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The Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management

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Abstract

The prevalence of obesity has increased globally over the last two decades. Although the body mass index (BMI) has been a convenient and simple index of obesity at the population level, studies have shown that obesity defined by BMI alone is a remarkably heterogeneous condition with varying cardiovascular (CV) and metabolic manifestations across individuals. Adipose tissue is an exquisitely active metabolic organ engaged in cross-talk between various systems; perturbation of which results in a pathologic response to positive caloric balance in susceptible individuals that directly and indirectly contributes to CV and metabolic disease. Inadequate subcutaneous adipose tissue expansion in the face of dietary triglycerides leads to visceral and ectopic fat deposition, inflammatory/adipokine dysregulation, and insulin resistance. Conversely, preferential fat storage in the lower body depot may act as a metabolic buffer and protect other tissues from lipotoxicity caused by lipid overflow and ectopic fat. Translational, epidemiologic, and clinical studies over the past 30 years have clearly demonstrated a strong link between visceral and ectopic fat and the development of a clinical syndrome characterized by atherogenic dyslipidemia, hyperinsulinemia/glucose intolerance, hypertension, atherosclerosis, and adverse cardiac remodeling/heart failure. This relationship is even more nuanced when clinical entities such as metabolically healthy obesity phenotype and the obesity paradox are considered. Although it is clear that the accumulation of visceral/ectopic fat is a major contributor to CV and metabolic risk above and beyond the BMI, implementation of fat distribution assessment into clinical practice remains a challenge. Anthropometric indices of obesity are easily implemented but newer imaging-based methods offer improved sensitivity and specificity for measuring specific depots. Lifestyle, pharmacologic, and surgical interventions allow a multidisciplinary approach to overweight/obesity that may improve outcomes and align with a public health message to combat the growing epidemic of obesity worldwide and build healthier lives, free of cardiovascular diseases.

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Obesity: Classification and the Scope of the Problem

The prevalence of obesity has doubled in over 70 countries since 1980 and continues to increase in most areas globally. Recent age-standardized estimates of global obesity prevalence report that at least 30% of men and 35% of women are obese in many countries worldwide including in North America, the Middle East, Asia, and Australia.^{1, 2} In the United States, obesity is now prevalent in greater than 35% of individuals in four states (Mississippi, Arkansas, Louisiana, and West Virginia) and present in at least 20% of the population in all other states (<http://stateofobesity.org/adult-obesity>).

Obesity is defined by body mass index (BMI), calculated as the weight in kilograms divided by the height in meters, squared, and stratified into categories according to the World Health Organization (Table 1).³ The purpose of this classification is to help clinicians and researchers standardize terminology and clinical severity based on a dose dependent relationship between BMI and health outcomes such as mortality. However, this relationship is in actuality a “J-shaped” curve, with increasing mortality also seen among individuals classified as underweight. In one systematic review incorporating data from 19 prospective studies of ~1.5 million adults, the lowest mortality was observed at a BMI of ~23 kg/m² with higher rates of mortality at either end of the BMI spectrum and with clear inflection points after a BMI of 30 kg/m² (the cutoff for “obesity”) and below 18.5 kg/m² (the cutoff for “underweight”).⁴

Although the BMI has been a convenient and simple index to monitor the growth in obesity prevalence at the population level, many metabolic and clinical studies have revealed that obesity, when defined on the basis of the BMI alone, is a remarkably heterogeneous condition.⁵ For instance, patients with similar body weight or BMI values have been shown to display markedly different co-morbidities and levels of health risk.⁶ Thus, if one were to evaluate critically the performance of BMI as a biomarker, it would fall short in several areas. First, the BMI has never emerged as a component of the Framingham or Pooled Cohort Equation⁷ cardiovascular disease (CVD) risk scores, because it has not demonstrated sufficient improvement in discriminatory capacity over traditional risk factors.

Second, although a proportion of individuals with obesity will develop type 2 diabetes and/or CVD, a significant minority will remain free of cardiometabolic disease during their lifetime. In one study from the National Health and Human Nutrition Examination Surveys (NHANES), 51.3% of overweight and 31.7% of obese adults were determined to be metabolically healthy.⁸ This phenotype, termed metabolically healthy obesity (MHO) has been associated with younger age, non-Hispanic black race/ethnicity, higher physical

activity and cardiorespiratory fitness levels, better overall nutritional quality and, with low levels of abdominal visceral adipose tissue and ectopic fat.⁹

Third, the relationship of BMI with health outcomes is further complicated by the concept of an “obesity paradox” in which overweight and obese people with established disease have a better prognosis compared with normal weight people.¹⁰ At least four obesity-related paradoxes in relation to mortality risk have been identified, including the classic obesity paradox (obesity is protective in chronic disease states), the pre-obesity paradox (overweight is protective in normal populations), the fat-but-fit concept (obesity is not a risk factor for mortality in fit individuals) and MHO.^{11–13} An obesity paradox has been observed in both cardiovascular diseases (hypertension, coronary heart disease¹⁴, heart failure, peripheral vascular disease, and stroke¹⁵) and non-cardiovascular diseases (e.g. end-stage renal disease, cancer, and chronic obstructive pulmonary disease), and in particular among the elderly.¹⁶ The obesity paradox concept is controversial, however, because its very existence has been questioned due to concerns about selection, survival, treatment, and confounding biases causing the paradoxical observations.^{12, 17–20} Several hypotheses have been proposed to explain the obesity paradox, including inability of BMI to differentiate between central and peripheral fat deposits, un-measured or unable to be-measured confounding factors, the effect of cardiorespiratory fitness (CRF)²¹, the benefit of surplus energy reserves to help combat the catabolic state of disease, and a deficiency of lean mass (sarcopenia) contributing to adverse health outcomes. These important limitations create an opportunity for new adiposity-related biomarkers to emerge that will impact clinical cardiovascular care while improving on the inherent shortcomings of BMI assessment.

In this review, we aim to describe the incredible cardiovascular and metabolic heterogeneity of obesity, including our evolving understanding of its biologic and mechanistic underpinnings, epidemiology, clinical challenges, and implications for management.

The Biology of Adipose Tissue Dysfunction: Adiposopathy

The concept of “adiposopathy”, or “sick fat” - a pathologic response by the adipose tissue organ to a stimulus - is a relatively recent concept in medicine.²² In the past, the adipose organ was thought to be relatively inert and act primarily as a storage depot for excess energy in the form of triglycerides with the sole function of building up or breaking down excess lipid into free fatty acids and glycerol based on the body’s metabolic needs and anabolic/catabolic balance. In more recent years, the adipose organ has been recognized to be quite metabolically active and engaged in cross-talk between various organ systems. Perturbation of this highly regulated system results in a pathologic response by adipose tissue to positive caloric balance in susceptible individuals that directly and indirectly contributes to cardiovascular and metabolic disease. The three central tenets of adiposopathy are: 1) deposition of ectopic fat (fat stores in body locations where fat is not physiologically stored, such as the liver, pancreas, heart, and skeletal muscle) and a shift to visceral adipose tissue distribution (fat storage in the intraperitoneal and retroperitoneal spaces); 2) inflammatory and adipokine dysregulation; and 3) insulin resistance. The presence or absence of adiposopathy, therefore, may help explain the heterogeneity of obesity and its

manifestations since the pathogenic potential of excess body fat is conditioned on adipose tissue dysfunction/ectopic fat deposition rather than simply on increased fat mass alone.

