overflow and fat deposition in the abdominal VAT depot and in non-adipose tissue (i.e., ectopic) depots (Virtue and Vidal-Puig, 2010). Thus, at the level of fat-specific depots, the difference between MHO and MUO seems to be reflected by the fitness of SAT: that is, a “healthy SAT” in the MHO versus a dysfunctional SAT in the MUO. Adipose tissue expandability has been saw in experimental studies connecting the improved ability to increase total fat mass in response to overfeeding with metabolic improvement, and in epidemiological studies linking increased SAT, but not VAT expansion, with protection from type 2 diabetes risk (i.e., MHO) (Kim et al., 2007, McLaughlin et al., 2011). Consistently, the limited expandability of SAT was associated with insulin resistance (Neeland et al., 2018). Adipocyte hypertrophy in VAT appears to be more closely linked to insulin resistance than adipocyte hypertrophy in SAT. In fact, a positive correlation was found between VAT adipocyte diameter and the degree of insulin resistance in obese women with metabolic syndrome, whereas a weak, nonsignificant association was found between SAT adipocyte size and metabolic parameters (Neeland et al., 2018). Another study demonstrated that, though SAT adipocytes were larger than VAT adipocytes in severe obesity, only the size of VAT adipocytes correlated positively with insulin levels, fasting glucose and insulin resistance (Ledoux et al., 2010). These findings suggest that the different risk factor profiles for metabolic abnormalities might be due to the different biological properties of adipocytes from SAT and VAT, rather than the location of the fat depot itself. VAT is considered a unique pathogenic depot that confers risk beyond its contribution to overall adiposity, but also SAT volume and quality, as assessed by computed tomography imaging, have been associated with incident metabolic risk factors (Abraham et al., 2015). Changes of fat depots reflect the functional and expansion capacity of adipose tissue, which depends also on the ability to increase the number (i.e., hyperplasia), not only the size (i.e., hypertrophy) of adipocytes. Consistently, reduced adipose tissue expandability has been linked to inability of adipocytes to differentiate properly (McLaughlin et al., 2007). The main pathophysiological features characterizing adiposopathy are impaired adipogenesis, reduced adipose tissue expandability, adipocyte hypertrophy, altered lipid metabolism, and adipose inflammation (Goossens, 2017, Pellegrinelli et al., 2016). Among these features, increasing evidence suggests that defective adipogenesis may be the upstream factor leading to adipose tissue dysfunction and related metabolic disorders. Human findings indicate that defective adipogenesis may be involved in the development of obesity-related systemic insulin resistance and inflammation, two major hallmarks of MUO (McLaughlin et al., 2010). In obese individuals, systemic insulin resistance is associated with an increased ratio of small-to-large adipocytes and decreased levels of adipogenic genes, which is suggestive of a reduced adipogenic potential of fat tissue. The metabolic health of obese individuals may ultimately depend on their adipogenic potential. An adequate adipogenic capacity would favor the energy-buffering activity of adipose tissue, ensuring metabolic health protection furthermore an impaired adipogenesis would anticipate and accelerate these events by restraining adipose tissue expandability and favoring adipocyte hypertrophy, ectopic fat accumulation and adipose/systemic inflammation, which instigate insulin resistance and abnormal glucose regulation. Interrogation of the biochemical profiles of human VAT originating from MHO and MUO with the aim of characterizing the altered metabolism associated with the pathology of metabolic syndrome revealed limited differences. Changes were detected in oxidative stress metabolites, ceramides, sphingolipids, and amino acid metabolism (Candi et al., 2018, Piro and Tesauro, 2020). These studies suggest the need to combine additional matrices (e.g., patients’ plasma) and technologies (transcriptomic, proteomic) in order to fully understand the pathophysiology of MHO and MUO.

