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REVIEW

Adipose tissue distribution and risk of metabolic disease: does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer?

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Abstract The relative effect of visceral and subcutaneous obesity on the risk of chronic metabolic disease has been a matter of long-term dispute. While ample data support either of the fat depots being causative or associative, valid argument for one depot often automatically belittles the other. Paradigms such as the visceral/portal hypothesis and the acquired lipodystrophy/ectopic fat storage and endocrine hypothesis have been proposed. Nevertheless, neither hypothesis alone explains the entire pathophysiological setting. Treatment of diabetes with thiazolidinediones selectively increases fat partitioning to the subcutaneous adipose depot but does not change visceral fat accumulation. This is in contrast to the preferential visceral fat mobilisation by diet and exercise. Surgical removal of visceral or subcutaneous adipose tissue yields relatively long-lasting metabolic improvement only when combined with procedures that ameliorate adipose tissue cell composition. These studies illustrate that human adipose tissue in different anatomic locations does not work in isolation, and that there is a best-fit relationship in terms of volume and function among different fat depots that needs to be met to maintain the systemic energy balance and to prevent the complications related to obesity.

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Abbreviations

AMPK	AMP-activated protein kinase
ATGL	adipose triacylglycerol lipase
C/EBP	CCAAT/enhancer binding protein
CT	computed tomography
HSL	hormone-sensitive lipase
L4–L5	at the level of the 4th and 5th lumbar vertebrae
LPL	lipoprotein lipase
MHO	metabolically healthy but obese
MONW	metabolically obese but normal weight
MRI	magnetic resonance imaging
PKA	protein kinase A
PPAR	peroxisome proliferator-activated receptor
RXR	retinoid X receptor
TZD	thiazolidinedione

Introduction

The rapidly growing prevalence of obesity in affluent countries in the late twentieth century is a predictable outcome of modern industrialisation, which has led to abundant food supply and substantially reduced daily physical exertion. In evolutionary terms, a lifestyle change in which energy intake continuously exceeds expenditure is in direct conflict to the evolved human ‘thrifty genotype’ that promotes energy storage as triacylglycerol in adipose cells to meet the demand in times of need. This predispo-

sition to excess body fat gain or to obesity in the human population may be further accentuated by the improved life expectancy that has contributed to the significant increases in morbidity and mortality associated with the non-communicable diseases that increase with age, including type 2 diabetes and atherosclerosis.

The relationship between body fat accumulation and the risk of developing chronic complex metabolic diseases is well recognised, albeit not fully understood. A large epidemiological survey conducted from 1976–1980 on 11,864 men and women clearly showed that people with a BMI of 28 kg/m^2 or higher have a significantly increased risk of developing type 2 diabetes, hyperlipidaemia and hypertension [1, 2]. Nevertheless, the level of risk differs among obese individuals; approximately 20% of people who meet the criteria for obesity are apparently insulin sensitive and metabolically normal, despite having large amounts of body fat. These individuals have been categorised as metabolically healthy but obese (MHO) subjects [3]. In contrast, there have also been reports that a considerable number of people, about 18% of the general population, are metabolically obese but have a normal body weight (MONW), i.e. they have a normal BMI or may be slightly overweight, but display several of the metabolic abnormalities associated with the metabolic syndrome [3]. Moreover, patients suffering from the lipodystrophy syndrome, which results in a partial to nearly total body fat loss, often have severely impaired insulin action and distorted metabolic profiles [4]. These findings raise the question: What is the relationship between body fat accumulation and the metabolic characteristics of an individual, given that the same metabolic disturbances develop in all these conditions, which feature diverse amounts of total body fat?

Metabolic disturbances are associated with diverse amounts of total body fat.

