

## Review Article

# Visceral Adipose Tissue-A Common Link to the Development of Nonalcoholic Fatty Liver Disease and Metabolic Syndrome

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### Abstract

Metabolic syndrome and Non-alcoholic fatty liver disease are common findings in obesity. In both conditions, despite many proposed mechanisms to their development, changes in adipose tissue vis-à-vis visceral adipose tissue as a highly metabolically active tissue seem to be a common pathway to their development in both the lean and obese populations. In this review, we detail how the changes that occur in adipose tissue are linked to the development of both metabolic syndrome and non-alcoholic fatty liver disease.

**Keywords:** Adipose tissue; Visceral adipose tissue; Subcutaneous adipose tissue; Metabolic syndrome; Non-alcoholic fatty liver disease

### 1. Introduction

Obesity is emerging as one of the main causes limiting life expectancy in developed countries [1]. It is linked to an increased risk of metabolic syndrome, while non-alcoholic fatty liver disease (NAFLD) is its most common complication [2]. Interestingly, a proportion of 30% of obese individuals do not develop NAFLD and metabolic aberrations; meanwhile a proportion of 20-30% of lean individuals develop NAFLD and associated

conditions [3], suggesting that the development of these complications might be related to adipose tissue distribution and functions. In fact, it has been shown that visceral adipose tissue in particular plays a critical role in the genesis of metabolic diseases and NAFLD independent of generalized obesity [4, 5]. This review will therefore consider the linkage that exists among adipose tissue in particular, visceral adipose tissue, the development of metabolic syndrome and that of NAFLD.

## 2. Adipose Tissue

Adipose tissue is a connective tissue as well as an endocrine organ, which is involved in energy homeostasis, glucose and lipid metabolism. Adipose tissue has the capability of expanding (either in the form of hypertrophy which is the increase in adipocytes volume or hyperplasia which is the increase in adipocytes number). Adipose tissue has different behaviour under different physiological conditions. For example, in excess nutrition (energy) conditions it stores the excess energy in the form of triglycerides, while during starvation or fasting conditions it supplies energy to other tissues through the process of lipolysis [6]. Adipose tissue is divided into white adipose tissue (WAT) and brown adipose tissue (BAT).

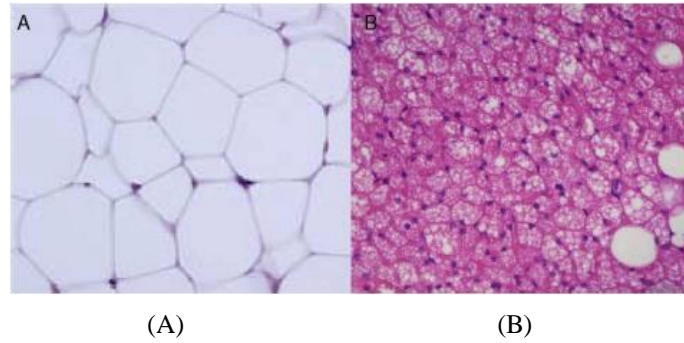
### 2.1 White adipose tissue (WAT)

WAT is the more abundant of the two and is distributed into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). WAT is characterised with large single lipid droplets (unilocular) and contains few mitochondria inside (Figure 1A) [7]. WAT secretes a number of different hormones that play various roles in energy

metabolism and endocrine function. Among many other hormones secreted by this tissue are: adiponectin, leptin and resistin [8, 9]. Interestingly, Lee et al demonstrated that SAT was strongly associated with leptin while VAT was strongly associated with adiponectin [10]. These outcomes probably explain the biological functional differences between the two WAT subtypes. In fact, VAT is more highly metabolically active than SAT and has been associated with metabolic disorders [4, 5]. VAT depots include mesenteric, omental, perirenal and peritoneal regions [11, 12]. Contrary to the association of VAT with metabolic disorders, SAT on the other hand has been attributed to offer “protection” from metabolic disorders. Kim et al showed that an increase in the SAT area was significantly associated with regression of NAFLD [13] while Kwon et al. showed that SAT area was not associated with the incidence of metabolic syndrome [14].