Prevention and Therapy: Lifestyle changes

Regular physical exercise reduces the risk of diseases such as diabetes and atherosclerosis, and is indubitably associated with improved well-being and longer live expectancy (Barton, 2013, Barton and Cardillo, 2020 Jul 23). Exercise may be prescribed for primary prevention or adjunctive treatment for a variety of disorders, including obesity, type 2 diabetes, dementia, cardiovascular diseases, and cancer. The best-characterized exercise change is the increase of catecholamines (Von Euler and Hellner, 1952) thus, demonstrating that the three major branches of metabolism, which are energy metabolism, anabolism, and catabolism, are profoundly changed in response to acute and chronic physical exercise. In addition, marked changes were observed associated with increased aerobic fitness in many other classes of metabolic substrates, such as arginine metabolites, endocannabinoids, nucleotides, markers of proteolysis, products of fatty acids oxidation, microbiome-derived metabolites, markers of oxidative stress, and substrates of coagulation (Koay et al., 2021). One of the arginine metabolites, the dimethylguanidino valeric acid (DMGV), was able to track a maladaptive metabolic response to exercise (Koay et al., 2021). The participants with greater post-exercise increment in plasma levels of DMGV had higher values of some variables associated with cardiovascular risk, such as body fat, total and LDL-cholesterol, and systolic blood pressure. DMGV has also been previously identified as a strong, independent biomarker of nonalcoholic fatty liver disease (NAFLD) by an investigation in the offspring cohort of the Framingham Heart Study integrating nontargeted metabolomics, genetics and detailed phenotyping (O’Sullivan et al., 2017). Thus, DMGV circulating levels were significantly elevated in patients with biopsy-proven nonalcoholic steatohepatitis, a condition that is highly interconnected to visceral adiposity and cardiometabolic risk (Porter et al., 2013). The potential prognostic significance of DMGV, maintaining or achieving normal body weight in combination with a regular exercise remains the most important and cost-effective intervention for primary and secondary prevention of arterial hypertension, diabetes, cardiovascular disease, and dementia, inhibiting inflammatory activation and improving endothelial cell functions (Barton et al., 2016, Barton and Cardillo, 2020 Jul 23).

Prevention and Therapy: Bariatric Surgery

Ruitz and colleagues have demonstrated a moderate weight loss of about 10% may be sufficient to modify an obesity phenotype with cardiometabolic abnormalities in MHO. Bariatric surgery (BS) has been shown to be equally effective in MHO compared to MUO patients concerning cardiometabolic outcomes (Lavie et al., 2018). BS might reverse type 2 diabetes and other components of the so-called "metabolic syndrome", including hypertension, dyslipidemia, and non-alcoholic steatosis hepatitis (NASH), and may improve the metabolic profile in patients diagnosed with polycystic ovary syndrome (PCOS); BS is,often the best possible treatment for asthma and gastroesophageal reflux disease, even before significant weight loss. BS reduces long-term mortality from coronary heart disease and diminish the prevalence of solid tumors by more than 70% within 5 years of surgery (Julia Xu et al., 2013, Ruiz et al.,

2013). Mechanical explanations for BS success such as limiting stomach volume and intestinal malabsorption have given way to physiological explanations due to changes in gastrointestinal signals to other organs. The two most commonly used bariatric procedures are the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) (Sica et al., 2011, EuroSurg 2016). RYGB leaves the patient with a small pouch in the stomach under the esophagus and the anatomy of the intestine is reorganized so that the nutrients are diverted from the upper to the central part of the small intestine (Biancone et al., 2008). RYGB not only induces significant weight loss, but also improves insulin resistance with the remission of type 2 diabetes in many cases. SG is a surgical procedure, generally laparoscopic, which consists in removing about 80% of the stomach along the major curvature Alterations of the gastrointestinal anatomy have profound effects on physiology, including alterations of intestinal hormone secretion important for the regulation of nutrition and metabolism. These metabolic changes, associated with BS may be related not only to the reduction of adipose tissue but also to the different anatomical deposits of adipose tissue that are affected (Frikke-Schmidt et al., 2016). The reduction of adipocyte hypertrophy is a dominant feature of loss of fat mass. Adipocyte size affects intracellular metabolic function because larger adipocytes are associated with type 2 diabetes and metabolic diseases (O'Connell et al., 2010, Henninger et al., 2014). However, it is clear that overall bariatric surgery reduces both the size of individual deposits and the adipocytes and reduces the VAT/SAT ratio. These changes are well-known for their beneficial impact on metabolic health and support a contributing role in the improvement of fat metabolic function after bariatric surgery. This notion is supported by clinical data after bariatric surgery showing that shorter duration of type 2 diabetes and better hyperglycemic parameters are the main determinants of diabetes remission and metabolic syndrome reduction (Blüher, 2020, Marafini et al., 2015).