Body Fat Distribution: A Key Factor in Obesity Heterogeneity

The ability of the abdominal subcutaneous depot to expand is the physiologic response to a positive energy balance leading to an increased demand for triglyceride storage in adipose tissue. It is important to note, however, that the body's response to excess energy accumulation is not uniform – there is significant individual variation in how much and where fat is deposited or stored. Studies in rodents where activation of mitochondrial pathways results in massive expansion in the subcutaneous fat pad via hyperplasia resulted in decreased lipid oxidation, increased storage, and a compensatory healthy adipose tissue expansion with preserved glucose tolerance.²³ Similarly, transplantation of adipose tissue from the subcutaneous flank depot in mice into the visceral cavity resulted in decreased body weight, total fat mass, and glucose and insulin levels; whereas these effects were observed to a lesser extent when subcutaneous fat was transplanted to the subcutaneous area and no changes seen when visceral fat was transplanted into the visceral area.²⁴

Humans exhibit remarkable variability in body fat distribution for a given BMI. Susceptibility to store fat either subcutaneously or viscerally is in part determined by genetics first demonstrated in overfeeding studies of monozygotic twins by Bouchard and colleagues over two decades ago.²⁵ For example, Figure 1 shows T1-weighted MRI coronal abdominal images in two persons, one individual with a BMI of 25 kg/m² (normal weight) and one individual with a BMI of 30 kg/m² (obese). Knowledge of the BMI in isolation fails to demonstrate the extreme variation in intraabdominal (or visceral) fat distribution between the two subjects. Furthermore, the individual with the lower BMI has a significantly greater burden of visceral adipose tissue (VAT, red shaded) whereas the subject with the higher BMI has more abdominal subcutaneous adipose tissue (SAT, blue shaded). Variation in visceral fat that is not always readily apparent from anthropometric data alone is a key element to risk assessment, due to the fact that VAT and SAT differ greatly in their functional significance and response to weight gain. Imaging studies using computed tomography conducted more than 25 years ago had shown that among equally obese individuals, men and women with high levels of VAT were characterized by an atherogenic dyslipidemia, hyperinsulinemia, and glucose intolerance whereas obese individuals with low levels of VAT did not show these metabolic abnormalities compared to non-obese controls.⁵ In one study, individuals matched for abdominal SAT with low or high VAT had different levels of glucose tolerance, whereas those matched for VAT had similar glucose tolerance testing between high and low SAT.²⁶ Further evidence for a contributory role of visceral adiposity to type 2 diabetes comes from data in the Dallas Heart Study where visceral fat mass was shown to be independently associated with the development of both type 2 diabetes and prediabetes in a cohort of otherwise healthy obese individuals.²⁷ Neither BMI nor waist circumference were associated with incident diabetes in this study. VAT in obese persons has been associated with dyslipidemia, atherosclerosis, and adipocytokine dysfunction whereas SAT seems to be relatively neutral in this population.²⁸ Furthermore, differences in gene expression, inflammatory milieu, and development of traditional risk factors may also differ between depots.²⁹

The *sine qua non* of adiposopathy is the accumulation of fat in the abdominal cavity in the form of visceral adipose tissue. There are several factors, both modifiable and non-modifiable, associated with excess VAT (Figure 2). Some factors may predispose individuals to higher levels of VAT for a given BMI whereas others are consequences of dysfunctional adiposity related to VAT. Sex-based differences in VAT may relate to higher levels of estrogens and lower levels of testosterone in women compared with men; expansion of visceral adiposity in women after menopause have been postulated as one cause for increased cardiovascular risk seen during this stage of a women's lifespan. Race-based differences in VAT are well known and have important clinical implications for classification and risk assessment of obesity and metabolic syndrome. For example, it has been observed that Asian Americans, in particular South Asians, manifest type 2 diabetes at lower BMI levels compared with whites.^{30, 31} This may be explained, in part, by racial/ethnic differences in visceral adiposity even when adjusted for differences in body composition.³² These observations have led to the International Diabetes Federation to recommend race/ethnic-specific cutoffs for waist circumference in the diagnosis of metabolic syndrome (Table 2).³³ Black individuals are less likely to be viscerally obese and have increased lipolytic activity and more efficient clearance of dietary triglycerides compared with whites.³⁴ Nevertheless, the relationships between visceral adiposity and adverse cardiometabolic traits persist in blacks.

From an epidemiological standpoint, associations have been shown between visceral adiposity and incident hypertension,³⁵ atherosclerotic CVD,³⁶ and cardiac dysfunction/failure, characterized by concentric remodeling, lower cardiac output, and higher systemic vascular resistance.³⁷ Retroperitoneal fat, in particular, has been of considerable interest due to its proximity to the kidneys and potential local paracrine effects on renal sodium handling and downstream impact on blood pressure. VAT, and in particular retroperitoneal fat, had a graded association with incident hypertension in the Dallas Heart Study even after adjusting for traditional hypertension risk factors.³⁵ Further research shows that both intraperitoneal and retroperitoneal fat may also impact blood pressure variability over the short- and long-term such that greater amounts of visceral fat are linked to persistently elevated, less variable systolic blood pressure with potential contribution to cardiac hypertrophy and failure.³⁸ Excess visceral adiposity, in particular concomitant with diabetes, has also been linked to decrements in systolic and diastolic strain rate (a measure of myocardial deformation), excess intra-myocardial triglyceride, and prolonged myocardial T1 by MRI (a measure of relaxation time).³⁹ Other localized fat depots around the heart, including pericardial and epicardial fat, have also been shown to associate with coronary events in the general population independent of traditional risk factors. However, the precise role of these localized fat depots in development of the atherosclerotic process is controversial. The presence of excessive pericardial or epicardial fat incidentally seen on a CT scan performed to evaluate coronary calcium or for obstructive coronary heart disease may complement the information gained from these tests for use in CVD risk assessment and prognostication.

Recent work to clarify the genetics of obesity/central obesity lend support to the potential causality of excess adiposity for adverse cardiovascular outcomes. A technique called Mendelian Randomization that seeks to use natural genetic variation to assess the causality of modifiable risk factors has been used to demonstrate a "causal" relationship between

genetic risk for higher BMI and hypertension, coronary heart disease, type 2 diabetes,⁴⁰ and atrial fibrillation,⁴¹ and separately, genetic risk for central obesity (as a surrogate for visceral adiposity) and coronary heart disease and type 2 diabetes.⁴² Advancements in methods to detect small amounts of metabolites in large population based screening studies (“metabolomics”) have also contributed to a better understanding of the metabolic milieu surrounding obesity. Studies evaluating the relationships between metabolomic pathways and imaging-based assessments of VAT independent of BMI or glucose tolerance are ongoing.

