



# Central obesity as a clinical marker of adiposopathy; increased visceral adiposity as a surrogate marker for global fat dysfunction

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## Purpose of review

Subcutaneous adipose tissue (SAT) is often described as 'protective'. Visceral adipose tissue (VAT) is often described as 'pathologic'. However, both SAT and VAT have protective and pathologic potential, with interdependent biologic functions.

## Recent findings

Most of the body's (excess) energy is stored as fat in SAT. If during positive caloric balance, SAT does not undergo adequate adipogenesis, then excess energy may result in adipocyte hypertrophy, leading to hypoxia, immunopathies, and endocrinopathies. Energy overflow may promote accumulation of pericardial fat, perivascular fat, and myocardial fat, which may directly contribute to atherosclerotic cardiovascular disease (CVD). Lipotoxic free fatty acid delivery to nonadipose body organs (e.g. liver, muscle, and pancreas) may indirectly contribute to CVD by promoting the most common metabolic disorders encountered in clinical practice (e.g. high blood sugars, high blood pressure, and dyslipidaemia), all major CVD risk factors. Finally, SAT energy overflow may increase VAT accumulation, which is also associated with increased risk of metabolic diseases and CVD.

## Summary

Increased VAT is a surrogate marker for SAT dysfunction which increases waist circumference, reflecting a shared pathologic process leading to the pathogenic fat accumulation of other fat depots and fatty infiltration of nonadipose body organs. Central obesity is a clinical marker for adiposopathy.

## Keywords

adiposopathy, central obesity, obesity, visceral adipose tissue

## INTRODUCTION

Adiposopathy ('sick fat') is defined as adipose tissue dysfunction promoted by positive caloric balance and sedentary lifestyle in genetically and environmentally susceptible individuals. Anatomically, adiposopathy is classically characterized by adipocyte hypertrophy and visceral fat accumulation [1] (see Fig. 1). Pathophysiologically, adiposopathy is manifest by adipocyte and adipose tissue endocrine and immune disorders that contribute to metabolic diseases and increased risk of cardiovascular disease (CVD) [1] (see Fig. 1).

## SUBCUTANEOUS AND VISCERAL ADIPOSE TISSUE: PROTECTIVE AND PATHOLOGIC EFFECTS

SAT and VAT are often described as two intrinsically different organs, with different genetic lineages, whose accumulation promotes different, if not

opposing health consequences [7]. Peripheral SAT is often described as 'protective' [8]. VAT is often described as 'pathologic' (i.e. a 'unique pathogenic fat depot') [9]. However, both SAT and VAT have 'protective' and 'pathologic' properties.

In addition to storing fuel in the form of lipids, adipose tissue produces hormones and immune factors [2]. These functions may be 'protective'

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## KEY POINTS

- Adipose tissue depots undergo cross-talk and biologic interactions, resulting in interdependent fat function and deposition.
- Limited adipogenesis in peripheral subcutaneous adipose tissue (SAT) may result in adipocyte hypertrophy, adipocyte and adipose tissue hypoxia, and adiposopathic endocrinopathies and immunopathies.
- Limited energy storage in peripheral SAT may result in energy overflow (e.g. increased circulating free fatty acid transport), resulting in increased accumulation of pericardial fat, perivascular fat, and visceral fat, as well as lipotoxicity and fatty infiltration to nonadipose body organs (e.g. liver, muscle, pancreas, heart, and kidney).
- Increased visceral adiposity often shares common pathologic processes leading to the adiposopathic accumulation of other fat depots, as well as lipotoxic fatty infiltration of nonadipose organs.
- Increased visceral adiposity can be measured by waist circumference; thus, central obesity is the most clinically accessible measure of adiposopathy and global adipose tissue dysfunction.

during periods of starvation, as well as potentially protective against endocrine and infectious provocations which might otherwise contribute to ill-health (e.g. SAT may protect against superficial skin wounds) [10]. Both SAT and VAT provide physical padding and insulation [10], which may provide musculoskeletal and thermal protection. VAT may provide physical protection against mechanical intraorgan damage (e.g. trauma or other forces that might otherwise jar the abdomen) and may protect against peritoneal catastrophes (e.g. perforated visceral organs) [10].