Future Investigations

While studying MHO and MUO, studies into genetic traits could bring insights into protective variants. In addition, the study of mechanisms resulting in a reduction of chronic inflammation could reveal protective patterns, possible to study by use of proteomics, while a better understanding of the role of gastrointestinal microbiota and its interaction with dietary patterns could provide new perspectives. The role of the "fat and fit" phenotype, with corresponding personality traits, should be probably studied more, as this could modify the current simplified message of weight loss in all obese subjects in a uniform way, and could futher elucidate the mechanisms underlying the health benefits of regular physical acitvity in obese patients (Barton and Cardillo, 2020 Jul 23). . Both observational studies on obesity and risk in different populations and ethnicities, as well as basic science studies are needed. Ideally, characteristics of adipocytes from MHO subjects as well as the cardiovascular phenotype, including blood pressure regulation, could be investigated further.

Conclusion

Visceral adipose tissue, in association with insulin sensitivity and adipose tissue inflammation, plays a central role in patients affected by MHO. The mechanisms underlying the conversion from MHO to MUO have not been fully clarified. However, predisposing factors such sex, age and metabolic damage due to chronic excess of adipose tissue and tendency to increase body weight, seem to play an important role in the mechanisms underlying lack of metabolic stability of MHO. The absence of a clear definition of MHO represents an important limitation for the evaluation of the various studies in which an attempt was made to calculate the cardiovascular and metabolic risk in these subjects compared to MUO and MHNW. Individuals with MHO tend to have a reduced risk of developing T2DM and CVD compared to MUO, but an increased cardiovascular risk compared to healthy and lean subjects. This is in line with our previous findings but also demonstrates impairment of endothelium-dependent regulation of arterial tone in MHO, confirming that obesity per se is associated with vascular alterations and that the presence of the metabolic syndrome exerts additive detrimental effects on the vascular endothelium. MHO should no longer be considered "benign" as MHO carries and increased cardiovascular and metabolic risk. The study of subjects with MHO represents a great opportunity for better recognition of the mechanisms underlying obesity-related vascular and metabolic complications, will help to identify new ways to improve prevention and may lead to personalized and stratified risk therapies in the future.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abraham, TM, Pedley, A, Massaro, JM., 2015. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. Circulation 132, 1639–1647.

Arnlöv, J, Ingelsson, E, Sundström, J, Lind, L., 2010. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 121, 230–236.

Bala, C., Craciun, A-E., Hancu, N., 2016. Updating the concept of metabolically healthy obesity. Acta Endocrinol (Buchar) 12, 197–205.

Bartelt, A, Heeren, J., 2014. Adipose tissue browning and metabolic health. Nat Rev Endocrinol 10, 24–36.

Barton, M, Cardillo, C., 2020 Jul 23. Exercise is medicine - key to cardiovascular disease and diabetes prevention. Cardiovasc Res doi:10.1093/cvr/cvaa226, cvaa226Online ahead of print.

Barton, M, Husmann, M, Meyer, MR., 2016. Accelerated vascular aging as a paradigm for hypertensive vascular disease: prevention and therapy. Can J Cardiol 32, 680–686 e684.

Barton, M., 2013. Prevention and endothelial therapy of coronary artery disease. Curr Opin Pharmacol 13, 226–241.

Bell, JA, Hamer, M, Batty, GD, Singh-Manoux, A, Sabia, S, Kivimäki, M., 2015. Incidence of metabolic risk factors among healthy obese adults: 20-year follow-up. J Am Coll Cardiol 66 (7), 871–873.

Bell, JA, Hamer, M, Sabia, S, Singh-Manoux, A, Batty, GD, Kivimaki, M., 2015. The natural course of healthy obesity over 20 years. J Am Coll Cardiol 65 (1), 101–102.

Bell, JA, Hamer, M, van Hees, VT, Singh-Manoux, A, Kivimäki, M, Sabia, S., 2015. Healthy obesity and objective physical activity. Am J Clin Nutr 102 (2), 268–275.