Lower body subcutaneous adipose tissue (LBAT) is defined as fat contained in body areas below the trunk and abdomen and includes the gluteal, femoral, and peripheral leg regions. It can be measured on a dual x-ray absorptiometry (DXA) scan that may be performed to evaluate bone density for osteoporosis or to assess composition of total body fat and fat-free mass. Although it is less frequently discussed in the clinical literature, this adipose tissue depot is very important with regard to cardiovascular and metabolic disease risk.

Epidemiological studies have demonstrated that greater LBAT is associated with a lower cardiac risk factor burden⁴³, lower risk of incident CVD³⁶ and cancer⁴⁴, and that individuals with more LBAT have less left ventricular concentric remodeling, greater cardiac output, and lower systemic vascular resistance³⁷ when adjusted for their body size. LBAT can therefore be considered as the diametric opposite of VAT. LBAT may impart these beneficial/protective effects by acting as a metabolic buffer of the influx of dietary lipids and protecting other tissues from lipotoxicity caused by lipid overflow and ectopic fat deposition. Indeed, it was reported >25 years ago that women with a high femoral adipose tissue lipoprotein lipase activity were characterized by higher levels of HDL-cholesterol, suggesting a link between the triglyceride clearance capacity of lower body fat and a healthier lipid profile.⁴⁵

Accordingly, investigations of femoral adipose tissue biopsies in lactating women have suggested that lipid mobilization is turned on during that period, suggesting that gluteal femoral fat may represent an energy reserve used to meet the demands of lactation.⁴⁶ Longitudinal studies of changes in LBAT with a weight loss intervention have shown that greater LBAT loss is associated with increases in diastolic blood pressure despite an overall decrease in body weight. However, other studies have not confirmed that selective reduction of LBAT worsens risk factors for diabetes and cardiovascular disease.⁴⁷ Overall, these and other data suggest that depot-specific fat loss with preservation or shifting of fat stores to the lower body subcutaneous depot may have beneficial health effects on CVD risk factors and outcomes despite being BMI- and overall weight-neutral. Although there are data that indicate a favorable shift in fat distribution from visceral to subcutaneous adipose depots is associated with improvements in hepatic and peripheral tissue insulin sensitivity with certain medications (e.g. thiazolidinediones), there are no large, randomized controlled trials evaluating use of these medications as a strategy to alter body fat distribution-related CVD risk.

Brown adipose tissue (BAT) is a subtype of adipocyte characterized by large number of mitochondria and increased expression of uncoupling protein-1 (UCP-1), a key mediator of thermogenesis. It is responsible for heat generation in response to cold exposure, primarily in non-human species such as rodents.⁴⁸ In humans, BAT is thought to play a minor role in adipose physiology given its relatively small quantity and remote location (e.g.

supraclavicular, paravertebral) observable with ^{18}F -fluorodeoxyglucose positron-emission tomographic/computed tomographic imaging⁴⁹ in newborns or cold-exposed adults.⁵⁰ The amount of human brown fat is inversely proportional to body weight and overweight/obese individuals tend to have less BAT mass and consequently less cold-induced thermogenesis. Cold stimulation in humans, however, leads to enhanced energy expenditure and weight loss, with increased glucose and fatty acid uptake in BAT, but not in other metabolically-active tissues like skeletal muscle or white fat.⁵¹ Recent advances in understanding the molecular heterogeneity of brown versus white (classical) adipose tissue suggest that one potential way to improve adipose tissue function may be through “browning” or “beiging” of white fat, which seeks to effect a transition in white adipose tissue to attain the gene expression patterns and immunohistochemical characteristics of brown fat with improved metabolic consequences. Beiging of white adipose tissue can be affected by cold, certain pharmaceuticals, such as thiazolidinediones and beta adrenergic agonists, and exercise.⁵² Rodent models have shown that beiging of white adipose tissue can resist diet induced obesity and improve metabolism.⁵² In humans, increasing BAT mass and/or activity and beiging of white adipocytes has been suggested to have the potential to increase energy expenditure, improve glucose and lipid metabolism, and improve body weight. However, translating the modulation of BAT physiology from animal model to human as a target for obesity and cardiometabolic disease has proven complex, since improved glycemic metabolism in BAT appears to be limited to conditions of prolonged cold exposure⁵³ and muscle glucose utilization during shivering seems to be a much more robust contributor to systemic glucose utilization than BAT.⁵⁴ Further investigation into the physiological differences between brown, beige, and white adipose depots and the potential contribution of brown/beige fat activation to treating metabolic disorders in humans will continue to enhance our understanding of obesity heterogeneity in the future.

Mechanisms of Adipose Effects on the Cardiovascular and Metabolic Systems

The mechanisms underpinning the pathogenic effects of adipocyte hypertrophy (as a response to excess caloric intake) on the cardiovascular and metabolic systems are well documented.⁵⁵ A multitude of pathways including, impaired adipogenesis, adipokine dysregulation, inflammation (including macrophage polarization), increased circulating free fatty acids, oxidative stress, adipose tissue hypoxia, lipotoxicity (both local and systemic), and altered energy storage/ectopic fat deposition can directly promote atherosclerosis and endothelial cell dysfunction and indirectly lead to cardiometabolic disease through modulation of risk factors such as hypertension, diabetes, dyslipidemia, and the metabolic syndrome.²² Appreciating the full pathogenic potential of adipose tissue requires an integrated perspective, recognizing the importance of ‘cross-talk’ and interactions between adipose tissue and other body systems.⁵⁵ Visceral obesity, for example, has a number of local effects on the myocardium including inducing cardiomyocyte hypertrophy, myocardial fibrosis, and activation of inflammatory pathways relating to macrophage infiltration and cytokine gene expression.⁵⁶ One current model for adiposity-related cardiac dysfunction integrates these data into a potential etiologic pathway leading from obesity to heart failure (Figure 3). Excessive fat accumulation in adipose tissue and ectopic sites, such as the

viscera, pericardium/epicardium, and liver, result in increasing circulating blood volume and local and systemic pro-atherogenic inflammatory factors which act to increased stroke volume, cardiac wall stress, and myocardial injury leading to concentric left ventricular hypertrophy, left ventricular remodeling, and ultimately diastolic and systolic cardiac failure.

Further data regarding a cardiac-adipose axis come from the observations that obesity, and in particular greater VAT, is associated with lower natriuretic peptide levels in asymptomatic individuals (so-called “natriuretic peptide deficiency”) whereas more LBAT is associated with higher natriuretic peptide levels.⁵⁷ Moreover, natriuretic peptides have been shown to increase after gastric bypass surgery induced weight loss by up to 50%.⁵⁸ From a mechanistic standpoint, atrial natriuretic and B-type natriuretic peptides (BNP) bind to NPR-A receptors on adipose tissue and stimulate lipolysis⁵⁹, promote browning of adipocytes⁶⁰, regulate body fat distribution by activation of peroxisome proliferator-activated receptor gamma gene expression⁶¹, enhance adiponectin secretion from adipocytes⁶², and improve human skeletal muscle oxidation fat and glucose utilization.⁶³ Mice that overexpress or are treated with exogenous infusions of natriuretic peptide exhibit reduced fat mass, improved glucose tolerance, and enhanced energy expenditure⁶⁰, suggesting that the “lipomobilizing” effects of natriuretic peptides may have salutary consequences on body fat metabolism and distribution. These experimental data provide evidence that natriuretic peptides released by cardiomyocytes may indeed exert beneficial effects on fat metabolism in a positive feedback loop resulting in differential effects of fat distribution on metabolism partly mediated through the heart. The question of whether the cardiac benefits of increasing circulating levels of endogenous natriuretic peptides, as seen in a recent heart failure trial⁶⁴, are in part mediated by metabolic and/or adipose modulation remains unanswered.

