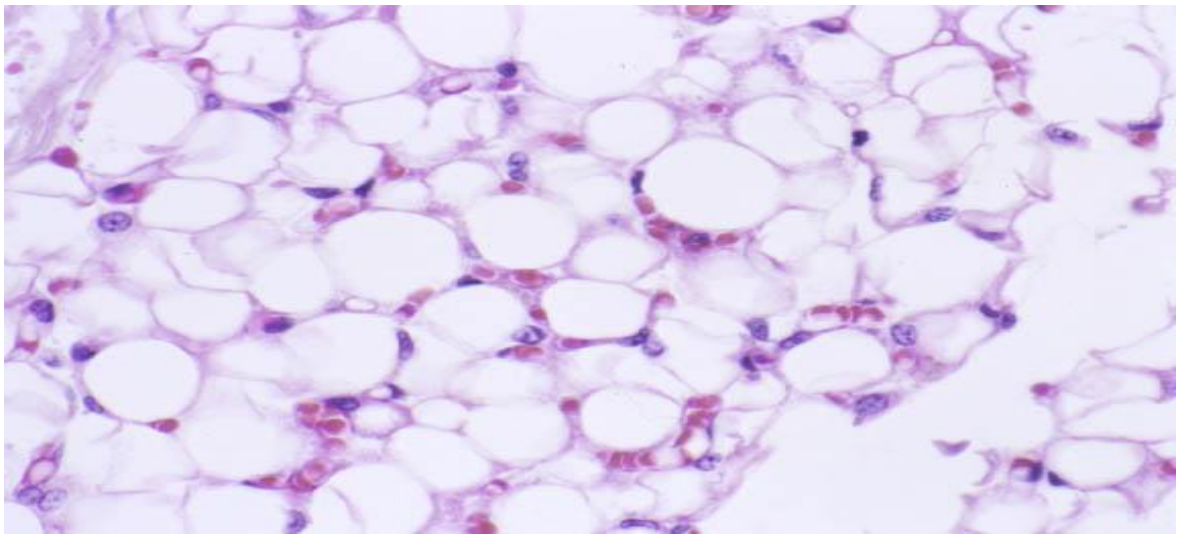
Obesity and Cardiovascular Disease: Not Just Skin Deep



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Department of Internal Medicine Grand Rounds
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This is to acknowledge that Ian J. Neeland, MD has disclosed that he receives advising/speaking fees from Boehringer-Ingelheim and is a member of the Scientific Advisory Board of Advanced MR Analytics AB. Dr. Neeland will be discussing off-label uses in his presentation.

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Biography:

Dr. Neeland earned his medical degree at Mount Sinai School of Medicine. He completed an internal medicine residency at Emory University School of Medicine and served as Chief Medical Resident at the Veteran's Affairs Hospital in Atlanta before coming to UT Southwestern in 2011 where he completed a combined clinical and research fellowship in cardiovascular medicine. He also holds a certificate in translational medicine from Emory's Laney Graduate School.

Dr. Neeland joined the UT Southwestern faculty in 2015. He is a general cardiologist with special expertise in obesity and cardiovascular disease, as well as in noninvasive imaging. Dr. Neeland is certified by the American Board of Internal Medicine in both internal medicine and cardiovascular diseases and he also holds a subspecialty certification in adult echocardiography from the National Board of Echocardiography.

Dr. Neeland is active in both research and patient care. His research focuses on cardiovascular disease, diabetes, and obesity. He is a member of professional organizations that include the AHA Council on Epidemiology and Prevention, as well as its Council on Lifestyle and Cardiometabolic Health; American College of Cardiology; American Society for Preventive Cardiology; and The Obesity Society.

Purpose and Overview: The purpose of this presentation is to discuss the heterogeneous manifestations of obesity-related cardiovascular disease and the central role of visceral adiposity in its pathophysiology.

Objectives: At the conclusion of this lecture, the listener should be able to: a) Describe the concept of the "obesity paradox" in established cardiovascular disease; b) Define "adiposopathy" and its three main tenets; c) Understand the physiologic and pathologic differences between varying adipose tissue depots and their impact on cardiovascular and metabolic diseases; d) Describe the clinical implications of obesity heterogeneity and visceral adiposity; and e) Identify several areas for future investigation and clinical adaptation of new paradigms of obesity as it relates to cardiovascular disease risk.

Obesity: Classification and the Scope of the Problem

Prevalence rates of obesity have been rising steadily in the United States since the 1990s; obesity is now present 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).[1] 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 (Figure 1). In one systematic review incorporating data from 19 prospective studies of ~1.5 million adults, the lowest mortality was seen at a BMI of ~23 kg/m^2 with higher rates of mortality at either end of the BMI spectrum and with clear inflection points after a BMI of 30 kg/m^2 (the cutoff for "obesity") and below 18.5 kg/m^2 (the cutoff for "underweight").[2] Lower socioeconomic status and greater comorbidity also track with BMI although these relationships tend to be more linear.