Bell, JA, Kivimaki, M, Hamer, M., 2014. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Rev 15, 504–515.

Biancone, L., Onali, S., Calabrese, E., Petruzziello, C., Zorzi, F., Condino, G., Sica, G.S., Pallone, F.Non-invasive techniques for assessing por in CD., 2008. Dig Liver Dis 40, 265–270.

Blüher, M., 2009. Adipose tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes 117 (6), 241–250.

Blüher, M., 2010. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. Curr Opin Lipidol 21 (1), 38–43.

Blüher, M., 2020. Metabolically healthy obesity. Endocrine Reviews 41, 1–16.

Bray, GA., 2003. Evaluation of obesity. Who are the obese? Postgrad Med 114, 19–27 38.

Caleyachetty, R, et al., 2017. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol 70 (12), 1429–1437.

Campia, U, Tesauro, M, Di Daniele, N, Cardillo, C., 2014. The vascular endothelin system in obesity and type 2 diabetes: pathophysiology and therapeutic implications. Life Sci 118 (2), 149–155. doi:10.1016/j.lfs.2014.02.028.

Candi, E, Tesauro, M, Cardillo, C, et al., 2018. Metabolic profiling of visceral adipose tissue from obese subjects with or without metabolic syndrome. Biochem J 475 (5), 1019–1035.

Chang, Y, Kim, BK, Yun, KE, Cho, J, Zhang, Y, Rampal, S, Zhao, D, Jung, HS, Choi, Y, Ahn, J, Lima, JA, Shin, H, Guallar, E, Ryu, S., 2014. Metabolically-healthy obesity and coronary artery calcification. J Am Coll Cardiol 63, 2679–2686.

Chen, DL, Liess, C, Poljak, A, Xu, A, Zhang, J, Thoma, C, Trenell, M, Milner, B, Jenkins, AB, Chisholm, DJ, Samocha-Bonet, D, Greenfield, JR., 2015. Phenotypic characterization of insulin-resistant and insulin-sensitive obesity. J Clin Endocrinol Metab 100 (11), 4082–4091.