The persistent turnover of mesenteric triglycerides in spite of hyperinsulinemia as seen with obesity delivers glycerol and fatty acids directly into the portal circulation, providing both a gluconeogenic substrate and energy for gluconeogenesis in the liver.⁶⁵ Glycerol contributes about 10% to total glucose production after an overnight fast in healthy non-obese participants, but recent data has demonstrated that visceral adiposity may significantly alter glucose production from glycerol. A study of obese adults without diabetes showed that individuals with high visceral fat had less incorporation of orally-ingested, biologically-labeled glycerol via hepatic gluconeogenesis compared with similarly BMI-matched obese persons with low visceral fat.⁶⁶ These results suggested a dilution effect from excess unlabeled endogenous glycerol substrates from the VAT contributing to gluconeogenesis. Furthermore, high visceral fat individuals who were non-fasting had even less exogenous glycerol incorporation into glucose. Overall, these findings provide intriguing evidence that excess VAT may act as a “constitutively fed state” and result in increased risk for hyperglycemia and type 2 diabetes through overstimulation of hepatic gluconeogenesis by chronic delivery of glycerol arising from mesenteric triglyceride turnover directly into the portal circulation and to the liver. A more thorough discussion of the multiple and complex mechanisms to explain how obesity can cause cardiovascular and metabolic disease is reviewed elsewhere.⁶⁷

Cardiovascular Risk of the Metabolically Healthy Obese Patient

The concept of “metabolically healthy obesity” has been heavily debated as the prevalence of presumably MHO subjects is largely determined by clinical cut-offs used to define abnormal levels of risk factors.⁶⁸ For example, having a blood pressure <130/85 mmHg does not mean that blood pressure is optimally controlled for maximum risk reduction. For instance, studies that have shown that MHO individuals nevertheless had an increased CVD event rate, also found that these individuals were characterized by subtle differences in their risk factor profile compared to healthy non-obese individuals.

MHO individuals have been estimated to account for as much as 30–40% of the obese adult population.⁶⁹ A meta-analysis of 8 studies (N = 61,386 patients with 3,988 events) designed to critically evaluate all-cause mortality or cardiovascular events (or both) in relation to clinical characteristics of 6 patient groups defined by BMI category (normal weight/overweight/obese) and metabolic status (healthy/unhealthy) found that MHO was nevertheless associated with an increased risk for events compared with metabolically healthy normal-weight (RR, 1.24; 95% CI, 1.02 to 1.55) when studies with 10 years of follow-up were considered.⁷⁰ All metabolically unhealthy groups had a similarly elevated risk: normal weight (RR, 3.14; CI, 2.36 to 3.93), overweight (RR, 2.70; CI, 2.08 to 3.30), and obese (RR, 2.65; CI, 2.18 to 3.12). The findings from this meta-analysis suggest that there is no healthy pattern of increased weight since, compared with metabolically healthy normal-weight individuals, obese persons are at increased risk for adverse long term outcomes even in the absence of metabolic abnormalities. However, the relationship between metabolic health and obesity may be more nuanced, since a population-based prospective cohort study from Norway with 12 years of follow-up found that in relation to acute myocardial infarction, obesity without metabolic abnormalities did not confer substantial excess risk, not even for severe or long-lasting obesity; whereas for heart failure, even MHO was associated with increased risk, particularly for long-lasting or severe obesity.⁷¹ More recently, investigators used a sample of 7,579 fasting adults from the 1999–2006 NHANES survey to compare all-cause mortality in six mutually exclusive groups: 1) metabolically healthy and normal weight (referent group), 2) metabolically healthy and overweight, 3) MHO, 4) metabolically abnormal and normal weight, 5) metabolically abnormal and overweight, and 6) metabolically abnormal and obese.⁷² The unweighted median follow-up was 103 months with 770,568 person-months of follow-up and an incidence rate of 1.18 deaths per 1000 person-months. When compared with those who were metabolically healthy and with a normal BMI, all other metabolic and weight groups showed an increased mortality risk. There was no evidence of effect modification by physical activity or demographic characteristics. A more recent meta-analysis assessing the risks of cardiovascular events and all-cause mortality in MHO individuals was recently published with data derived from 22 prospective studies, involving 584,799 participants using metabolically healthy normal weight as the reference group. This study showed that the MHO phenotype was associated with a higher risk of CVD events (HR 1.60, 95% CI 1.38 to 1.84), but not all-cause mortality (HR 1.07, 95% CI 0.92 to 1.25).⁷³

There are, however, inherent limitations associated with these meta-analyses which have an obvious influence on the conclusions reached. As mentioned before, the lack of a standard

definition for MHO makes study comparisons difficult and is an important factor contributing to the substantial heterogeneity observed between studies. Many studies have defined the MHO phenotype based on various combinations of four conventional metabolic criteria: 1) blood pressure, 2) HDL cholesterol, 3) triglycerides and 4) fasting plasma glucose. Other components less commonly used to define MHO have been insulin resistance (HOMA-IR) and C-reactive protein. Furthermore, most studies were performed in predominantly Caucasian populations. In addition, the term “healthy” may not be suitable to describe secular trends in populations because of the possibility of underestimating the long-term effects of obesity, as well as minimizing the public health importance of maintaining a normal weight. Weight gain, independent of one’s particular baseline risk factor profile, is an important risk factor for the development of metabolic abnormalities. However, no studies to date have reported data regarding weight changes during the follow-up. Another limitation of these meta-analyses was inadequate adjustment for many potentially important confounding factors such as age, sex, physical activity, regional body fat distribution and duration of disease.