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

Table 1. WHO Classification of Obesity[1]

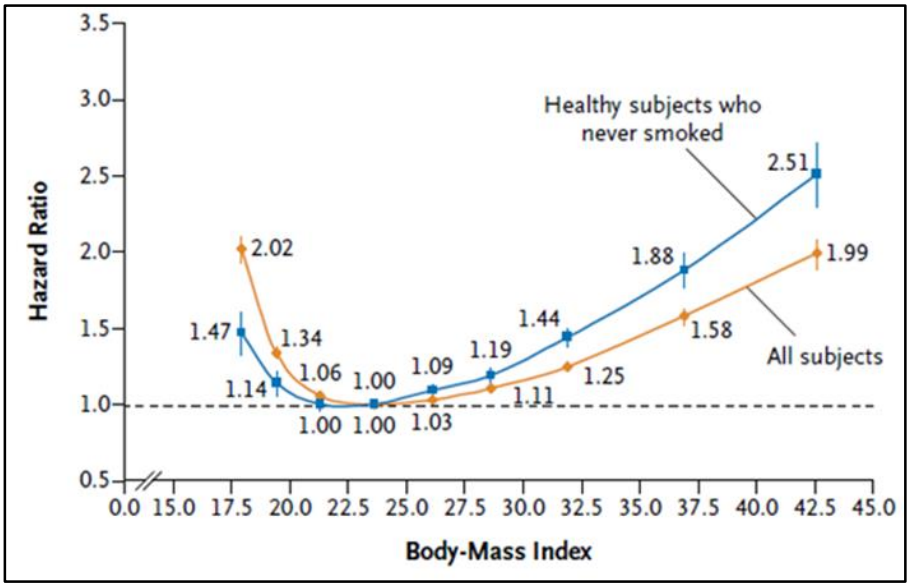


Figure 1. Body mass index and mortality among 1.46 million white adults[2]

However, in point of fact, obesity is a heterogeneous disorder with varying manifestations despite similar body weight or BMI. If one were to evaluate critically the performance of BMI as a biomarker, it would fall short in several areas. First, although a proportion of individuals with obesity will develop type 2 diabetes and/or cardiovascular disease (CVD), a significant minority will remain free of cardiometabolic disease during their lifetime. In one study from NHANES, 51.3% of overweight and 31.7% of obese adults were determined to be metabolically healthy.[3] Metabolically healthy obesity was associated with younger age, non-Hispanic black race/ethnicity, higher physical activity levels, and less central obesity.

Second, 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 have better prognosis compared with normal weight people.[4] An obesity paradox has been observed in both cardiovascular diseases (including hypertension, coronary heart disease, heart failure, and peripheral vascular disease) and non-cardiovascular disease (such as end-stage renal disease, cancer, and chronic obstructive pulmonary disease). We recently demonstrated the presence of an obesity paradox with mortality and hospitalization in older patients after ST-elevation myocardial infarction. Importantly, the paradox persisted in non-smokers and those with low comorbidity, evidence against a popularly held notion that the "paradox" is a misconstrued result of greater comorbidity from smoking and other chronic diseases seen in the underweight or normal weight population, implicating residual confounding, as opposed to lower BMI itself, as the culprit for a worse prognosis in this group. Other theories to help explain the obesity paradox have been postulated including a deficiency of lean mass (sarcopenia) and differences in body fat distribution (obesity heterogeneity).

Third, BMI has never emerged as a component of the Framingham or Pooled Cohort Equation[5] CVD risk scores, because it does not add sufficient discriminatory capacity over traditional risk factors. 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. The determinants of the heterogeneity of obesity including the obesity paradox, metabolically healthy obesity and, conversely, an adverse obesity phenotype associated with the development of cardiometabolic abnormalities remains an important question with practical preventative, diagnostic, and therapeutic implications.

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.[6] 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 breaking down or building up 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, and heart) 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.

There are many manifestations of ectopic fat in the literature that have been implicated in contributing or being associated with cardiometabolic disease. These include fat deposition in the liver, pancreas, heart (intramyocardial, epicardial, and pericardial), skeletal muscle, kidney, and perivascular space.[7] It is important to note, however, that the body's response to excess energy accumulation is not uniform – there is significant variation from one individual to the other in how much and where fat is deposited or stored. For example, in Figure 2 below, one individual has a BMI of 36 kg/m^2 whereas the other has a BMI of 31 kg/m^2. However, neither the BMI nor the waist circumference demonstrate the extreme variation in intraabdominal fat distribution between the two subjects – the individual with the lower BMI has a significantly greater burden of visceral adipose tissue (VAT) whereas the subject with the higher BMI has mostly abdominal subcutaneous adipose tissue (SAT). Variation in intraabdominal fat that is not readily apparent