During positive caloric balance, SAT accumulation may also be metabolically 'protective' if adipocyte proliferation and differentiation provides a sufficient number of functional fat cells to mitigate adiposopathy (e.g. 'sick fat disease') [11<sup>■</sup>,12]. This 'protects' against the adverse metabolic consequences of positive caloric balance, otherwise leading to adiposopathic endocrinopathies, inflammation, and lipotoxic energy overflow to other fat depots and body organs (i.e. via increased circulating free fatty acids [1,13–16]). However, if SAT is to be truly 'protective', then the increase in SAT mass cannot be of such magnitude as to cause 'fat mass disease', defined as abnormal biomechanical physical forces that cause pathogenic stresses on weight bearing joints, immobility, tissue compressions, and tissue friction [11<sup>■</sup>].

Thus, during positive caloric balance, SAT might be considered truly 'protective' only when sufficient functional adipocytes are made available to avoid sick fat disease, whereas at the same time, the amount of adipose tissue is not sufficient to cause fat mass disease. Such a balanced SAT response to positive caloric balance may help explain populations described as 'metabolically healthy, but obese' [11<sup>■</sup>,17]. Although this scenario is intriguing, it is likely to be the rare exception because amongst most individuals who are overweight or obese, SAT usually contributes to some form of sick fat disease (adiposopathy) and fat mass disease [1,18]. In fact, some have questioned the degree by which 'metabolically healthy, but obese' populations actually exist [19<sup>■</sup>,20<sup>■</sup>].

## ADIPOSE TISSUE PATHOPHYSIOLOGY

From an organ standpoint, SAT, VAT, and other fat depots are globally increased during positive caloric balance [8]. From a cellular standpoint, adipocyte size may be globally regulated, independent of the variations in body fat distribution [21]. This supports the interconnectivity and interdependency of body fat depots and adipocytes, wherein adipose tissue's pathogenic potential might best be based upon the global assessments of adipose tissue function or dysfunction, rather than assigning the binary 'protective' and 'pathologic' labelling, depot-by-depot, adipocyte-by-adipocyte.

At least since the 1920s, central obesity and increased VAT accumulation were known to correlate with metabolic diseases and increased CVD risk [22<sup>■</sup>]. Within the national and international metabolic syndrome definitions, central obesity is the only anatomic diagnostic criterion (with the other criteria being high blood sugar, high blood pressure, and dyslipidaemia) [22<sup>■</sup>]. When these clinical findings are coupled with the observations that SAT and VAT differ in genetic origins, cellular composition, physiology, endocrinology, immunology, innervation, blood flow, and metabolic activity [7], then this helps explain why phenotypic presence of VAT is often considered the fat depot best correlated with adverse metabolic health consequences. The most common clinical measure of VAT is waist circumference. When waist circumference is increased beyond race-specific cutoff points, then this is often termed 'central obesity' and reflects the metric beyond which pathologic adverse metabolic consequences are more likely to ensue within a population [22<sup>■</sup>]. However, although central obesity may be a phenotypic reflection of the adverse metabolic consequences of increased adiposity, this does not mean that an increase in central obesity is a

**FIGURE 1.** Adiposopathic changes of adipocytes and adipose tissue [1–6].**Anatomic changes**

Adipocyte hypertrophy with variable increases in adipocyte number, as regulated by intracellular proteins:

- o Sterol regulatory element binding protein1 (SREBP1), which is the human analogue to adipocyte determination and differentiation-dependent factor 1 (ADD1)
- o Peroxisome proliferator activated receptor (PPAR) gamma
- o CCAAT-enhancer-binding proteins (C/EBPs)

When adipogenesis (proliferation and differentiation) in peripheral subcutaneous adipose tissue (SAT) is inadequate to store excessive energy, then this may:

- o Further worsen adipocyte hypertrophy of existing adipocytes
- o Contribute to energy overflow with increased circulating free fatty acid blood levels, increasing size of other adipose tissue depots, including:
  - Visceral adipose tissue (VAT) accumulation
  - Subcutaneous abdominal adipose tissue accumulation
  - Pericardiac adipose tissue accumulation
  - Perivascular adipose tissue accumulation
- o Contribute to energy overflow with increased circulating free fatty acid blood levels, increasing fatty infiltration and lipotoxicity to:
  - Liver, resulting in nonalcoholic fatty liver disease (NAFLD), with subsets including hepatic steatosis, which may contribute in insulin resistance, and nonalcoholic steatohepatitis (NASH), an inflammatory state which may lead to insulin resistance, fibrosis and cirrhosis
  - Muscle, resulting in intramyocellular triglycerides and insulin resistance.
  - Pancreas, resulting in beta cell glycolipotoxicity, macrophage infiltration, and  $\beta$ -cell failure.
  - Heart, resulting in fat accumulation within cardiomyocytes, mitochondrial dysfunction, inflammation, and cardiac dysfunction.
  - Kidney, resulting in renal fat accumulation, immune cell infiltration, increased glomerular capillary wall tension, podocyte stress, focal and segmental glomerulosclerosis, proteinuria, and progressive renal dysfunction.