### 2.2 Brown adipose tissue (BAT)

BAT is characterized by less lipid droplets, highly irrigated with blood vessels, innervated with noradrenergic fibres, high content of uncoupling protein 1 (UCP1) and mitochondrial contents [15] (Figure 1B). UCP1 is also expressed by WAT at the mitochondrial level but only to a lesser degree [16], which is thought to induce “white to beige fat” transition, being referred to as “browning of white fat” or “synthesis of beige fat [17, 18].” The functions of both classical brown and beige adipose tissues are for thermogenesis and energy balance, with contribution to glucose homeostasis, mitigating insulin resistance and clearing triglycerides [19, 20].



**Figure 1:** (A) Light microscope image of white adipose tissue and (B) brown adipose tissue. Adapted from Ràfols [21].

### 3. Metabolic Syndrome

This is a constellation of metabolic abnormalities that includes: central obesity, insulin resistance, hypertension, and dyslipidaemia [22-24]. This syndrome is strongly associated with the increased risk for cardiovascular disease and type 2 diabetes

mellitus [23] and its prevalence is high in the obese population [25]. Notably, the prevalence varies with respect to gender, ethnicity/race, age and the criteria used for its diagnosis. Table 1 shows the summary of different criterion used to diagnose metabolic syndrome.

Clinical And Blood Biochemistry parameters	WHO 1998 [26]	EGIR 1999 [27]	NCEP ATP III 2001 [28]	AACE 2003 [29]	IDF 2005 [30]	AHA/NHLBI 2005 [31]	CONSENSUS (AHA/NHLBI + IDF) 2009 [32]
Insulin resistance	Impaired glucose tolerance, impaired fasting glucose, T2DM, or lowered insulin sensitivity <b>plus any two of the following:</b>	Plasma insulin concentration >75th percentile of non-diabetic patients, <b>plus any two of the following:</b>	<b>Any three of the following:</b>	Impaired glucose tolerance or impaired fasting glucose, <b>plus any of the following:</b>	N/A	<b>Any three of the following:</b>	<b>Any three of the following:</b>
Obesity	Abdominal obesity (waist-to-hip ratio >0.90 in men or >0.85 in women, or BMI >30 kg/m <sup>2</sup> )	WC ≥ 94 cm in men; ≥ 80 cm in women	WC >102 cm in men; >88 cm in women	BMI ≥ 25 kg/m <sup>2</sup>	BMI >30 kg/m <sup>2</sup> or WC with ethnicity-specific values, <sup>Y</sup> <b>plus any two of the following:</b>	WC ≥ 102 cm in men; ≥ 88 cm in women	Raised WC (population- and country-specific definitions)
Plasma glucose concentration <sup>Φ</sup>	Impaired glucose tolerance, impaired fasting glucose, or T2DM	FPG ≥110 mg/dL	FPG ≥110 mg/dL	Impaired fasting glucose, or Impaired glucose tolerance	FPG ≥100 mg/dL	FPG ≥100 mg/dL	FPG ≥100 mg/dL or on diabetes treatment
Plasma glucose concentration <sup>Φ</sup>	Impaired glucose tolerance, impaired fasting glucose, or T2DM	FPG ≥110 mg/dL	FPG ≥110 mg/dL	Impaired fasting glucose, or Impaired glucose tolerance	FPG ≥100 mg/dL	FPG ≥100 mg/dL	FPG ≥100 mg/dL or on diabetes treatment
Triglycerides (TG) <sup>Ψ</sup>	TG ≥150 mg/dL	TG ≥150 mg/dL or on treatment	TG ≥150 mg/dL	TG ≥150 mg/dL	TG ≥150 mg/dL or on treatment	TG ≥150 mg/dL or on treatment	TG ≥150 mg/dL or on treatment