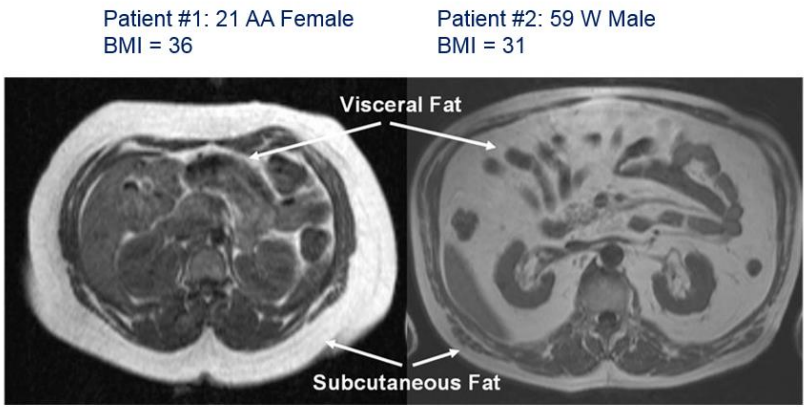


Figure 2. Extreme variation in abdominal fat distribution

from anthropometric data alone is a key element to risk assessment. VAT and SAT differ greatly in their functional significance and response to weight gain. In one study, individuals matched for 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.[8] Expansion of the abdominal subcutaneous depot is the physiologic response to excess triglyceride; studies in rodents where activation of mitochondrial pathways results in massive expansion in the subcutaneous fat pad via hyperplasia result in decreased lipid oxidation, increased storage, and a compensatory healthy adipose tissue expansion with preserved glucose tolerance.[9] 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.[10] VAT in obese persons has been associated with dyslipidemia, atherosclerosis, and adipocytokine dysfunction whereas SAT seems to be relatively neutral in this population. Furthermore, differences in gene expression, inflammatory milieu, and development of traditional risk factors may also differ between depots.[11] In the case above, the BMI and waist circumference would falsely indicate that the risk for cardiovascular and metabolic disease is greater in the subject on the left compared with the one on the right. Nevertheless, why excess fat is placed in particular depots/tissues in individuals with such wide variability remains a major knowledge gap in the field and an important opportunity for further research.

Visceral Adiposity

The sine qua non of adiposopathy is the accumulation of fat in visceral adipose tissue. There are several factors (both modifiable and non-modifiable) associated with excess VAT (Table 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; visceral adiposity increases in women after menopause and has been postulated as one cause for increased cardiovascular risk seen during this stage of a women's life. 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.[12] This may be explained, in part, by

racial/ethnic differences in visceral adiposity even when adjusted for differences in body composition.[13] 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 3).[14] This issue and others surrounding the role of visceral fat in metabolic syndrome was recently reviewed.[15] Black individuals are less likely to be viscerally obese and have increased lipolytic activity and more efficient clearance of excess triglycerides compared with whites.[16] Nevertheless, the relationships between visceral adiposity and adverse cardiometabolic traits persist in blacks.

Increasing age	Insulin resistance (HOMA-IR)
Sex (men>women)	Inflammation (hs-CRP)
Menopause	Small, dense LDL particles
Smoking	High triglycerides
Nutritional factors High caloric diet Sugar sweetened beverages	Aortic atherosclerosis
Sedentary behavior	Fatty liver
Genetics	Hypertension
Race (relative to BMI) Increased in South Asians Decreased in Blacks	Metabolic syndrome

Table 2. Factors associated with increased visceral adiposity

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

Table 3. Ethnic-specific vales for waist circumference[14]

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 atrial fibrillation, and separately, genetic risk for central obesity (as a surrogate for visceral adiposity) and coronary heart disease and type 2 diabetes.[17] 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 visceral adiposity. We recently presented preliminary data showing that at least 37 distinct metabolites implicated in various protein synthesis and metabolic pathways were associated with imaging-based assessments of VAT independent of BMI or glucose tolerance.

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 heath, outcomes, and interventions to reduce body weight (Table 4).[18] Although anthropometric indices of central obesity (such as waist circumference and waist-height or –hip ratios) are easy to implement clinically, the 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

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

Table 4. Potential clinical utility of methods for adiposity assessment (modified from ref #18)

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. Both of these 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. We recently showed 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. 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.

Lower Body Subcutaneous Adipose Tissue

Use of DXA to assess body fat distribution also has the added benefit of being able to measure lower body subcutaneous adipose tissue (LBAT). LBAT is defined as the region delineated by two oblique lines crossing the femoral necks and converging below the pubic symphysis and continuing through the knees on the DXA scan (Figure 3). This region includes gluteal and femoral fat. Although it is infrequently discussed in the clinical literature, this adipose tissue depot is very important with regard to cardiovascular and metabolic disease risk. Epidemiological studies, including our own in the Dallas Heart Study, have demonstrated that greater LBAT is associated with a lower cardiac risk factor burden, lower risk of incident CVD and cancer (Figure 4), and that individuals with more LBAT have less concentric remodeling of their left ventricle, greater cardiac output, and lower systemic vascular resistance 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 sink and buffering the influx of dietary lipids and protecting other tissues from lipotoxicity caused by lipid overflow and ectopic fat deposition.