Adipose tissue between-depot issues

The idea that it is the distribution rather than the total amount of body fat that affects the risk of chronic disease was first suggested by the French physician Jean Vague more than 50 years ago, when he observed that people with upper-body (android type) fat accumulation were more prone to the development of diabetes, gout and atherosclerosis than people with lower-body (gynoid type) obesity. Several large epidemiological investigations performed in Sweden and the United States in the early 1980s, using skinfold thickness, waist circumference or WHR as surrogate markers of truncal fatness, confirmed the association between abdominal (upper-body or central) obesity and the risk of cardiovascular disease and diabetes [1, 2]. While the anthropometrical measurements do not distinguish between intra-abdominal and abdominal subcutaneous fat accumulation, soft-tissue composition analyses of the abdominal region, using cross-sectional computed tomography (CT) scans or magnetic resonance imaging (MRI) at the level of the 4th and 5th lumbar vertebrae (L4–L5, or umbilicus), have revealed increased abdominal visceral fat accumulation as a critical characteristic that distinguishes MHO subjects from obese people with metabolic disorders and from MONW individuals [5]. Visceral obesity has since been reproducibly implicated as an independent risk factor for insulin resistance and glucose intolerance, which predict type 2 diabetes and cardiovascular disease in different ethnic populations [1, 2]. One of the hypotheses proposed to explain the link between visceral obesity and the chronic complex metabolic diseases is the visceral/portal hypothesis, in which: (1) an increased hepatic uptake of the ‘first pass’ of NEFAs released from visceral fat lipolysis into the portal vein may reduce the hepatic extraction of insulin and thus impair insulin-induced suppression of hepatic gluconeogenesis, leading to increased endogenous glucose production; (2) an increased hepatic lipase activity may remove lipids from LDL and HDL, which, in combination with the decreased degradation of apolipoprotein B and the increased esterification of NEFAs, results in the increased synthesis and secretion of VLDL and smaller, denser LDL and HDL particles into the systemic circulation, distorting the circulating lipid profile; and (3) an increased systemic NEFA flux may impair insulin action in skeletal muscle and other key tissues via malonyl-CoA/acetyl-CoA carboxylase β fuel-sensing and regulation mechanisms [1, 2, 6].

The visceral/portal hypothesis is mainly based on a possible high rate of visceral fat lipolysis per unit mass, i.e. the larger the visceral fat depot, the greater the NEFA release in visceral obesity, and these NEFAs from the portal circulation may potentially add to the NEFAs in the hepatic artery. However, clinical studies of NEFA kinetics do not support this hypothesis [1, 7]. It has been reported that, in effect, post-absorptive NEFA levels are not different between obese women with a visceral adipose tissue area of ≥65 cm^2 and those with an area of ≥65 cm^2, as measured by CT at the level of L4–L5 [1, 2]. In addition, obese men with a visceral fat area of ≥130 cm^2 have normal fasting plasma NEFA levels, and the increased postprandial NEFA concentrations in these subjects appear to be related to impaired triacylglycerol clearance [1, 2]. Furthermore, a recent study that assessed systemic and splanchnic NEFA kinetics, using a technically demanding catheter and tracer method combined with mathematical modelling, has shown that, although visceral/portal NEFA flux increases with increasing amounts of visceral fat, its actual

contribution to the total NEFAs in the systemic circulation is small—generally less than 5%. The relative contribution of visceral lipolysis to the total amount of NEFAs delivered to the liver varies substantially among subjects, and can range from 0% to 45% in people with a visceral fat area of ~150 cm^2, as measured by CT at L2–L3, and in extreme cases, subjects who have large amounts (~300 cm^2) of visceral fat display a lower visceral NEFA release than subjects with a visceral adipose tissue area of 10 cm^2 [7]. These data show that, in practice, it is difficult to estimate an individual's visceral/portal NEFA flux by analysing his/her body composition and body fat distribution. The same study reported that, while obesity increases both splanchnic and leg NEFA release and uptake, obese men show a lower upper-body, non-splanchnic NEFA release than the lean control subjects, despite having large amounts of abdominal subcutaneous fat. This finding may indicate a potential buffering effect of subcutaneous adipose tissue on the high rate of visceral lipolysis in these obese male subjects [7, 8]. Apart from NEFA metabolism, there remains considerable metabolic heterogeneity among people with similar amounts of visceral adipose tissue. In addition, in many obese or type 2 diabetic patients, the presence and severity of metabolic disturbances are clearly contingent on subcutaneous rather than on visceral fat accumulation, although the visceral fat mass of the patients has been large [1, 2]. These studies collectively suggest that visceral lipolysis alone cannot sufficiently explain systemic, particularly extra-hepatic, insulin resistance, and other cooperative mechanisms must be involved.