HDL-cholesterol (HDL-C) <sup>β</sup>	HDL-C <40 mg/dL in men and <50 mg/dL in women	HDL-C <39 mg/dL in men or women, or on treatment	HDL-C <40 mg/dL in men and <50 mg/dL in women	HDL-C <40 mg/dL in men and <50 mg/dL in women	HDL-C <40 mg/dL in men and <50 mg/dL in women, or on treatment	HDL-C <40 mg/dL in men and <50 mg/dL in women, or on treatment	HDL-C <40 mg/dL in men and <50 mg/dL in women, or on treatment
Additional	Urinary albumin excretion ≥20 µg/min, or ACR ≥30 mg/g	N/A					

AACE, American Association of Clinical Endocrinologists; ACR, albumin-creatinine ratio; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; EGIR, European Group for Study of Insulin Resistance; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); NHLBI, National Heart, Lung, and Blood Institute; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization. <sup>Y</sup> Waist circumference: for Europids, sub-Saharan Africans, Eastern Mediterranean and Middle East populations >94 cm in men and >80 cm in women; for South Asians, Chinese, Japanese, Central and South American >90 cm in men and >80 cm in women. <sup>Φ</sup> Glucose concentration conversion factor: 1 milligram per decilitre = 0.0555 millimoles per litre. <sup>Ψ</sup> Triglyceride concentration conversion factor: 1 milligram per decilitre = 0.0113 millimoles per litre. <sup>β</sup> HDL-cholesterol concentration conversion factor: 1 milligram per decilitre = 0.02586 millimoles per litre. Adapted from McCracken et al. [23].

**Table 1:** Various diagnostic criterion for metabolic syndrome [26-32].

## 4. Link Between Visceral Adipose Tissue and Metabolic Syndrome

Several theories linking adipose tissue to the development of metabolic syndrome have been proposed but the widely accepted ones are: insulin resistance with fatty acid flux [23], neurohormonal activation, low-grade chronic inflammation and oxidative stress [33-35].

### 4.1 Insulin resistance hypothesis

Insulin inhibits lipolysis and hepatic gluconeogenesis, at the same time it increases glucose uptake in the muscle and liver. In an event of insulin resistance in the adipose tissue, the insulin-mediated inhibition of lipolysis is impaired resulting in an increase in the circulating free fat acids (FFAs). This increase in circulating FFAs further inhibits the antilipolytic effect of insulin [36]. This increase in circulating FFAs results in two simultaneous but independent processes: (1) they inhibit protein kinase activation in the muscle leading to reduced glucose uptake, and (2) they increase protein kinase activation in the liver leading to the promotion of gluconeogenesis and lipogenesis. The net effect of this chain reaction results in excess levels of insulin circulating in the blood relative to the level of glucose [24]. Overtime, the compensation fails and insulin secretion diminishes. Additionally, the FFAs are toxic to the beta cells in the pancreatic islet of Langerhans as they decrease the secretion of insulin [37]. Insulin resistance further adds to the genesis of hypertension due to vasoconstriction caused by FFAs and the loss of vasodilator effects of insulin [38]. Moreover, insulin resistance has been found to increase serum viscosity that induces thrombophilia, and release of proinflammatory cytokines from the

adipose tissue, which contributes to, increased risk of cardiovascular diseases [39].

Visceral adipose tissue does contribute to insulin resistance. Visceral lipolysis contributes to an elevated supply of FFAs to the liver via the celiac, superior mesenteric, inferior mesenteric arteries and the portal vein. This increase in FFAs ensues in an amplified triglycerides formation and the manufacture of apolipoprotein B containing triglyceride-rich very low-density lipoprotein cholesterol (LDL-C) in the liver [40]. The elevated levels of apolipoprotein B are an indirect effect of insulin resistance following an obliterated lipid metabolism in the liver. This elevation in the levels of apolipoprotein B corresponds to elevated levels of LDL-C and a reduction in high-density lipoprotein cholesterol (HDL) [24].