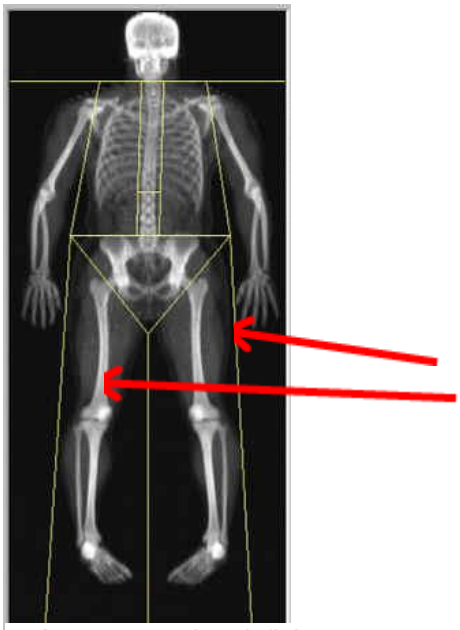


Figure 3. Region defining lower body subcutaneous adipose tissue by DXA

Interestingly, 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. These and other data suggest that depot-specific fat loss with

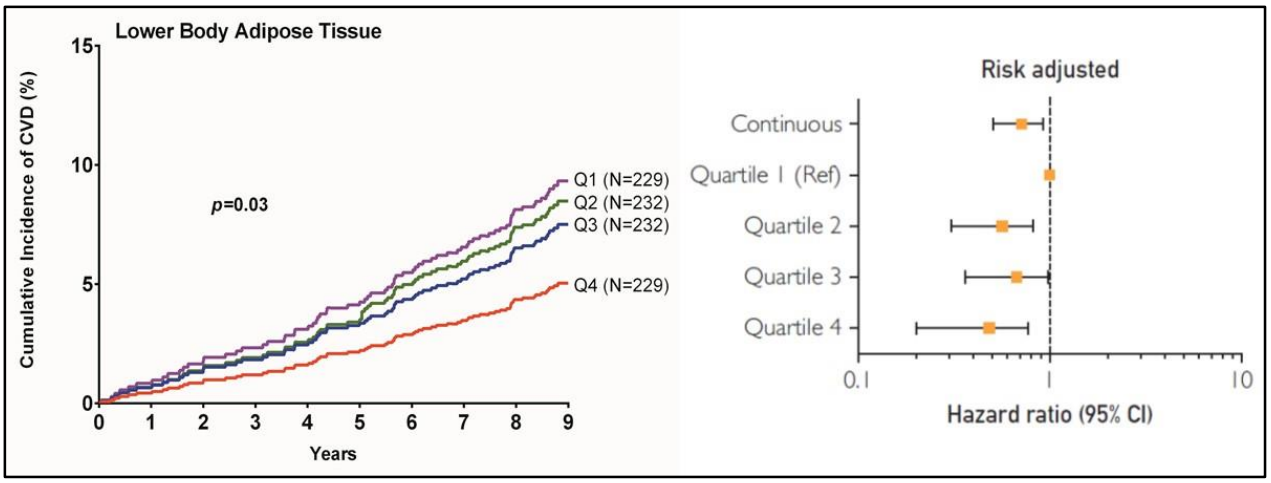


Figure 4. Risk for incident CVD (left) and cancer (right) by LBAT quartiles in the Dallas Heart Study

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 that is associated with improvements in hepatic and peripheral tissue sensitivity to insulin with certain medications (such as with thiazolidinedione treatment), there are no randomized controlled trials evaluating use of these medications as a strategy to alter body fat distribution-related risk of CVD.

Visceral Adiposity and Type 2 Diabetes

Abdominal obesity and excess visceral fat have strong associations with insulin resistance, hyperglycemia and type 2 diabetes. However the amount of VAT in most individuals represents only a relatively small fraction of body fat burden, generally less than 15%. The disproportionate influence of visceral fat on systemic metabolism has been attributed to resistance of mesenteric fat cells to the anti-lipolytic effects of insulin. Consequently, persistent turnover of mesenteric triglycerides in spite of hyperinsulinemia delivers glycerol and fatty acids directly into the portal circulation, providing both a gluconeogenic substrate and energy for gluconeogenesis in the liver. Glycerol contributes about 10% of total glucose production after an overnight fast in healthy non-obese participants, but recent data from our lab has demonstrated that visceral adiposity may disrupt glucose production from glycerol. In a recent study enrolling obese adults without diabetes, we 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.[19] 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.