**Histological and functional changes**

Adipocyte and adipose tissue hypoxia because of

- o Growth of adipose tissue beyond vascular supply
- o Inadequate angiogenesis
- o Impaired blood flow (possibly neurologically mediated)

Increased adipocyte apoptosis

Increased reactive oxygen species and oxidative stress

Extracellular matrix abnormalities

Intraorganelle dysfunction

- o Mitochondrial stress
- o Endoplasmic reticulum stress

Changes in adipose tissue neural network and innervations

**Adiposopathy may result in endocrinopathies involving dysfunctional adipocyte and adipose tissue processes involving:**

Angiogenesis  
 Adipogenesis  
 Extracellular matrix dissolution and reformation  
 Lipogenesis  
 Growth factor production  
 Glucose metabolism  
 Production of factors associated with the renin–angiotensin system  
 Lipid metabolism  
 Enzyme production  
 Hormone production  
 Steroid metabolism  
 Immune response  
 Haemostasis  
 Element binding

Adipose tissue has receptors for traditional peptides and glycoprotein hormones, receptors for nuclear hormones, other nuclear receptors, receptors for cytokines or adipokines with cytokine-like activity, receptors for growth factors, catecholamine receptors, and other receptors.

**Adiposopathy may result in immunopathies involving dysfunctional adipocyte and adipose tissue immune processes involving:**

Proinflammatory adipose tissue factors
 

- o Factors with cytokine activity
- o Acute-phase response proteins
- o Proteins of the alternative complement system
- o Chemotactic or chemoattractants for immune cells
- o Eicosanoids and prostaglandins

 Anti-inflammatory adipose tissue factors

reflection of adipose tissue pathologic processes exclusive to VAT. Waist circumference not only measures VAT, but also measures abdominal SAT. If only VAT was pathologic, and if all SAT were protective, then the adverse health consequences of waist circumference would require subtracting the contribution of the 'protective' abdominal SAT from total waist circumference. However, accumulation of abdominal SAT (especially, deep-layer SAT) is a strong predictor of global insulin resistance, liver-specific insulin resistance, Framingham Risk Score, and has higher expression of proinflammatory, lipogenic, and lipolytic genes, and contains higher proportions of saturated fatty acids [23]. These are not unlike the pathologic findings often described with VAT.

Also, amongst patients with the adiposopathic clustering of CVD risk factors, SAT often exhibits a pathogenic endocrine and immune profile (not a 'protective' profile). Specifically, in patients with metabolic syndrome, SAT may have increased macrophage recruitment, increased SAT-secreted adipokines, and decreased SAT adiponectin secretion, all of which contribute to a proinflammatory and insulin-resistant state [24<sup>■</sup>]. Moreover, when SAT is unable to adequately store excessive energy because of impaired or limited adipocyte proliferation and differentiation [25], then this suggests an underlying type of 'acquired lipodystrophy' [26]. Limited SAT adipogenesis during positive caloric balance may lead to pathologic hypertrophy of existing fat cells [25], and energy overflow (e.g. increased circulating free fatty acid delivery) [27] to other body organs and other fat depots. Adiposopathic SAT endocrinopathies, inflammation, and energy overflow to pericardial fat, perivascular fat, and myocardial fat may directly contribute to atherosclerotic CVD [1,28,29]. Increased circulating free fatty acids to other body organs such as the liver, muscle, and pancreas may also result in lipotoxicity [30,31]. Lipotoxicity promotes the most common metabolic diseases encountered in clinical practice (e.g. high blood sugars, high blood pressure, and dyslipidaemia), which are major CVD risk factors that may indirectly contribute to CVD [1,14]. Finally, SAT endocrinopathies, inflammation [32], and energy overflow may increase VAT itself, resulting in central obesity, which may contribute to metabolic diseases and increased CVD risk [1,2,14,16]. This helps explain why waist circumference has scientific rationale as a clinically reliable, time-tested clinical measure of the pathogenic potential of adipose tissue amongst populations.