Ultimately, the notion of a MHO phenotype may depend on the context of the disease/ outcome for which it impacts. For example, whereas an obese patient may be metabolically normal for the endocrinologist, obesity-related health outcomes may be very different in the view of the orthopedic surgeon. Indeed, from a clinical perspective, anthropometric-based classification schemes for excess adiposity do not incorporate assessments of obesity-related comorbidity and impairment in a patient’s functional status. One alternative paradigm that had been developed is a clinical staging system that ranks individuals with excess adiposity on a 5-point ordinal scale, while incorporating obesity-related comorbidities and functional status into the global clinical patient assessment (Table 3).⁷⁴ Investigators examined the ability of this paradigm, called the Edmonton obesity staging system, in predicting mortality using data from the NHANES III (1988–1994) and the NHANES IV (1999–2004) surveys, with mortality follow-up through 2006 in overweight or obese adults. The obesity staging system was independently associated with increased mortality even after adjustment for contemporary methods of classifying adiposity. It may offer improved clinical utility as an adjunctive tool to current anthropometric classification systems in assessing obesity-related risk.⁷⁵ Limitations of this staging system include lack of visceral adiposity assessment, one of the major cardiovascular risk factors of obesity⁷⁶, and the fact that comorbidities within the Edmonton obesity staging system, such as diabetes and osteoarthritis, were arbitrarily assigned to be equivalent in terms of their burden of illness. It is not yet clear whether certain comorbidities should be given more emphasis when assessing risk for clinical health outcomes. Importantly, this staging system includes an assessment of functional status, which is an under-recognized predictor of adverse health outcomes independent of adiposity. Low exercise capacity has been associated with worse outcomes independent of traditional risk factors⁷⁷ and a higher level of cardiorespiratory fitness substantially attenuated the adverse effects of obesity in a number of studies.^{78–80} Studies have also demonstrated that cardiorespiratory fitness could play a central role in the prognosis of MHO individuals.^{81, 82} On that basis, it has been argued that a greater emphasis should be placed on improving cardiorespiratory fitness rather than weight loss *per se* in the primary and secondary prevention of CVD in the presumably MHO patient. Finally, although such overweight/

obesity phenotypes do exist, we postulate that the prevalence of overweight/obese patients with optimal level of CVD risk factors have been overestimated in most studies.

Furthermore, since chronic, non-communicable diseases have always been seen as a continuum rather than a categorical phenomenon, MHO should be considered as a temporary/transition state for most obese individuals rather than a permanent state. For example, in a study with a 20 year follow-up, approximately half of the MHO adults became unhealthy by the end of the study.⁸³ The increased risk for CVD events among MHO participants was particularly high over the long-term and similar risk estimates were observed when MHO was defined by other approaches. A recent study considering the full range of possible definitions for MHO suggested that the risk associated with the MHO phenotype increased with longer follow-up times.⁸⁴ This systematic review and meta-analysis of prospective studies suggests that obese participants classified on the basis of different metabolic parameters as “metabolically healthy” phenotype are indeed characterized by subtle abnormalities and that they are on the path of developing an altered risk factor profile compared with metabolically healthy normal-weight participants. Nevertheless, their risk was lower than that of metabolically unhealthy obese participants, suggesting an intermediate risk state. In summary, the data available suggest that the MHO phenotype as defined in most studies is not a benign condition over the long-term.

Clinical Implications of Obesity Heterogeneity

Measuring Adiposity

There are many anthropometric methods available clinically to assess a patient’s adiposity that have been used for decades and have a large body of literature detailing their relationships with markers of cardiometabolic health, outcomes, and interventions to reduce body weight (Table 4).⁸⁵ Several prospective studies including a recent analysis of the EPIC cohort have shown that within each BMI category an increased waist circumference was associated with an increased mortality risk.^{86, 87} It is important to point out that, when used in isolation, waist circumference is also an index of total body fat which only shows slightly stronger associations with obesity-related clinical outcomes compared to BMI. It is really in the context of the patient BMI that waist circumference provides incremental information to the clinician. For instance, a waist circumference of 102 cm in a middle aged man with a BMI of 25 kg/m² clearly indicates the presence of abdominal obesity whereas the same waist value in a man with a BMI of 32 kg/m² rather suggests “overall obesity” which is associated with a different health risk. In a large international cardiometabolic CT imaging study (INSPIRE ME IAA), it was found that within every single BMI unit category, an increased waist circumference was predictive of an increased level of visceral adipose tissue.⁸⁸ As visceral obesity is often accompanied by more liver fat content driving an increased production of triglyceride-rich very low density lipoproteins, it has been proposed that the combined presence of an elevated waistline and of increased triglyceride levels was associated with a high probability (~80%) for the patient to be characterized by high levels of visceral adipose tissue.⁸⁹ Several studies have since confirmed the notion that the so-called “hypertriglyceridemic waist” phenotype is a simple and quick clinical tool to screen for the presence of excess visceral adipose tissue/ectopic fat.⁹⁰ Therefore, within every BMI

category, the presence of an increased waist circumference accompanied by elevated hypertriglyceridemia (above 2 mmol/l in men and 1.5 mmol/l in women) should flag the need for further investigation as it may identify patients with increased levels of VAT and liver fat.

Although anthropometric indices of central obesity (such as waist circumference and waist-height or –hip ratios) are easy to implement clinically, their correlation with direct imaging-based assessments of visceral adiposity are modest; furthermore, these indices incorporate both the abdominal subcutaneous and visceral depots which, as discussed above, are anatomically and functionally distinct. Newer imaging-based methods offer more sensitivity and specificity for measuring specific adipose depots including visceral and ectopic fat. However, the two most widely utilized methods in research (CT and MRI) have significant drawbacks limiting their use in clinical practice. CT imaging can be done rapidly and interpreted using commercial software that segments the adipose depots and measures their area or volume. CT segmentation is based on the difference in Hounsfield units (a CT measurement of radiodensity) between adipose tissue and other soft tissues. However, CT exposes the subject to radiation so it is not ideal for serial assessments over time or to evaluate change after an intervention. MRI imaging is more time consuming and expensive, but does not involve radiation, and may therefore be used for serial assessments over time. Growing interest in this area has seen the emergence of research-based companies specializing in advanced body fat imaging, such as Advanced MR Analytics (Linköping, Sweden, www.amra.se), that offer cloud-based, 3-D volumetric assessments of body fat distribution using a rapid 6 minute MRI scan. However, both CT and MRI imaging modalities are cost-intensive and require a specially trained technologist to administer the exams, making them less attractive for office based assessment. Dual x-ray absorptiometry (DXA), historically used to measure bone mineral density and body composition, is now being investigated as a lower cost, lower radiation alternative to MRI and CT. It has been recently shown that DXA assessment of visceral adiposity using a commercial software program was highly accurate compared with the gold-standard MRI in >2000 multiethnic men and women in the Dallas Heart Study.⁹¹ DXA can be an office based procedure and given its low radiation profile is ideal for serial assessments. However, currently, measurement of VAT using DXA is not reimbursed by most commercial insurances or Medicare.

Therapeutic Implications

Recent guidelines from the American Heart Association, American College of Cardiology, and The Obesity Society on the management of overweight and obesity in adults⁹² recommend measurement of waist circumference and height and weight to calculate BMI at least annually, but are silent on assessment of body fat distribution or visceral adiposity. Other professional societies such as the International Atherosclerosis Society which recently held a Visceral Adiposity Working Group session, are becoming increasingly focused on integrating more detailed assessments of body fat distribution into risk assessment and treatment paradigms. For example, at a Think Tank⁹³ on metabolic syndrome sponsored by the American College of Cardiology and American Association of Clinical Endocrinologists in 2015, visceral adiposity/ectopic fat was included in a novel staging system for the

metabolic syndrome and incorporated as a specific risk factor for metabolic syndrome in the absence of any other diagnostic criteria. Furthermore, the staging system recommended specific therapies to address visceral adiposity/ectopic fat including increasing physical activity, improved nutritional choices, and obesity prevention.