Additional paradigms concerning adipose cell development, adipose tissue endocrine function, and ectopic fat accumulation have been proposed. The acquired lipodystrophy/ectopic fat storage hypothesis and the endocrine paradigm [9] postulate that a failure of adipose cell proliferation, which renders the adipose tissue incapable of expanding to accommodate excess energy, results in ectopic fat storage in the liver and skeletal muscle. Additionally, impaired adipocytokine production as a result of impaired adipogenesis may inhibit leptin- and adiponectin-activated AMP-activated protein kinase (AMPK)/malonyl CoA signalling in the liver and muscle, and thus prevent the ectopically stored fat from being oxidised, both of which can promote insulin resistance.

Hypotheses claiming that either visceral or subcutaneous adipose tissue depots play a causative role in the pathogenesis of chronic metabolic diseases have been proposed and have been supported by ample clinical and laboratory data.

Biological differences between visceral and subcutaneous adipose tissue

Upper-body (central) fat refers to the abdominal subcutaneous fat depot located immediately beneath the skin and on top of the abdominal musculature in the upper abdominal region, and the visceral depot in the abdominal cavity. The subcutaneous depot in this region is compartmentalised into superficial and deep layers by a fascia, fascia superficialis, and the two compartments show different relationships with clinical metabolic variables [10]. Visceral fat refers to the intraperitoneal fat composed of the greater and lesser omentum and mesenteric adipose tissue. Visceral fat accounts for approximately 20% of total body fat in men but only 6% in pre-menopausal women [11]. Lower-body fat is mainly represented by subcutaneous adipose tissue in the gluteal and femoral regions, which are metabolically less active than upper-body adipose tissue and may be protective against the development of metabolic disorders [8]. Sex-related differences in adipose tissue distribution become increasingly less prominent with age [1, 2].

While both serve as energy repositories to maintain the systemic equilibrium of energy intake and expenditure, visceral and subcutaneous adipose tissue depots adopt certain constitutive differences in terms of morphology and physiological function that are characteristic of their primary physiological roles [1, 2]. These differences are maintained through integrated neural/humoral regulation at the levels of lipid mobilisation, adipocytokine production, and adipose cell recruitment and maturation, and may be fundamental in determining the relative effect of the visceral or subcutaneous depot on the systemic homeostasis of metabolism in pathological conditions, as well as the response to diet, exercise or drug treatment [1, 2].

NEFA disposal and lipolysis NEFAs originate from the hydrolysis of adipocyte-stored triacylglycerol, in a reaction catalysed by adipose triacylglycerol lipase (ATGL) [12] and hormone-sensitive lipase (HSL), or from triacylglycerol-rich lipoproteins, in a reaction catalysed by lipoprotein lipase (LPL). HSL, the rate-limiting enzyme of adipose tissue triacylglycerol hydrolysis, is regulated through reversible phosphorylation. To initiate lipolysis, catecholamines bind to β-adrenergic receptors to activate adenylyl cyclase, which results in increased intracellular concentrations of cyclic AMP and, thus, activated protein kinase A (PKA). PKA phosphorylates HSL and perilipin, with subsequent translocation of HSL from the cytosol to the lipid droplets [13], leading to the hydrolysis of triacylglycerols. Catecholamine release is increased when there is an increased energy demand (e.g. during physical exercise, trauma or stress), which enhances NEFA efflux from the