With further regard to lipotoxicity, intra-adipocyte lipolysis occurs when adipose triglyceride lipase hydrolyses triglycerides into diacylglyceride, which undergoes further breakdown by hormone-sensitive

lipase (stimulated by beta-adrenergic signalling and suppressed by insulin signalling) into free fatty acids, which are released in the circulation, bound to albumin, and then delivered to other body tissues such as muscle for oxidation or liver for oxidation and triglyceride synthesis. (Glycerol is delivered to the liver for glucose production [7].) VAT is often described as more pathogenic than SAT because VAT adipocytes are reported to have higher basal lipolysis, greater sensitivity to catecholamines, and less sensitivity to insulin [33], leading to increased release of lipotoxic free fatty acids. Furthermore, because of its unique blood drainage through the portal system, VAT is often described as uniquely flooding the liver with free fatty acids through the portal system, again, leading to lipotoxicity to the liver, which then leads to insulin resistance and dyslipidaemia [33]. However, although some studies suggest VAT is less sensitive to the antilipolytic effects of insulin [7], other studies (at least in non-obese individuals) suggest insulin signalling may be greater in VAT than SAT [34]. Also, whereas VAT has predominantly portal venous return, SAT has both systemic and portal venous return. Given that SAT is often about 80% of total fat mass compared to about 10–20% for VAT, the vast majority of systemic circulating free fatty acid delivery to extrahepatic organs (for example muscle) originates from SAT, not VAT [2,35]. Thus, to the extent that extrahepatic lipotoxicity contributes to total body insulin resistance, SAT is more 'pathogenic' than VAT. Even within the portal system, the majority of free fatty acids delivered to the liver are from SAT, not VAT [36]. Thus, regarding lipotoxicity and adverse metabolic consequences [37<sup>■</sup>], SAT has substantial pathogenic potential and is not always 'protective'.

Finally, if SAT was 'protective' and VAT was 'pathogenic', then a straight-forward therapeutic intervention would be to simply remove VAT, which should logically 'cure' associated metabolic abnormalities. However, at least in humans, surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults [38]. This supports VAT as being a surrogate for global fat dysfunction, rather than a uniquely pathogenic organ. It helps explain why the best surgical interventions to improve adiposopathic metabolic abnormalities are those that reduce total body fat, as often achieved with bariatric surgery, which represents among the most effective treatment for metabolic disease, and CVD risk reduction in individuals who are overweight or obese [39].

In summary, a lack of SAT expandability and its associated endocrinopathies and immunopathies are pathologic in promoting metabolic disease [18]. It is the lack of adequate fat storage in SAT



which results in increases in fatty infiltration of non-adipose tissue organ (e.g. liver, muscle, pancreas, heart, and kidney), as well as increased accumulation of other fat depots (e.g. pericardiac, perivascular fat), including increased VAT accumulation. At minimum, both SAT and VAT have potential protective and pathologic properties, with their potential for contributions to health and ill-health being interdependent. So, rather than binary labelling of any fat depot as being 'protective' or 'pathologic', different adipose tissue compartments might best be considered heterogeneous in their potential to contribute to metabolic disease [18]. As such, an increase in VAT accumulation is a surrogate measure of global fat dysfunction, and central obesity is a clinical marker for adiposopathy.

### **WAIST CIRCUMFERENCE AS THE BEST CLINICAL MARKER FOR ADIPOSOPATHY**

If multiple fat depots are potentially pathogenic, then what diagnostic measures are most clinically useful to assess adipose tissue's global pathogenic potential?

Visceral adiposity is one of two of the sentinel anatomic findings of adiposopathy. Fat cell hypertrophy is another [2] (see Fig. 1). This suggests adipocyte size, based upon adipose tissue biopsy, may be useful in diagnosing adiposopathy. Increased fat cell size often accompanies increased circulating free fatty acids and 'ectopic' fat accumulation (i.e. visceral, pericardiac, perivascular, as well as intra-organ fat accumulation in liver, muscle, pancreas, heart, and kidney). Excessive fat cell enlargement may lead to adipocyte hypoxia and 'stress' to intra-adipocyte organelles, such as endoplasmic reticulum and mitochondria. These adiposopathic derangements contribute to endocrine and immune responses, metabolic disease, and increased CVD risk [1,40–42]. Consistent with the theme that the pathogenic potential of adipose tissue is best viewed collectively, rather than depot by depot, adipocyte mitochondrial oxidative capacity is reduced in both SAT and VAT amongst those with obesity. This impairment of adipocyte intraorganelle function does not appear to be because of differences in fat cell size, but rather because of increased global adiposity [43].