Chen, GC, Arthur, R, Iyengar, NM, et al., 2019. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J 40 (34), 2849–2855.
Cherqaoui, R, Kassim, TA, Kwagyan, J, et al., 2012. The metabolically healthy but obese phenotype in African Americans. J Clin Hypertens (Greenwich) 14 (2), 92–96.
Clinical guidelines on the identification, 1998 Nov. evaluation, and treatment of overweight and obesity in adults: the evidence report. National Institutes of Health, National Heart, Lung, and Blood Institute. Obes Res 6 (6), 464.
Cui, Z, Truesdale, KP, Bradshaw, PT, Cai, J, Stevens, J., 2015. Three-year weight change and cardiometabolic risk factors in obese and normal weight adults who are metabolically healthy: the atherosclerosis risk in communities study. Int J Obes (Lond) 39 (8), 1203–1208.
Eckel, N, Meidtner, K, Kalle-Uhlmann, T, Stefan, N, Schulze, MB., 2016. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 23 (9), 956–966.
Espinosa De Ycaza, AE, Donegan, D, Jensen, MD., 2018. Long-term metabolic risk for the metabolically healthy overweight/obese phenotype. Int J Obes (Lond) 42 (3), 302–309.
EuroSurg, 2016. A new European student-driven research network in surgery. Colorectal Disease 8, 214–215. doi:10.1111/codi.13260.
Frikke-Schmidt, O'Rourke, R.W., Lumeng, C.N., Sandoval, D.A., Seeley, R.J., 2016. Does bariatric surgery improve adipose tissue function? Obes Rev 17, 795–809.
Gaggini, M, Morelli, M, Buzzigoli, E, et al., 2013. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 5, 1544–1560.
Geetha, L, Deepa, M, Anjana, RM, Mohan, V., 2011. Prevalence and clinical profile of metabolic obesity and phenotypic obesity in Asian Indians. J Diabetes Sci Technol 5 (2), 439–446.
Ghaben, AL, Scherer, PE., 2019. Adipogenesis and metabolic health. Nat Rev Mol Cell Biol 20 (4), 242–258.
Goossens, GH., 2017. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. Obes Facts 10, 207–215.
Guo, F, Garvey, WT., 2015. Development of a weighted cardiometabolic disease staging (CMDS) system for the prediction of future diabetes. J Clin Endocrinol Metab 100 (10), 3871–3877.
Hamer, M, Bell, JA, Sabia, S, Batty, GD, Kivimäki, M., 2015 Nov. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. Eur J Endocrinol 173 (5), 703–708 (46).
Hamer, M, Stamatakis, E., 2012. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab 97, 2482–2488.
Henninger, AM, Eliasson, B, Jenndahl, LE, Hammarstedt, A., 2014. Adipocyte hypertrophy, inflammation and fibrosis characterize subcutaneous adipose tissue of healthy, non-obese subjects predisposed to type 2 diabetes. PLoS One 9, e105262.
Hwang, YC, Hayashi, T, Fujimoto, WY, Kahn, SE, et al., 2015. Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. Int J Obes (Lond) 39, 1365–1370.
Iacobini, C, Pugliese, G, Blasetti Fantauzzi, C, Federici, M, Menini, S, 2019. Metabolically healthy versus metabolically unhealthy obesity. Metabolism 92, 51–60.
Iyengar, NM, Gucalp, A, Dannenberg, AJ, Hudis, CA., 2016. Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol 34 (35), 4270–4276.
Janssen, I, Katzmarzyk, PT, Ross, R., 2002. Body Mass Index, Waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 162 (18), 2074–2079.
Julia Xu, X., Pories, Walter J., Dohm, Lynis G., Ruderman, Neil B., 2013. What distinguishes adipose tissue of severely obese humans who are insulin sensitive and resistant? Curr Opin Lipidol 24, 49–56.
Kabat, GC, Wu, WY, Bea, JW, Chen, C, Qi, L, Stefanick, ML, Chlebowski, RT, Lane, DS, Wactawski-Wende, J, Wassertheil-Smoller, S, Rohan, TE., 2017 Jan. Metabolic phenotypes of obesity: frequency, correlates and change over time in a cohort of postmenopausal women. Int J Obes (Lond) 41 (1), 170–177.
Kang, YM, Jung, CH, Cho, YK, Jang, JE, Hwang, JY, Kim, EH, Lee, WJ, Park, JY, Kim, HK., 2017 Jun 23. Visceral adiposity index predicts the conversion of metabolically healthy obesity to an unhealthy phenotype. PLoS One 12 (6), e0179635. doi:10.1371/journal.pone.0179635.
Karelis, AD., 2008. Metabolically healthy but obese individuals. Lancet 372, 1281–1283.
Kim, JY, van de Wall, E, Laplante, M, et al., 2007. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 117, 2621–2637.
Koay, YC, Stanton, K, Kienzle, V, Li, M, Yang, J, Celermajer, DS, O'Sullivan, JF, 2021. Effect of chronic exercise in healthy young male adults: a metabolomic analysis. Cardiovasc Res.
Kramer, CK, Zinman, B, Retnakaran, R., 2013. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 159, 758–769.
Kuk, JL, Rotondi, M, Sui, X, Blair, SN, Ardern, CI., 2018. Individuals with obesity but no other metabolic risk factors are not at significantly elevated all- cause mortality risk in men and women. Clin Obes 8 (5), 305–312.
Lallukka, S, Yki-Järvinen, H., 2016. Non-alcoholic fatty liver disease and risk of type 2 diabetes. Best Pract Res Clin Endocrinol Metab 30 (3), 385–395.
Lavie, CJ, Laddu, D, Arena, R, Ortega, FB, Alpert, MA, Kushner, RF., 2018. Healthy weight and obesity prevention: JACC health promotion series. J Am Coll Cardiol 72 (13), 1506–1531.
Ledoux, S, Coupaye, M, Essig, M, et al., 2010. Traditional anthropometric parameters still predict metabolic disorders in women with severe obesity. Obesity 18, 1026–1032.
Lin, H, Zhang, L, Zheng, R, Zheng, Y., 2017. The prevalence, metabolic risk, and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article. Medicine (Baltimore) 96 (47), e8838.
Liu, C, Wang, C, Guan, S, et al., 2019. The prevalence of metabolically healthy and unhealthy obesity according to different criteria. Obes Facts 12 (1), 78–90.
Marafini, I, Monteleone, I, Di Fusco, D, et al., 2015. TNF-α producing innate lymphoid Cells (ILCs) are increased in active celiac disease and contribute to promote intestinal atrophy in mice. PLoS One 10, e0126291. doi:10.1371/journal.pone.0126291.