adipose tissue to ensure energy supply to other key tissues. In contrast, as an antagonist of the lipolytic effect of catecholamines, insulin activates phosphodiesterase-3B, which reduces intracellular cAMP levels, leading to reduced PKA and HSL activation. Unlike HSL, ATGL is not regulated by PKA and is mainly involved in basal triacylglycerol hydrolysis [14]. Adipocytes from the visceral adipose depot have a low basal, but a high catecholamine-stimulated, rate of lipolysis compared with cells from abdominal, gluteal, and femoral subcutaneous fat depots. This is consistent with the high number of β-adrenoceptors and the low number of α-adrenoceptors in adipocytes from visceral fat (Table 1). Additionally, in visceral adipose tissue, the anti-lipolytic action of insulin, adenosine and prostaglandins are blunted, which may further augment lipid mobilisation [1, 2].

LPL hydrolyses the triacylglycerol carried by chylomicrons and VLDL, and the activity of this enzyme is closely related to the ability of a tissue to incorporate lipoprotein triacylglycerols and NEFAs. Since human adipose tissue derives most of its lipid for storage from dietary triacylglycerol, LPL is a critical regulator of body fat accumulation [1, 2]. Compared with subcutaneous adipose tissue, visceral adipose tissue has a higher rate of NEFA and triacylglycerol uptake (Table 1). In men, omental adipose tissue takes up approximately 50% more lipids than abdominal subcutaneous adipose tissue. However, this is not directly correlated with tissue LPL activity. It has been found that visceral and subcutaneous fat depots in men have similar basal levels of LPL activity. Insulin-stimulated LPL activation and acylation-stimulating protein content are higher in subcutaneous than in visceral fat in both men and women (Table 1). Thus, LPL activity may not alone explain the ultimate rate of adipocyte lipid uptake [1, 2]. Indeed, while LPL-derived NEFAs may either be released into the circulation or taken up and esterified with glycerol 3-phosphate for storage in adipocytes, the relative proportion of NEFAs that undergo each fate is closely dependent on the intracellular HSL activity. In the fasting state, where HSL is active and the intracellular lipolytic rate is high, the uptake of LPL-derived NEFAs is low, whereas the opposite is true after a meal [1, 2]. The visceral lipid store, with its high turnover, may constitute part of the body's buffering capacity during the postprandial lipid flux and protect the tissues from exposure to the diurnal fluctuation of lipids in the circulation [8].

Adipocytokine production Adipose tissue secretes peptide and non-peptide molecules, collectively termed adipocytokines, that function as hormones, regulating the biological activities of neighbouring or distant tissues and organs [15]. Some of the adipocytokines, such as adiponectin, are produced exclusively by adipocytes, whereas others are produced by other cell types in the adipose tissue. Generally, the rate of secretion of most adipocytokines is a function of the amount of fat stored in the adipose cells, a phenomenon that may partly represent a means of adjusting cellular functional activity in a timely manner for the maintenance of optimal adipose tissue physiology and morphology. For example, increased adipose tissue production of TNFα and IL-6 in obesity may upregulate HSL and downregulate GLUT4 and LPL production and activity, limiting further entry of dietary lipid metabolites into the hypertrophic adipocytes [1, 15].

Leptin and adiponectin, the two most studied adipocytokines to date, may exert regulatory effects on the hypothalamus, liver, pancreatic islets and skeletal muscle [15]. Leptin functions as an afferent signal of a negative feedback loop to regulate body weight. A decrease in leptin levels signifies insufficient energy stores, promotes energy intake, reduces energy expenditure, and increases the partitioning of energy to fat, leading to positive energy balance and, consequently, raised leptin levels. An increase in leptin levels induces the opposite effects [16]. Similar to leptin, adiponectin production also responds to systemic energy status. However, while adiposity increases leptin levels, it significantly reduces plasma adiponectin concentrations [17]. Despite their opposing relationships with fat accumulation, adiponectin and leptin both regulate the AMPK pathway to enhance fatty acid oxidation in the target tissues, through either direct action on the AMPK pathway [18, 19] or modulation of sympathetic nervous system activity [20].