However, adipogenesis is a process that includes both proliferation and differentiation, both influenced by genetic and environmental factors [1,2]. Impairment of either of these processes may contribute to adiposopathic and lipodystrophic effects. So, although impaired adipogenesis and proliferation may lead to adipocyte hypertrophy (a classic anatomic finding for adiposopathy), impaired adipocyte differentiation may also result in adipocyte

dysfunction, albeit not necessarily manifest by an increase in adipocyte size. Thus, although the finding of smaller fat cells is generally regarded as more functional, this may not always be the case. HIV lipodystrophy treated with certain antiretroviral therapies is illustrative of a disease process and intervention manifest by impairment of adipocyte differentiation (with a reduction in mean fat cell size), possible decrease in adipocyte proliferation, decrease in SAT accumulation, and an increase in VAT accumulation, all resulting in adiposopathic onset of hyperglycaemia and dyslipidaemia [44]. Measures of adipocyte functionality via gene expression of various markers assessed from adipose tissue biopsy may conceivably prove to be clinically useful; however, adipocyte biopsy histologic assessment of adipocyte size alone may not always be sufficiently diagnostic for fat cell function and dysfunction.

Other potential measures of adiposopathy might include the assessment of nonadipose, intra-organ fat. In addition to the SAT-mediated accumulation of non-SAT fat depots (e.g. perivascular, pericardiac, and visceral depots), increased circulating free acids may contribute to pathogenic intra-organ fat to the liver, muscle, pancreas, heart, and kidney [1–4]. As noted previously, an increase in visceral fat may reflect SAT adiposopathic endocrine, immune, and adipogenic dysfunctions. Similarly, an increase in hepatic or muscle fat may likewise reflect SAT adiposopathic dysfunction. Increased body fat associated with an increase in liver fat increases metabolic diseases risk [45] and an increase in liver fat may be more linked with metabolic complications than visceral fat [46]. Conversely, if an increase in body fat is not associated with an increase in liver fat, then this may reflect sufficient functionality of SAT and/or 'flexibility' of the liver to manage any increased fatty acid delivery, both which would be expected to mitigate metabolic disease [47]. The same principle may apply to the degree by which muscle is 'flexible' in metabolizing triglycerides, which may help distinguish between patients with increased body fat and metabolic disease (e.g. prediabetes), versus those with normal glucose tolerance [48]. Thus, a potential alternative to waist circumference to measure adiposopathy and global fat dysfunction may be hepatic imaging studies and or liver and muscle biopsies to assess intraorgan fat. Amongst these choices, hepatic imaging (e.g. ultrasound or magnetic resonance spectroscopy) is the least invasive.

In summary, although body fat can be assessed by imaging studies [e.g. computerized tomography, MRI, magnetic resonance spectroscopy, and dual-energy X-ray absorptiometry (DEXA)], waist circumference has proven to be a validated clinical measure

of the pathogenic potential of adipose tissue amongst populations, especially as it relates to metabolic disease and CVD risk. Also, waist circumference has the practical advantage as being reasonably applicable to the clinical setting. For the reasons previously discussed, hepatic imaging for hepatic fat may also play a role. Although increased adipocyte size highly correlates with intraorgan fat accumulation (both being potentially pathogenic) [49], biopsies of adipose tissue is mainly limited for research purposes, and not currently accepted as routine clinical measures of adiposopathy and global fat dysfunction. The same applies to muscle and liver biopsy.

### CONCLUSION

VAT accumulation may share similar adipose tissue pathologic processes leading to pericardiac and perivascular fat accumulation, as well as fatty infiltration of the liver, muscle, pancreas, heart, and kidney. Both SAT and VAT have potential protective and pathogenic effects [5,6]. Whereas hepatic imaging for liver fat and DEXA studies may assist in the diagnosis of adiposopathy, and although biopsy of fat, muscle, and liver may have relevance from a research perspective, the most clinically practical measure of adiposopathy is waist circumference (at least for overweight patients with BMI  $\leq 35 \text{ kg/m}^2$ ) [50]. That is because increased VAT is a surrogate marker for global fat dysfunction, and central obesity is a validated and time-tested clinical marker of adiposopathy and its adverse metabolic and CVD health consequences.

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### Conflicts of interest

There are no conflicts of interest.

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