Marafini, I., Monteleone, G., Di Fusco, D., Cupi, M.L., Paoluzi, O.A., Colantoni, A., Ortenzi, A., Izzo, R., Vita, S., De Luca, E., Sica, G., Pallone, F., Monteleone, G., 2015. TNF-α producing innate lymphoid cells (ILCs) are increased in active celiac disease and contribute to promote intestinal atrophy in mice. PLoS ONE 10, e0126291.
Mather, KJ, Lteif, A, Steinberg, HO, Baron, AD., 2004. Interactions between endothelin and nitric oxide in the regulation of vascular tone in obesity and diabetes. Diabetes 53, 2060–2066.
McLaughlin, T, Deng, A, Yee, G, et al., 2010. Inflammation in subcutaneous adipose tissue: relationship to adipose cell size. Diabetologia 53, 369–377.
McLaughlin, T, Lamendola, C, Liu, A, et al., 2011. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab 96, E1756–E1760.
McLaughlin, T, Sherman, A, Tsao, P, et al., 2007. Enhanced proportion of small adipose cells in insulin-resistant versus insulin-sensitive obese individuals implicates impaired adipogenesis. Diabetologia 50, 1707–1715.
Mongraw-Chaffin, M, Foster, MC, Anderson, CAM, et al., 2018. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 71 (17), 1857–1865.
Mongraw-Chaffin, M, Foster, MC, Kalyani, RR, et al., 2016. Obesity severity and duration are associated with incident metabolic syndrome: evidence against metabolically healthy obesity from the multi-ethnic study of atherosclerosis. J Clin Endocrinol Metab 101, 4117–4124.
Moussa, O, et al., 2019. Fate of the metabolically healthy obese-is this term a misnomer? A study from the Clinical Practice Research Datalink. Int J Obes (Lond) 43 (5), 1093–1101.
Neeland, IJ, Poirier, P, Després, JP., 2018. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 137, 1391–1406.
O'Connell, J, Lynch, L, Cawood, TJ, et al., 2010. The relationship of omental and subcutaneous adipocyte size to metabolic disease in severe obesity. PLoS One 5, e9997.
O'Sullivan, JF, Morningstar, JE, Yang, Q, Zheng, B, Gao, Y, Jeanfavre, S, Scott, J, Fernandez, C, Zheng, H, O'Connor, S, Cohen, P, Vasan, RS, Long, MT, Wilson, JG, Melander, O, Wang, TJ, Fox, C, Peterson, RT, Clish, CB, Corey, KE, Gerszten, RE, 2017. Dimethylguanidino valeric acid is a marker of liver fat and predicts diabetes. J Clin Invest 127, 4394–4402.
Pellegrinelli, V, Carobbio, S, Vidal-Puig, A., 2016. Adipose tissue plasticity: how fat depots respond differently to pathophysiological cues. Diabetologia 59, 1075–1088.
Piro, MC, Tesauro, M, et al., 2020. Free-amini acid metabolic profiling of visceral adipose tissue from obese subjects. Amino Acids in press.
Porter, SA, Pedley, A, Massaro, JM, Vasan, RS, Hoffmann, U, Fox, CS., 2013. Aminotransferase levels are associated with cardiometabolic risk above and beyond visceral fat and insulin resistance: the Framingham Heart Study. Arterioscler Thromb Vasc Biol 33, 139–146.
Prince, RL, Kuk, JL, Ambler, KA, Dhaliwal, J, Ball, GD., 2014. Predictors of metabolically healthy obesity in children. Diabetes Care 37 (5), 1462–1468.
Purnamasari, D, Badarsono, S, Moersadik, N, Sukardji, K, Tahapary, DL., 2011. Identication, evaluation and treatment of overweight and obesity in adults: Clinical practice guidelines of the obesity clinic, Wellness Cluster Cipto Mangunkusumo Hospital, Jakarta, Indonesia. JAFES 26, 117–121.
Rexrode, KM, Carey, VJ, Hennekens, CH, et al., 1998. Abdominal adiposity and coronary heart disease in women. JAMA. 280 (21), 1843–1848.
Rey-López, JP, de Rezende, LF, Pastor-Valero, M, Tess, BH., 2014. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes Rev 15 (10), 781–790.
Ross, R, Aru, J, Freeman, J, et al., 2002. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 282, E657–E663.
Ruiz, JR, Ortega, FB, Labayen, I., 2013. A weight loss diet intervention has a similar beneficial effect on both metabolically abnormal obese and metabolically healthy but obese premenopausal women. Ann Nutr Metab 62 (3), 223–230.
Samocha-Bonet, D, Chisholm, DJ, Tonks, K, et al., 2012. Insulin-sensitive obesity in humans – a 'favorable fat' phenotype? Trends Endocrinol Metab 23, 116–124.
Schinzari, F, Iantorno, M, Campia, U, Mores, N, Rovella, V, Tesauro, M, Di Daniele, N, Cardillo, C., 2015 Nov 1. Vasodilator responses and endothelin-dependent vasoconstriction in metabolically healthy obesity and the metabolic syndrome. Am J Physiol Endocrinol Metab 309 (9), E787–E792.
Schinzari, F, Tesauro, M, Bertoli, A, et al., 2019. Calcification biomarkers and vascular dysfunction in obesity and type 2 diabetes: influence of oral hypoglycemic agents. Am J Physiol Endocrinol Metab 317 (4), E658–E666. doi:10.1152/ajpendo.00204.2019.
Schinzari, F, Tesauro, M, Campia, U, Cardillo, C., 2020. Increased fractalkine and vascular dysfunction in obesity and in type 2 diabetes. Effects of oral antidiabetic treatment. Vascul Pharmacol 128-129, 106676. doi:10.1016/j.vph.2020.106676.
Schinzari, F, Tesauro, M, Cardillo, C., 2017. Endothelial and perivascular adipose tissue abnormalities in obesity-related vascular dysfunction: novel targets for treatment. J Cardiovasc Pharmacol 69 (6), 360–368.
Schinzari, F, Tesauro, M, Cardillo, C., 2018. Increased endothelin-1-mediated vasoconstrictor tone in human obesity: effects of gut hormones. Physiol Res 67 (Suppl 1), S69–S81. doi:10.33549/physiolres.933821.
Schinzari, F, Tesauro, M, Rovella, V, et al., 2010. Generalized impairment of vasodilator reactivity during hyperinsulinemia in patients with obesity-related metabolic syndrome. Am J Physiol Endocrinol Metab 299 (6), E947–E952. doi:10.1152/ajpendo.00426.2010.