Further evidence for a contributory role of visceral adiposity to type 2 diabetes comes from data in the Dallas Heart Study where we showed that visceral fat mass was independently associated with the development of both type 2 diabetes and prediabetes in a cohort of otherwise healthy obese individuals (Figure 5).[20] Neither BMI nor waist circumference were associated with incident diabetes in this study. Other factors associated with incident diabetes included fructosamine levels (an intermediate term marker of glycemia), fasting blood glucose, systolic blood pressure, family history of diabetes, and weight gain. Reduction of body weight and visceral adiposity has also shown promise in the treatment of type 2 diabetes. Bariatric surgery is one such treatment method where significant improvements or remission of type 2 diabetes have been demonstrated. In a recent meta-analysis of 6 studies reporting rates of diabetes after surgery, remission rates ranged from 75% with gastric bypass to 28.6% with gastric banding. Improvements in glycosylated hemoglobin, fasting blood glucose, and reduction in the need for glucose lowering therapies were also seen with bariatric surgery.

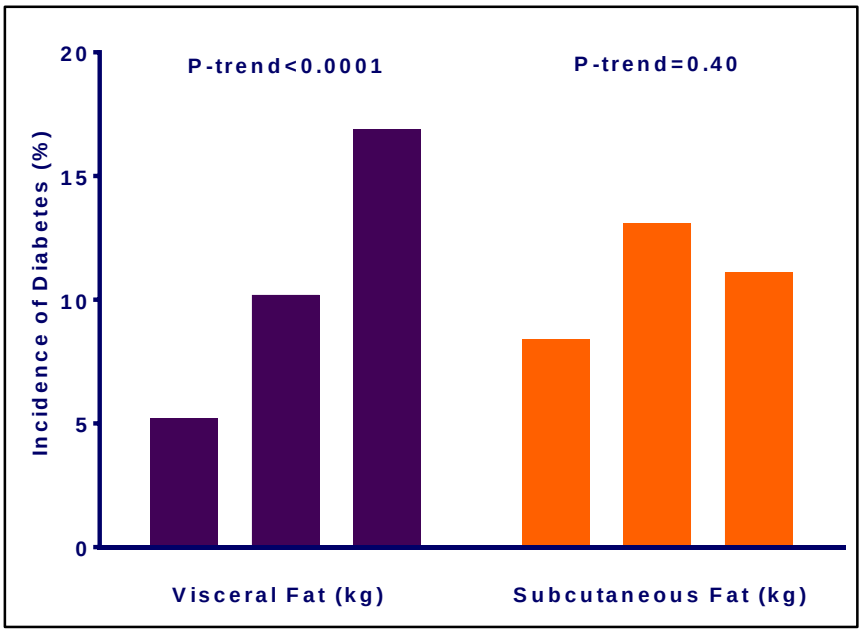


Figure 5. Diabetes incidence by tertiles of abdominal fat distribution in the Dallas Heart Study[20]

Visceral Adiposity and Cardiovascular Disease

Body fat distribution is strongly linked to the development of many cardiovascular diseases. Visceral obesity 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. From an epidemiological standpoint, we and others have shown associations between visceral adiposity and incident hypertension, atherosclerotic CVD, and cardiac dysfunction/heart failure. 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. We recently showed that 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. Further research shows that both intraperitoneal and retroperitoneal fat may 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.[21]

The individual relationships between various fat depots and incident cardiovascular diseases including both atherosclerotic and non-atherosclerotic have been recently described in the multiethnic Dallas Heart Study. Visceral fat, but not abdominal subcutaneous or liver fat, was independently associated with incident CVD (HR 1.21, 95% CI 1.02-1.43), with consistent effects across outcomes including fatal and non-fatal coronary heart disease, stroke, and peripheral arterial disease. Lower body subcutaneous fat showed a protective effect against CVD (HR 0.59, 95% CI 0.45-0.76).[22] When the relationship of these depots with cardiac structural and functional parameters were investigated using cardiac MRI, we found that VAT was associated with concentric remodeling characterized by lower left ventricular end-diastolic volume, higher concentricity, greater left ventricular wall thickness, lower cardiac output, and higher systemic vascular resistance, all important factors contributing to risk for heart failure.[23] In contrast, lower body subcutaneous fat was associated with the completely opposite phenotype (Figure 6). Excess 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). 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, although the role of these localized fat depots in