A number of inflammatory cytokines are secreted by adipose tissue, mostly by the non-adipocytes in the tissue bed [21]. As with adipose tissue NEFA release, one way to consider the primary mechanisms of action of adipose tissue-produced inflammatory cytokines is according to the anatomic location of the fat depot in which the cytokines are produced. Thus, cytokines released by the visceral depot would exert a greater effect on hepatic carbohydrate and lipid metabolism and stimulate hepatic release of inflammatory proteins [22, 23], whereas cytokines produced by the subcutaneous depot would mainly affect adipose cell development and function locally [24] and exert systemic effects on, for example, skeletal muscle (Fig. 1). The former may represent the mechanism whereby inflammatory cytokines induce hepatic insulin resistance and chronic systemic inflammation, while the latter diminish adipose tissue storage of lipids, leading to ectopic fat accumulation in the liver and skeletal muscle [8, 9].

Levels of leptin expression and secretion are about two- to threefold higher in subcutaneous than in visceral adipose tissue, and are proportional to the amount of triacylglycerol stored in adipose cells [25] and, thus, to adipose cell size [26, 27]. In contrast, visceral fat secretes more adiponectin

Table 1 Characteristics of visceral vs subcutaneous adipose tissue

	Visceral adipose tissue	Subcutaneous adipose tissue	Reference
Lipogenesis			
Basal rate of glucose uptake	++	+	[63, 64]
Insulin-stimulated glucose uptake	++	+	[63, 65]
Fatty acid and triacylglycerol uptake	++	+	[66, 67]
Lipoprotein lipase	Women +	Women ++	[1, 26, 68]
	Men +	Men +	
Insulin-stimulated lipoprotein lipase activity	+	++	[68]
Acylation stimulating protein	+	++	[1]
Lipid synthesis	++	+	[69]
Lipolysis			
Basal rate of lipolysis	+	++	[69–72]
	Obesity ++	Obesity ++	
ATGL	++	+	[14]
	Obesity ++	Obesity ++	
HSL content	++	+	[72]
HSL activity	+	++	[70, 72]
Catecholamine-induced lipolysis	+++	+	[67, 71, 73]
β-Adrenoceptor-dependent lipolysis	++++	+	[74]
α_2-Adrenocetpor-dependent anti-lipolysis	+	++	[75, 76]
Anti-lipolytic effect of insulin	+	+++	[67, 77]
Adipocytokine secretion			
Adiponectin secretion	++	+	[78]
Leptin secretion	+	++++	[1, 71, 79]
Plasminogen activator inhibitor 1	++	+	[1, 21, 80]
IL-6 secretion	+++	+	[1, 21, 81]
IL-8 secretion	++++	+	[82]
TNFα secretion	+	+	[1, 71, 83]
Angiotensinogen	++	+	[1]
Cell development			
Proliferation in vitro	+	++	[84]
Differentiation in vitro	+	++	[71, 84, 85]
PPARγ production	+	++	[1, 86, 87]
	Obesity ++	Obesity +	
C/EBPα and RXRα production	+	++	[86, 87]
Response to TZD treatment in vitro	+	++	[87, 88]
Response to TZD treatment in vivo	+	++	[32–38]
Response to RXR ligands	+	++	[87]
Adipose cell size	Omental +	++	[69, 79, 89]
	Mesenteric +++		
Susceptibility to apoptosis	+	+	[90, 91]
Steroid hormones and receptors			
Androgen receptor	++	+	[92]
Androgen concentration	++	+	[93]
Glucocorticoid receptor	++	+	[94]
11β-hydroxysteroid dehydrogenase	++	+	[95]

than subcutaneous fat which, in turn, is more sensitive to insulin and TZDs (Table 1). In addition, visceral fat releases more IL-6, IL-8, plasminogen activator inhibitor 1 and angiotensinogen than subcutaneous fat, while TNFα production is low and shows no consistent depot-related differences (Table 1).