A growing body of evidence on the lifestyle, pharmacologic, and surgical interventions for visceral adiposity suggests that a multidisciplinary approach to risk stratification in obese individuals and targeted treatment strategies may improve outcomes while limiting therapies to persons who are most likely to benefit. First, it is important to emphasize that even in the absence of weight loss, targeting the lifestyle of viscerally obese patients will be associated with clinical benefits. For instance, lifestyle intervention studies using physical activity/exercise have reported improvements in indices of plasma glucose-insulin homeostasis which were more closely related to the loss of visceral adipose tissue than to body weight or fat loss.^{94, 95} Furthermore, in the landmark PREDIMED trial involving 7,447 patients with 50% of them having type 2 diabetes, it was reported that an approach favoring the adherence to a Mediterranean diet (by providing olive oil and nuts to patients) was associated with a significant reduction in CVD outcomes over the 4.8 year intervention period.⁹⁶ It is important to point out that such remarkable clinical benefits were observed in the absence of weight loss. Although no similar physical activity/exercise randomized trial has been conducted in abdominally obese patients, studies that have compared the CVD event rates in physically active vs. physically inactive men and women with/without abdominal obesity and with features of the metabolic syndrome have shown a remarkable impact of physical activity on reducing CVD, even among those who were abdominally obese.⁹⁷ These results are critical to emphasize the importance of targeting lifestyle *per se* in abdominally obese patients, even in the absence of weight loss. Thus, improving nutritional quality, increasing physical activity level, and improving cardiorespiratory fitness (as an index of regular participation in vigorous physical activity/exercise) are important and clinically relevant targets in abdominally obese patients. Simple tools to assess “lifestyle vital signs” in clinical practice have been proposed and this topic is currently a fertile area of investigation.

In addition to the clinical benefits of lifestyle, weight loss in viscerally obese patients has also been reported to predict improvements in several markers of cardiometabolic risk. For instance, clinical studies in overweight and obese patients show that visceral, and not abdominal subcutaneous, adiposity reduction drives the benefits of a 1-year lifestyle modification program.⁹⁴ Multiple systematic reviews and meta-analyses have been published detailing the effects of diet and exercise on visceral fat reduction in the short term (usually <12 weeks). Both very-low calorie diet⁹⁸ and exercise⁹⁹ produce preferential loss of VAT, with aerobic (rather than resistance) exercise having the greatest benefits.¹⁰⁰ Unpublished meta-analysis data including 12 studies between 2000 and 2014 evaluated the impact of a sustained intervention (6 months) on VAT and demonstrated significant reductions in VAT area with both lifestyle and pharmacologic interventions. Exercise showed a greater, more sustained impact on changes in visceral adiposity compared with pharmacological therapies. In addition, because exercise training can potentially increase lean body mass and since VAT represents a relatively minor component of total body fat, it has also be reported that a reduction of VAT with a lifestyle modification program including regular exercise could even be observed in the absence of body weight loss. In those

situations (visceral loss and lean body mass gain), the measurement of waist circumference may allow the clinician to perceive that diabetogenic/atherogenic visceral adipose tissue was lost. On that basis, it has been suggested that waist loss may be a more preferable therapeutic target than weight loss, particularly in high risk prediabetic or diabetic obese patients who have more visceral adipose tissue at any BMI than nondiabetic individuals. Loss of visceral adipose tissue in high risk viscerally obese patients is a marker that the size of ectopic fat depots has been reduced. Indeed, lifestyle intervention studies have shown a reduction in liver, cardiac and skeletal muscle fat and these changes also contributed to the improvements in the cardiometabolic risk profile, although the specific contribution of each of these ectopic fat depots is currently under investigation.¹⁰¹

Multiple medications are now FDA-approved for sustained treatment of obesity as adjuncts to lifestyle modification to induce weight loss. Medications such as sustained-release phentermine/topiramate, liraglutide, lorcaserin, naltrexone-bupropion, and orlistat all help reduce body weight to varying degrees by ~2 to 10 kg over 6 months to 1 year (Table 5).¹⁰² Few data are available describing the effects of these medications on visceral and ectopic fat depots. Preliminary data in small dedicated sub-studies within larger randomized trials of some medications such as liraglutide¹⁰³ and naltrexone/bupropion have showed promising results with greater reductions in visceral fat compared with subcutaneous fat. Whether these reductions in visceral adiposity translate to improvement in surrogate outcomes (e.g. lipid levels, inflammatory markers, markers of cardiac injury or hemodynamic stress) in high risk individuals remains an open question. A randomized, placebo-controlled clinical trial has been recently launched to address this question using liraglutide in order to better assess its impact on body fat distribution and markers of cardiometabolic risk in a population of overweight and obese individuals at high risk for CVD (Clinicaltrials.gov number, NCT03038620).

Surgical therapies for weight loss such as gastric bypass, gastric sleeve, and laparoscopic gastric banding are being increasingly used to treat severe obesity and type 2 diabetes.¹⁰⁴ Both gastric bypass and gastric sleeve significantly reduce visceral fat by ~40–50% with more modest reduction in abdominal subcutaneous fat (~10%).¹⁰⁵ Peripheral glucose utilization in both skeletal muscle and in adipose tissue is also improved after bariatric surgery. In a recent meta-analysis of 6 studies, diabetes remission rates after surgery ranged from 66.7% with gastric bypass to 28.6% with gastric banding. Improvements in glycated hemoglobin, fasting blood glucose, and reduction in the need for glucose lowering therapies were also seen with bariatric surgery.¹⁰⁶ Multiple observational case series also suggest long term benefits for heart failure with both preserved and reduced ejection fraction after bariatric surgery.¹⁰⁷ Evidence that sustained weight loss through surgery can modulate visceral and epicardial fat¹⁰⁸ also supports a potential role for bariatric surgery in the treatment of obesity-related cardiovascular risk.

Unanswered Questions, Future Directions, and Public Health Messaging

Although it is clear that the accumulation of visceral and ectopic body fat is a major contributor to cardiovascular and metabolic risk above and beyond the BMI, implementation of fat distribution assessment into clinical practice remains a challenge. Future endeavors

should focus on better understanding the factors that influence an individual's body fat distribution profile in order to answer *why* a person preferentially accumulates fat in one depot over another. Although evidence of genetic predisposition is available, molecular mechanisms responsible for such genetic susceptibility are largely speculative at this time. In addition, how type and makeup of diet, or other lifestyle factors play a role will be important areas of investigations for the future. Emerging technologies allow assessment of visceral and lower body adiposity that is faster, cheaper, and at less risk than ever before. A focus on implementation of visceral and lower body fat measurements into clinical practice should be a priority over the next 5–10 years and clinical assessment of visceral and lower body adiposity should be incorporated into risk paradigms in order to refine risk evaluation and develop improved and effective preventive and therapeutic strategies for high risk obesity. Drug and device companies have a unique opportunity to develop targeted interventions that reduce visceral fat and induce fat re-distribution that could result in body fat remodeling to a more acceptable, healthier body fat profile without necessarily requiring overall or substantial weight loss.