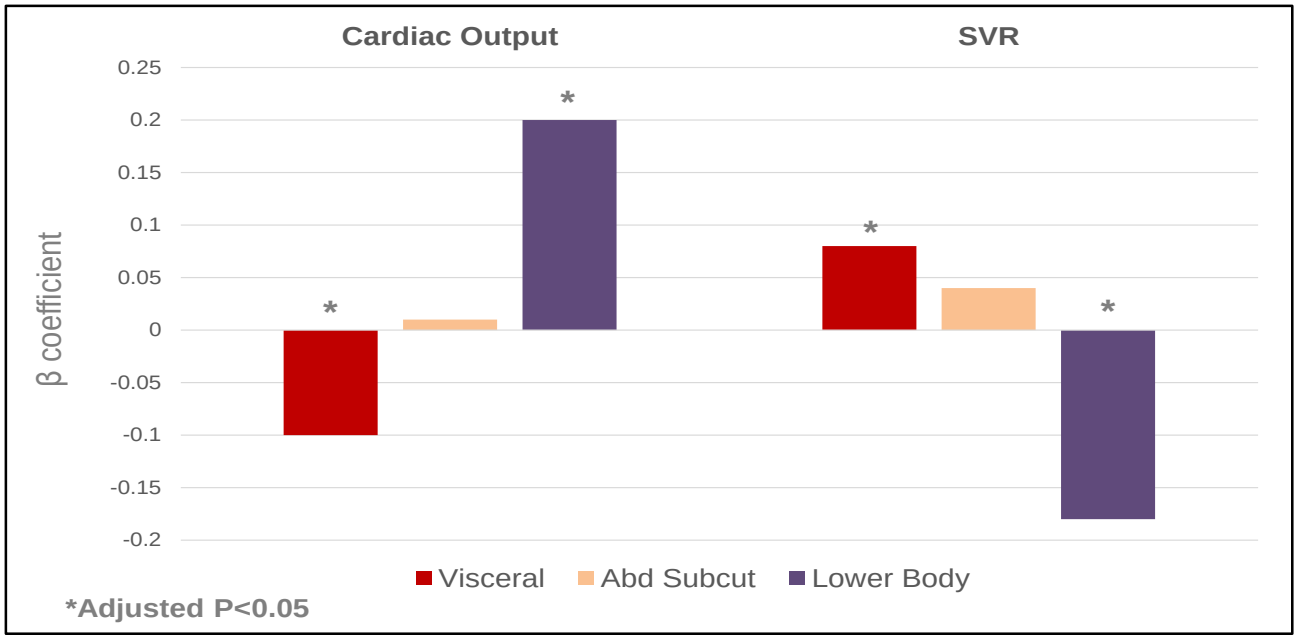
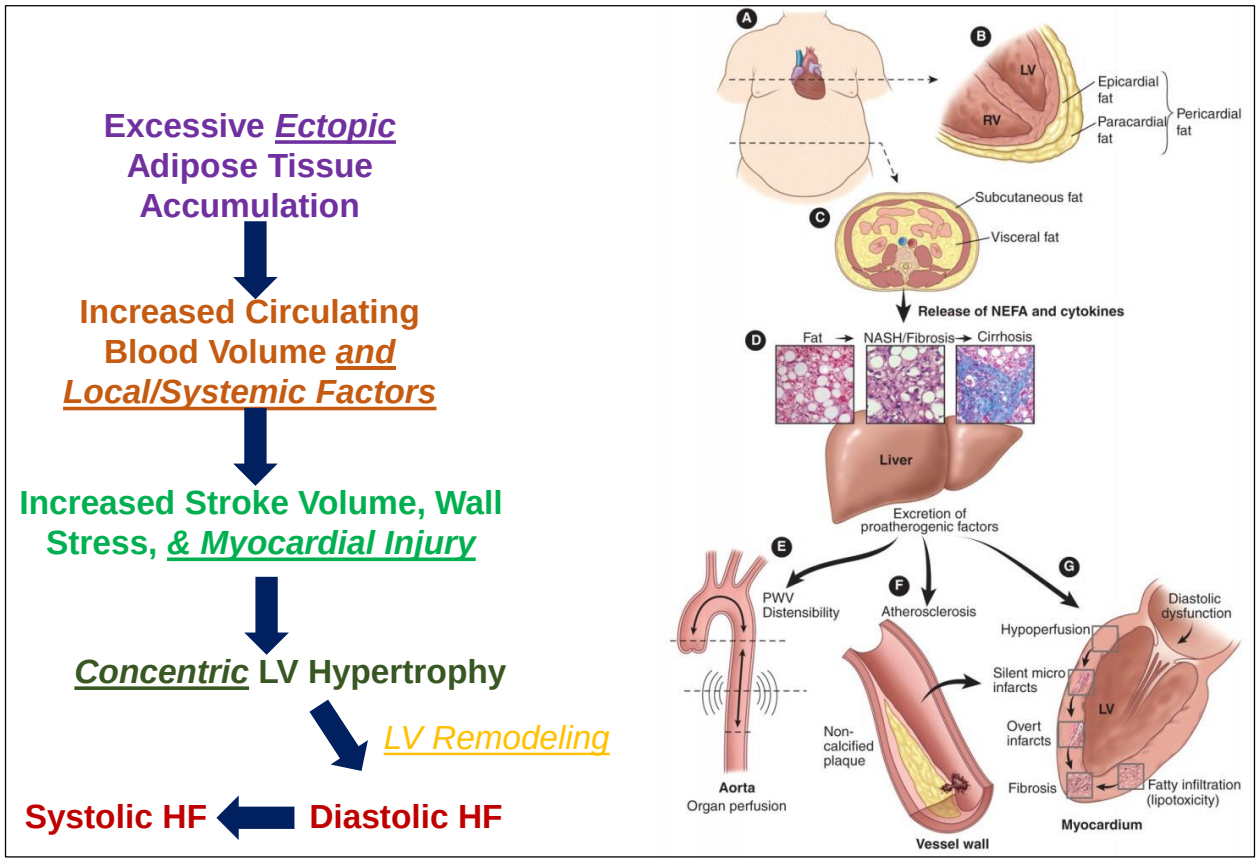