Schinzari, F, Tesauro, M, Rovella, V, et al., 2013. Leptin stimulates both endothelin-1 and nitric oxide activity in lean subjects but not in patients with obesity-related metabolic syndrome. J Clin Endocrinol Metab 98 (3), 1235–1241. doi:10.1210/jc.2012-3424.

Schinzari F, Veneziani A, Mores N, et al. Beneficial effects of apelin on vascular function in patients with central obesity. Hypertension. 2017;69(5):942-949. doi:10.1161/HYPERTENSIONAHA.116.08916

Schinzari F, Veneziani A, Mores N, et al. Vascular effects of obestatin in lean and obese subjects. Diabetes. 2017;66(5):1214-1221. doi:10.2337/db16-1067

Schröder, H, et al., 2014. Determinants of the transition from a cardiometabolic normal to abnormal overweight/obese phenotype in a Spanish population. Eur J Nutr 53 (6), 1345–1353.

Sica, GS, Iaculli, E, Biancone, L, et al., 2011. Comparative study of laparoscopic vs open gastrectomy. World Journal of Gastroenterol 17, 4602–4606.

Sileri, P, Sica, G, Gentileschi, P, et al., 2004. Ischemic preconditioning protects intestine from prolonged ischemia. Transplant Proc 36 (2), 283–285. doi:10.1016/j.transproceed.2004.01.078.