Adipose tissue cell composition The biological activity of an adipocyte changes as its lipid storage increases. Compared with small adipocytes, large cells are more insulin-resistant and lipolytic, release more inflammatory cytokines and less adiponectin [24, 28], and are more frequently found in people with obesity-related metabolic disorders [29, 30]. Therefore, adipose tissue cell composition, expressed as the relative number of large adipose cells in a given fat depot, is an important determinant of the metabolic activity and response to environmental changes of that depot.

Adipose cells are slow-turnover cells. In non-obese people, adipose tissue depot expansion during development from a young age to middle age is mainly the result of a uniform increase in fat cell size [1, 2]. In men, there is an increase in adipocyte number in the subcutaneous depot of the abdominal region, while this is not readily seen in women. Unlike obesity developed in childhood or adolescence, which is usually hyperplastic and is commonly seen in MHO subjects [1–3], most adult-onset obesity is related to the hypertrophic expansion of existing adipocytes, i.e. an increase in cell size [1, 2]. Studies on adipose tissue cellularity have reported that adipocytes become severely insulin-resistant when filled with more than 1 μg of lipid per cell, and new adipocyte recruitment normally occurs when the lipid content of the cells reaches ~0.7–0.8 μg/cell [29]. The new cell recruitment may be triggered by a progressively altered secretion of proteins and lipid metabolites from the enlarging adipocytes [24, 28], which could act as signalling molecules on the precursor cells in the adipose tissue bed to initiate and regulate adipogenesis.

Adipose cell recruitment occurs throughout life and overall is regulated by the basal metabolic rate and energy uptake and expenditure. Acquirement of a full adipocyte phenotype entails precursor cell adipose lineage commitment followed by preadipocyte proliferation and differentiation, a process that is characterised by the activation and inactivation of specific genes through the induction of transcription factors such as CCAAT/enhancer binding proteins (C/EBPs) and peroxisome proliferator-activated receptor γ (PPARγ) [31].

Like other aspects of adipose tissue biology, adipose tissue cellularity is differently regulated in the visceral and subcutaneous depots, and is determined by specific hormone receptor expression, blood supply, innervation and the parasympathetic-sympathetic nervous system activity in the respective depots. The potential of adipogenic precursor cells to perform adipogenesis is also intrinsically different between the two depots. Preadipocytes derived from subcutaneous adipose tissue express higher levels of PPARγ, C/EBPα and retinoid X receptor α (RXRα), and more readily proliferate and differentiate in vitro than cells from visceral fat depots (Table 1). In addition, these cells are more sensitive to TZD treatment in vitro, which is consistent with the selective increase in subcutaneous fat mass in patients treated with TZDs [32–39].

Visceral and subcutaneous adipose tissue depots adopt constitutive biological differences that are characteristic of their physiological roles

What do we learn from body fat distribution?

Human evolution has left its trace on our body fat distribution. Because of the fast intrauterine growth of fetal brain relative to maternal pelvis, human infants are born prematurely and need to be carried and nursed for several years. Evolution has provided a solution to the problem of how to cover the energy demand of both the mother and the child during this period in the form of the lower-body, pelvic-gluteal-femoral fat accumulation in women, which is