### 4.2 Neurohormonal activation hypothesis

As discussed earlier, adipose tissue is not only a connective tissue but an endocrine organ as well. It secretes hormones in particular leptin and adiponectin. Adiponectin regulates glucose levels and breaks down fatty acids. This protein has been associated with metabolic syndrome and cardiovascular disease [41]. Similarly, leptin regulates energy balance by inhibiting hunger that in turn reduces fat storage in adipocytes by acting on cell receptors in the arcuate nucleus of the hypothalamus. The onset of obesity increases leptin levels, and this increase is directly related to increased cardiovascular risks [24]. In antagonism to the effects of leptin, adiponectin on the other hand provides counter effects of leptin as an anti-inflammatory and anti-atherogenic adipokine. Thus, adiponectin has been considered a protective factor

against the development of diabetes mellitus, hypertension and acute myocardial infarction [42, 43]. Obesity correlates with reduced adiponectin and higher leptin levels that eventually increase the cardiovascular risks.

Neurohumoral activation increases the activity of the sympathetic nervous system, renin-angiotensin system, vasopressin and atrial natriuretic peptide [44]. Of interest is the renin-angiotensin system that has also been shown to contribute to the development of metabolic syndrome. Adipose tissue produce angiotensin II following the activation of angiotensin-converting enzyme [24]. Obesity and insulin resistance have been associated with increased production of angiotensin II [45]. Activation of angiotensin II leads to the generation of reactive oxygen species through the activation of nicotinamide adenine dinucleotide phosphate oxidase [46]. The generation of reactive oxygen species result in multiple effects including among many others the expression of lectin-like oxidized low-density lipoprotein receptor-1 on the endothelium and vascular smooth muscle cells [47]. These elements: renin-angiotensin system, reactive oxygen species and low-density receptor-1 have an intertwined positive response loop that initiates a vicious cycle of inflammation, endothelial damage and fibroblast proliferation which contributes to the onset of metabolic syndrome cluster of abnormalities; hypertension, dyslipidaemia, diabetes, cardiac hypertrophy and cardiovascular disease [48].

#### **4.3 Low-grade chronic inflammation and oxidative stress hypothesis**

As the adipose tissue undergo hyperplasia and hypertrophy (related to inflammation) in response to

excess nutrition, the tissue cells tend to outgrow their blood supply resulting in hypoxia [49]. In turn, cell necrosis with macrophage infiltration and the production of adipocytokines ensue [23]. Among the adipocytokines produced are: Interleukin-6 (IL-6), tumour necrosis factor alpha (TNF- $\alpha$ ) and prothrombotic mediator plasminogen activator inhibitor-1 (PAI-1) [50].

**4.3.1 Interleukin-6:** Interleukin-6 as a proinflammatory cytokine plays an important role in the pathogenesis of insulin resistance and type 2 diabetes mellitus [51]. Its production has been shown to increase with the increase in body fat and insulin resistance [24]. The effect of IL-6 in the liver for instance, increases the production of C-reactive protein (CRP) [24]. High CRP levels have been associated with the development of metabolic syndrome, diabetes mellitus and cardiovascular disease [51-53].

**4.3.2 Tumour necrosis factor alpha:** Tumour necrosis factor alpha (TNF- $\alpha$ ) is secreted by the adipose tissue. Its production is exponential to the increase in adipose tissue mass [24]. TNF- $\alpha$  induces phosphorylation and inactivation of insulin receptors in the adipose tissue including muscle cells, increases FFAs production through lipolysis and inhibits adiponectin release [54]. Increased levels of TNF- $\alpha$  are correlated with components of metabolic syndrome i.e. obesity and insulin resistance [55].

**4.3.3 Prothrombotic mediator plasminogen activator inhibitor-1:** Prothrombotic mediator plasminogen activator inhibitor-1 (PAI-1) inhibits tissue plasminogen activator and is a prothrombotic protein [23]. Although the mechanism of PAI-1 in the

pathogenesis of metabolic syndrome are not yet clearly understood, obesity induced oxidative stress has been suggested. Oxidative stress is a “phenomenon caused by an imbalance between production and accumulation of oxygen reactive species in cells and tissues and the ability of a biological system to detoxify these reactive products [56].” It has been shown that circulating PAI-1 are increased in obese subjects with metabolic syndrome [57].