Soriguer, F, Gutierrez-Repiso, C, Rubio-Martin, E, et al., 2013. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab 98, 2318–2325.

Stefan, N, Häring, HU, Schulze, MB., 2018. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol 6 (3), 249–258.

Stenbit, AE, Tsao, TS, Li, J, Burcelin, R, Geenen, DL, Factor, SM, Houseknecht, K, Katz, EB, Charron, MJ., 1997. GLUT4 heterozygous knockout mice develop muscle insulin resistance and diabetes. Nat Med 3 (10), 1096–1101.

Sun, K, Kusminski, CM, Scherer, PE., 2011. Adipose tissue remodeling and obesity. J Clin Invest 121 (6), 2094–2101.

Tchernof, A, Després, JP., 2013. Pathophysiology of human visceral obesity: an update. Physiol Rev 93, 359–404.

Tesauro, M, Canale, MP, Rodia, G, Di Daniele, N, Lauro, D, Scuteri, A, Cardillo, C., 2011. Metabolic syndrome, chronic kidney, and cardiovascular diseases: role of adipokines. Cardiol Res Pract Mar 7;2011.

Tesauro, M, Mauriello, A, Rovella, V, et al., 2017. Arterial ageing: from endothelial dysfunction to vascular calcification. J Intern Med 281 (5), 471–482. doi:10.1111/joim.12605.

Tesauro, M, Rizza, S, Iantorno, M, et al., 2007. Vascular, metabolic, and inflammatory abnormalities in normoglycemic offspring of patients with type 2 diabetes mellitus. Metabolism 56 (3), 413–419.

Tesauro, M, Schinzari, F, Adamo, A, et al., 2013. Effects of GLP-1 on forearm vasodilator function and glucose disposal during hyperinsulinemia in the metabolic syndrome. Diabetes Care 36 (3), 683–689. doi:10.2337/dc12-0763.

Tesauro, M, Schinzari, F, Caramanti, M, Lauro, R, Cardillo, C., 2010. Cardiovascular and metabolic effects of ghrelin. Curr Diabetes Rev 6 (4), 228–235. doi:10.2174/157339910791658871.

Tesauro, M, Schinzari, F, Rovella, V, et al., 2008. Tumor necrosis factor-alpha antagonism improves vasodilation during hyperinsulinemia in metabolic syndrome. Diabetes Care 31 (7), 1439–1441.

Twig, G, et al., 2014. Diabetes risk among overweight and obese metabolically healthy young adults. Diabetes Care 37 (11), 2989–2995.

Van Guilder, GP, Hoetzer, GL, Dengel, DR, Stauffer, BL, DeSouza, CA., 2006. Impaired endothelium-dependent vasodilation in normotensive and normoglycemic obese adult humans. J Cardiovasc Pharmacol 47, 310–313.

Van Vliet-Ostaptchouk, JV, Nuotio, ML, Slagter, SN, et al., 2014. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord 14, 9.

Virtue, S, Vidal-Puig, A., 2010. Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective. Biochim Biophys Acta 1801, 338–349.

Von Euler, US, Hellner, S., 1952. Excretion of noradrenaline and adrenaline in muscular work. Acta Physiol Scand 26 (2-3), 183–191.

Weil, BR, Westby, CM, Van Guilder, GP, Greiner, JJ, Stauffer, BL, DeSouza, CA., 2011. Enhanced endothelin-1 system activity with overweight and obesity. Am J Physiol Heart Circ Physiol 301 (3), H689–H695. doi:10.1152/ajpheart.00206.2011.

Yoon, DY, Lee, YA, Lee, J, Kim, JH, Shin, CH, Yang, SW., 2017. Prevalence and clinical characteristics of metabolically healthy obesity in Korean children and adolescents: data from the Korea national health and nutrition examination survey. J Korean Med Sci 32 (11), 1840–1847.

Zheng, R, Zhou, D, Zhu, Y., 2016. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta–analysis. J Epidemiol Community Health 70 (10), 1024–1031.

Zhu, ShanKuan, Wang, ZiMian, Heshka, Stanley, Heo, Moonseong, Faith, Myles S, Heymsfield, Steven B, 2002 Oct. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. Am J Clin Nutr 76 (4), 743–749.