The study of the causes and consequences of excess visceral adiposity/ectopic fat have major clinical implications considering the worldwide epidemic of type 2 diabetes. The current confusion around the health risk of overweight/obesity clearly shows the need to better define its health risk and the importance of measuring/targeting visceral adiposity/ectopic fat and its environmental and genetic determinants. We need to go beyond body weight, BMI, dietary caloric restriction, and generalized weight loss to help patients in clinical practice and in our public health messages. As an example, a national educational campaign on the “waist of the nation” would put this simple index of abdominal obesity on the radar screen of its citizens, the way similar campaigns were conducted in the 1970's to emphasize the risk of hypertension. However, improving behaviors at the national level is a daunting objective and will require that the healthy behaviors become the easy, default decisions. To help achieve this ambitious goal, on the basis of the scientific evidence available, we propose that it is time to at least align our public health and clinical messages and approaches in our combat against obesity. The impact of obesity on cardiovascular and metabolic diseases is more than just skin deep and we, as a scientific community, have only scratched the surface. So much more can be learned to help combat the growing epidemic of obesity worldwide and build healthier lives, free of cardiovascular diseases for the future.

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Abbreviations

BMI	body mass index
CRF	cardiorespiratory fitness

CT	computed tomography
CVD	cardiovascular disease
DXA	dual x-ray absorptiometry
LBAT	lower body subcutaneous adipose tissue
MHO	metabolically healthy obesity
MRI	magnetic resonance imaging
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue

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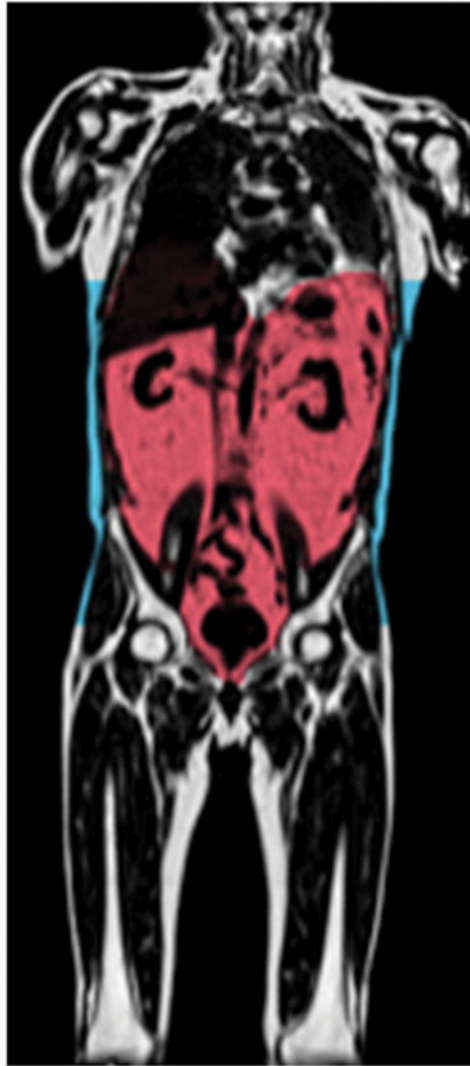
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67 year old male
BMI 25 kg/m²
Visceral fat 2.58 L/m²



53 year old male
BMI 30 kg/m²
Visceral fat 0.88 L/m²

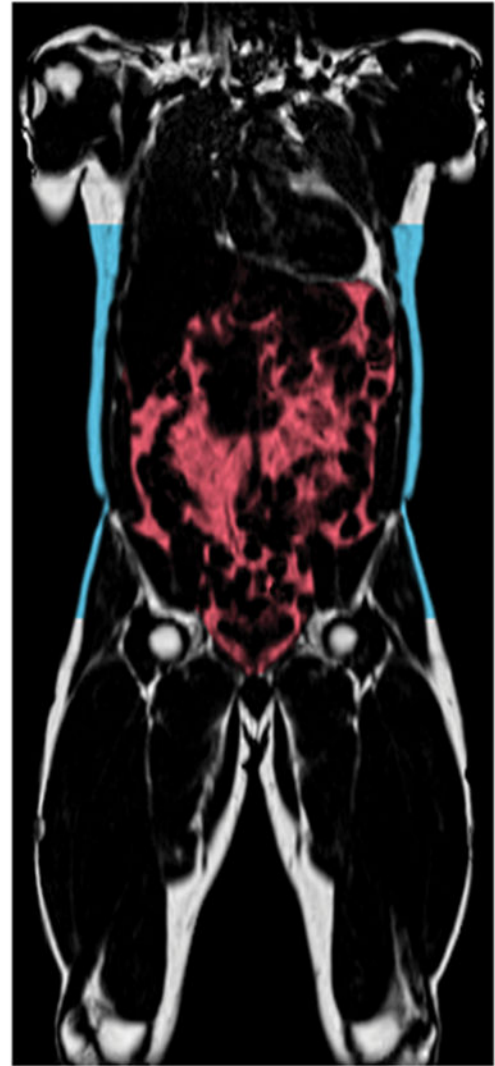


Figure 1. Extreme Variation in Abdominal Fat Distribution

T1-weighted coronal neck-to-knee magnetic resonance images demonstrating variation in visceral fat (shaded red) and abdominal subcutaneous fat (shaded blue) between two individuals with normal weight (left) and obesity (right). Images courtesy of Advanced MR Analytics (Linköping, Sweden)