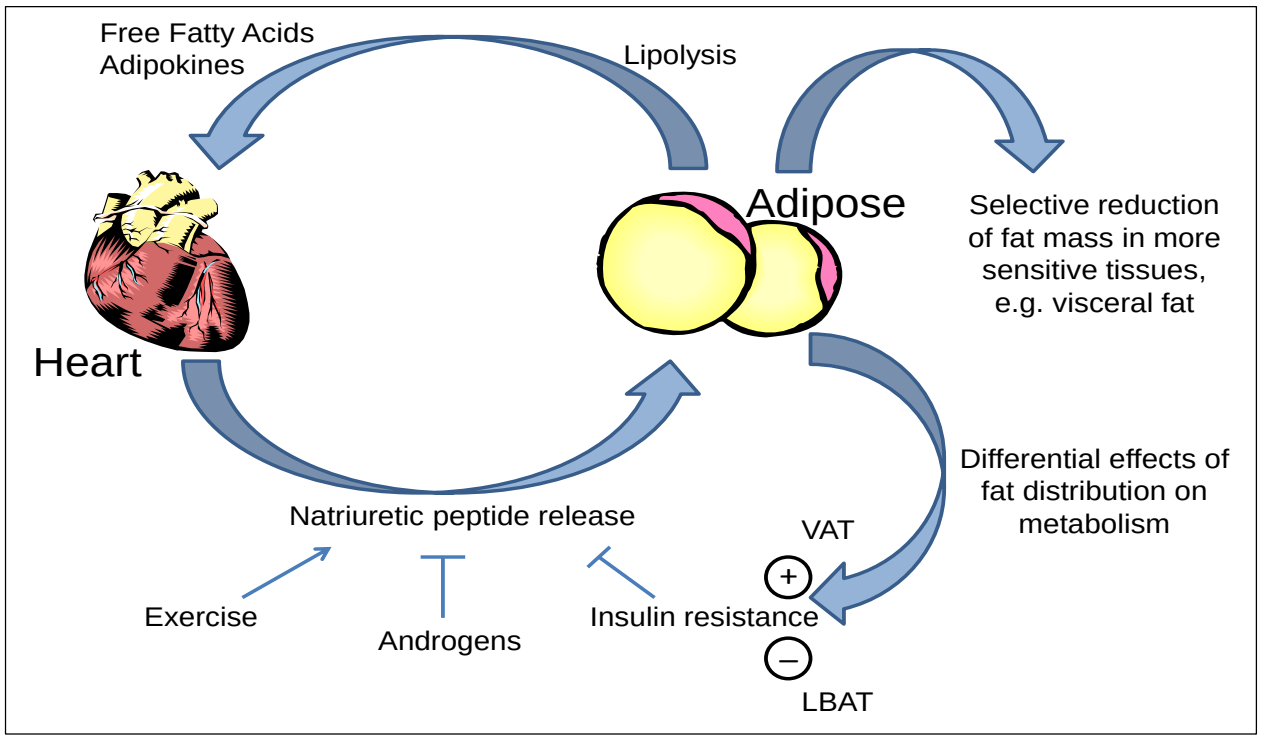
Figure 6. Hemodynamics by fat depot in the Dallas Heart Study[23]

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. There is also evidence from observational studies in bariatric surgery patients that sustained weight loss through surgery can modulate visceral and epicardial fat, potentially supporting a role for bariatric surgery in the treatment of obesity-related cardiovascular risk.

One current model for adiposity-related cardiac dysfunction integrates these data into a potential etiologic pathway leading from obesity to heart failure (Figure 7). 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 healthy individuals (so-called “natriuretic peptide deficiency”) whereas more lower body subcutaneous fat is associated with higher natriuretic peptide levels. These data suggest that natriuretic peptides released by cardiomyocytes may exert beneficial effects on fat metabolism in a positive feedback loop resulting in differential effects of fat distribution on metabolism mediated through the heart (Figure 7).