### 5. Link Between Visceral Adipose Tissue and NAFLD

NAFLD is defined as liver fat content  $\geq 5\%$  of hepatocytes by histology or intrahepatic triglyceride content  $\geq 5.5\%$  by MRI in non-alcoholics (i.e. 30 g/d of alcohol in men and 20 g/d in women) [58]. NAFLD is a chronic liver disease and a predominant marker for: type 2 diabetes mellitus, chronic kidney disease, cardiovascular disease, metabolic syndrome and liver related deaths [59, 60]. The pathophysiology of NAFLD and its progression is induced by multiple factors, in a “multiple parallel hit” model, encompassing an interplay at an individual level of multiple genetic, behavioral, environmental factors and adipose tissue dysfunction. (Comprehensively reviewed by Azzu et al. [1], Fang et al. [61] and Yu et al. [62]).

Of interest briefly is the adipose tissue dysfunction. The state of “increased fat” as commonly observed in obesity [63], has been found to be a primary trigger of metabolic disorders [64]. The onset of obesity stimulates remodelling in the adipose tissue as a response to the changes in the energy status [65, 66]. This remodelling induces dysregulation of the adipose tissue derived cytokines, hormones and

metabolites resulting in metabolic stresses and disorder in metabolic organs [67-69]. Actually, these inflammatory adipokines and cytokines that result due to dysregulation of the adipose tissue impede with adipocyte differentiation and insulin signalling, lipid accumulation and increase adipocyte lipolysis. This results in a poor ability of the stressed and hypertrophic adipocytes to take up and release free fatty acids, thus, inducing redistribution of fat in other areas (ectopic) like visceral adipose tissue, skeletal muscle, liver, pancreas, and heart [70]. When lipid supply exceeds oxidative capacity in these tissues, intracellular lipid accumulation occurs, risking an obliteration of organ function [70]. Interestingly, greater rates of lipolysis, increased insulin resistance and increased cytokines release have been associated with hypertrophied subcutaneous adipocytes while visceral adipocyte hypertrophy has been associated with dyslipidaemia [71]. The latter is understood to be one of the many mechanisms to the development of NAFLD through the excess delivery of “toxic” free fat acids directly into liver through the portal circulation.

Given these proposed mechanisms, the evidence is overwhelming to link adipose tissue vis-à-vis VAT as the most metabolic adipose tissue subtype to both NAFLD and metabolic syndrome. Actually, a number of studies have shown the association between increased VAT volumes with NAFLD. For instance, VAT area was found to be independently associated with fatty liver disease [72, 73]. At the same time it has been shown that increase in VAT mass irrespective of the ethnicity and method used to measure VAT volume has at least 2 times greater risk to the development of NAFLD [72, 74]. These outcomes reiterate the critical mediatory role VAT



plays to the development and complication of NAFLD.

Similarly, multiple studies have also shown that the increase in VAT volume (irrespective of the method used to measure VAT mass) is strongly associated with metabolic syndrome in all BMI categories [14, 75, 76]. Moreover, many other studies have shown that VAT area/volume adds a risk and is an independent predictor to the development of metabolic syndrome. For instance, Bi et al. [77] and Nakao et al. [78] found that VAT area was an independent predictor of metabolic syndrome. Bi et al. [77] further showed the risk of metabolic syndrome increased 3-fold with each standard deviation of VAT area. Lu et al. [79] involving 3259 subjects with normal BMI demonstrated that subjects with high VAT amounts presented a much higher risk for metabolic syndrome. Likewise, Ding et al. [80] showed that lean subjects with metabolic dysfunction had increased VAT volume compared to the controls, with nearly 4-folds greater risk for NAFLD, 20-30% lower glucose disposal rates/insulin sensitivity and 30-40% greater insulin secretion rates.

Given this overwhelming evidence linking visceral adipose to metabolic dysfunction and fatty liver disease, It can almost be safely concluded therefore that increased VAT mass whether arising from adipocyte hypertrophy or hyperplasia and obliteration in its intrinsic functions as a connective tissue and as an endocrine organ has a causal effect in the development of metabolic syndrome and NAFLD. Interventions targeted at VAT loss or inhibition of metabolic functions of VAT may be helpful to ameliorate metabolic syndrome and NAFLD in both the lean and obese population.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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