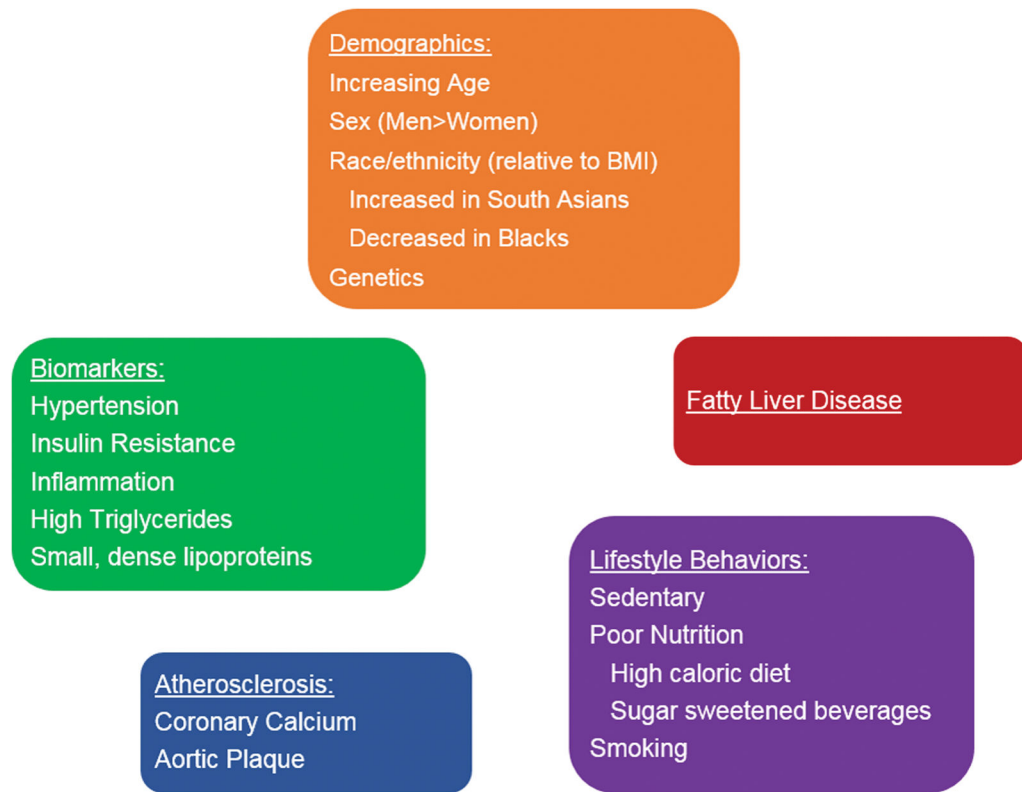


Figure 2. Factors Associated with Increased Visceral Adiposity

Both modifiable and non-modifiable factors both contribute to and result from excess visceral adiposity and ectopic fat deposition

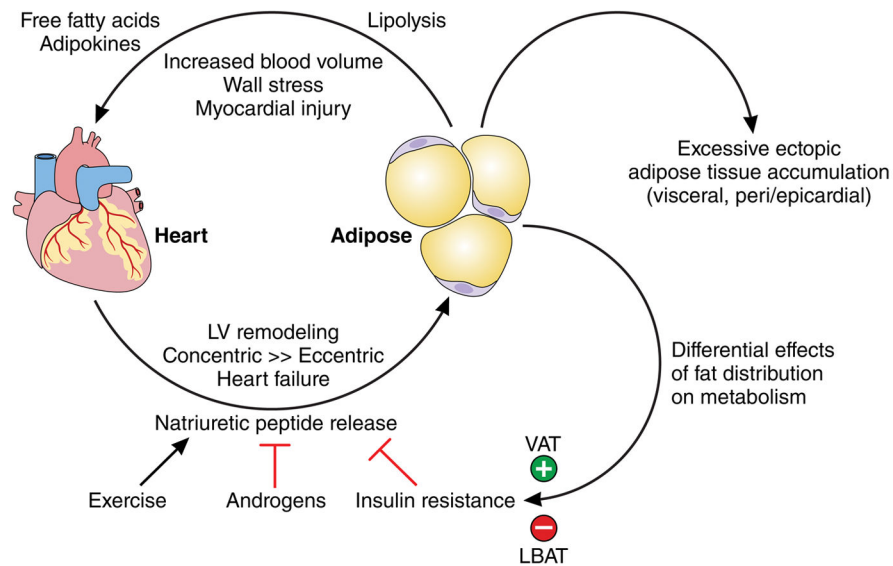


Figure 3. Mechanistic Model for Effects of Obesity on Cardiac Dysfunction and Heart Failure

Model for adiposity-related cardiac dysfunction integrates our understanding of body fat distribution into a potential etiologic pathway leading from obesity to heart failure. Excessive fat accumulation in visceral and ectopic sites result in increasing circulating blood volume and local and systemic pro-atherogenic inflammatory factors which act to increased stroke volume, cardiac wall stress, and myocardial injury leading to concentric left ventricular hypertrophy, left ventricular remodeling, and ultimately diastolic and systolic cardiac failure. Natriuretic peptides released by cardiomyocytes may exert differential effects on fat metabolism in a positive feedback loop modified by factors such as exercise, sex hormones, and insulin resistance. LBAT=lower body subcutaneous adipose tissue; VAT=visceral adipose tissue

Table 1

World Health Organization Classification of Obesity

Classification	Body Mass Index (kg/m ²)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25–29.9
Obese	
Class I	30–34.9
Class II	35–39.9
Class III	40

Modified from reference 3

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Table 2

Ethnicity-Specific Cut-off Values for Waist Circumference

Ethnic Group	Waist Circumference (marker of central obesity)
European origin	
Men	94 cm
Women	80 cm
South Asians	
Men	90 cm
Women	80 cm
Chinese	
Men	90 cm
Women	80 cm
Japanese	
Men	85 cm
Women	90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available

Modified from reference 33

Table 3

The 5-Point Edmonton Obesity Staging System

Stage	Obesity-Related Health Status
0	No apparent risk factors (blood pressure, serum lipid and fasting glucose levels within normal range), physical symptoms, psychopathology, functional limitations and/or impairment of well-being related to obesity
1	Presence of obesity-related subclinical risk factors (borderline hypertension, impaired fasting glucose levels, elevated levels of liver enzymes), mild physical symptoms (dyspnea on moderate exertion, occasional aches and pains, fatigue), mild psychopathology, mild functional limitations and/or mild impairment of well-being
2	Presence of established obesity-related chronic disease (hypertension, type 2 diabetes, sleep apnea, osteoarthritis), moderate limitations in activities of daily living and/or well-being
3	Established end-organ damage such as myocardial infarction, heart failure, stroke, significant psychopathology, significant functional limitations and/or impairment of well-being
4	Severe (potentially end stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well-being

Modified from reference 74

Table 4

Potential Clinical Utility of Methods to Assess Adiposity

Method	Clinical Use	Surrogate for Visceral Adiposity
Body mass index	+++	+
Waist circumference	+++	++
Waist-height ratio	++	++
Waist-hip ratio	++	++
Hypertriglyceridemic waist	+++	++
Computed tomography (CT)	???	+++
Magnetic resonance imaging (MRI)	???	+++
Dual x-ray absorptiometry (DXA)	???	+++

Modified from reference 85

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Table 5
Pharmacotherapy for Long-Term Obesity Management in the United States in 2017

Drug (generic)	Dosage	Mean Weight Loss above Lifestyle	Common Side Effects	Contraindications	Special Populations
Phentermine/Topiramate	7.5/46 mg daily	6.6 kg, 1 year	Insomnia, dry mouth, nausea	Pregnancy, multiple drug interactions	Young, no CV D risk factors
Liraglutide	3.0 mg daily	5.8 kg, 1 year	Nausea, vomiting, pancreatitis	Medullary thyroid cancer, MEN-2	Type 2 diabetes
Lorcaserin	10 mg bid	3.6 kg, 1 year	Headache, nausea	Pregnancy, multiple drug interactions	CV D risk factors
Naltrexone/Bupropion	32/360 mg qid	4.8 kg, 1 year	Nausea, constipation	Seizure, eating disorder, drug or ETOH withdrawal	Addiction disorders
Orlistat (Rx and OTC)	60/120 mg tid	2.9–3.4 kg, 1 year	Steatorrhea, flatulence, fecal discharge	Cyclosporine, malabsorption, pregnancy, certain meds	Available over-the-counter

Modified from reference 102