Figure 7. Mechanistic model for effects of obesity on cardiac dysfunction and heart failure





Clinical Implications of Obesity Heterogeneity

Recent guidelines from the American Heart Association, American College of Cardiology, and The Obesity Society on the management of overweight and obesity in adults[24] 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 in Prague, are becoming increasingly focused on integrating more detailed assessments of body fat distribution into risk assessment and treatment paradigms. For example, at a Think Tank[15] on metabolic syndrome sponsored by the American College of Cardiology and American Association of Clinical Endocrinologists in 2015, 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 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 (Figure 8). Clinical studies in overweight and obese

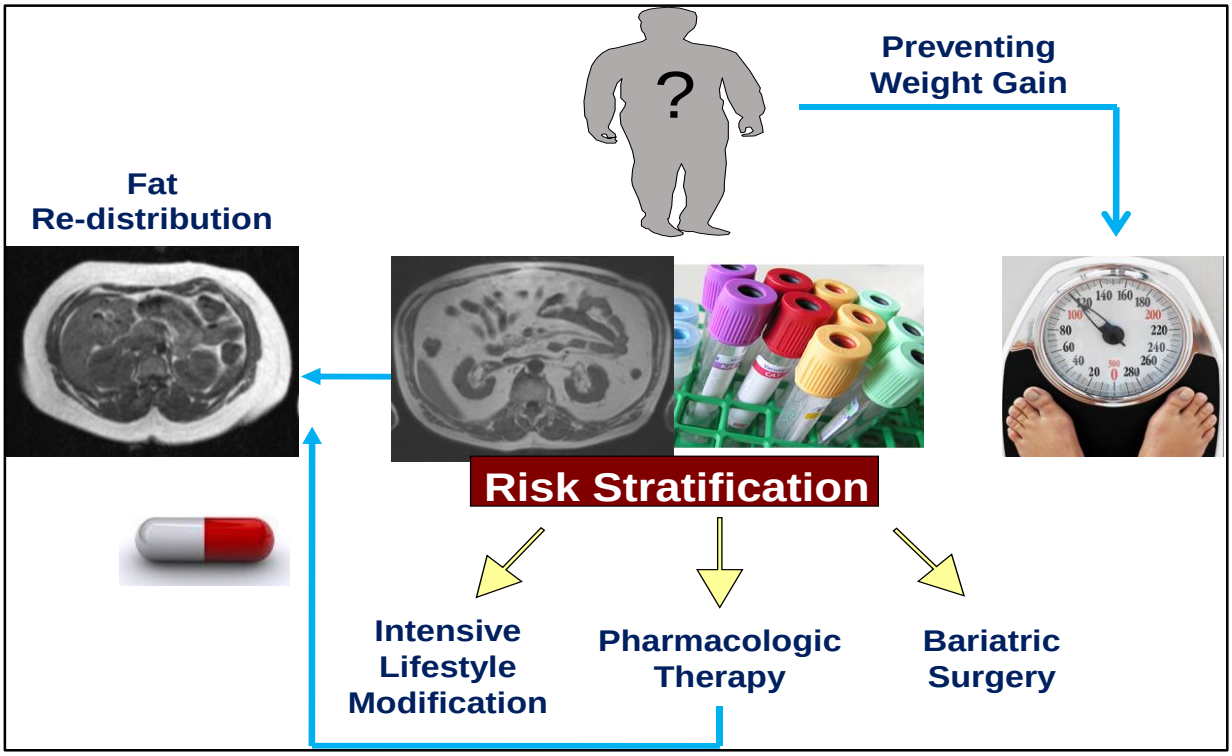


Figure 8. Clinical strategies for risk stratification and treatment of obesity based on fat distribution

patients show that visceral, and not abdominal subcutaneous, adiposity reduction drives the benefits of a 1-year lifestyle modification program. A meta-analysis recently presented by our group including 17 studies published 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. In particular, diet and exercise showed a greater, more sustained impact on changes in visceral adiposity compared with pharmacological therapies, with low- or very-low calorie diets and aerobic (rather than resistance) exercise, having the greatest benefits.

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. Both gastric bypass and gastric sleeve significantly reduce visceral fat by ~40-50% with more modest reduction in abdominal subcutaneous fat (~10%). Peripheral glucose utilization in both skeletal muscle and in adipose tissue is also improved after bariatric surgery.

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).[25] Few data are available describing the effects of these medications on visceral and ectopic fat depots.

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 CVD 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	CVD 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

Table 5. Pharmacotherapy for long-term obesity management in the United States in 2017 (modified from ref #25)

Preliminary data in small dedicated sub-studies within larger randomized trials of some medications such as liraglutide 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. We have recently started a randomized, placebo-controlled clinical trial 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.

Unanswered Questions, Future Directions, and Conclusions

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. Whether genetic predisposition, type and makeup of diet, or other factors play a role remains to be seen. 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 measurement 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 guide 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 weight loss. The impact of obesity on cardiovascular disease 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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