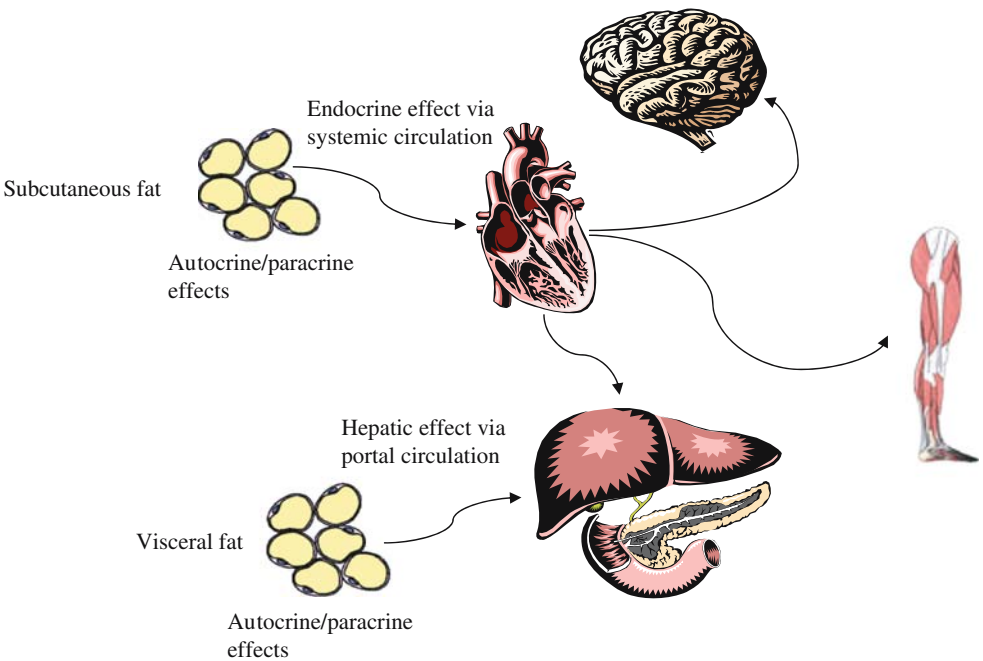

Fig. 1 Endocrine effects of cytokines released from visceral or subcutaneous adipose tissue: the cytokines released from visceral depot would primarily alter carbohydrate and lipid metabolism and stimulate production of acute phase response proteins in the liver, whereas the cytokines produced by subcutaneous depot would mainly affect adipose cell development and function locally as well as exert systemic effects on, for example, the skeletal muscle

a unique human aspect of the evolution of the animal kingdom. In addition to the sex-related pattern of fat distribution, selective fat partitioning to individual adipose tissue depots, such as the visceral and subcutaneous depots, may occur under a variety of circumstances in which a person's nutritional or endocrine status is changed [1, 2].

Visceral adipose tissue area measured from a single MRI scan at the L4–L5 level has a correlation of 0.96 with visceral adipose tissue volumes calculated from multiple (up to 41) scans [11]. Therefore, a single cross-sectional CT or MRI scan at the L4–L5 level is considered to provide an accurate assessment of visceral fat quantity, for which typical values range from 15–260 cm^2 [40]. Some studies emphasising visceral fat as a risk factor for metabolic disease have specified threshold values to identify subjects at risk, e.g. a visceral fat area of ≥100 cm^2 has been used to identify MONW Japanese individuals [41]. However, there have been discrepancies between studies that have used such values, and the differences are not completely explained by ethnic- or sex-related confounders across investigations. For example, in a study on 220 pre- and post-menopausal white women from 18–77 years of age, a visceral fat area of ≥110 cm^2 was suggested to identify individuals at high risk of cardiovascular and metabolic disease [42], while other studies on 98 post-menopausal Mexican women aged 50–65 years or on 146 healthy men aged 30–71 years, the value was set at ≥117.8 cm^2 or ≥130 cm^2, respectively [43, 44]. Similarly, one intervention study has claimed that a reduction in visceral fat area to <60 cm^2 is necessary to improve risk factors for CHD [45], whereas another study found improvements in plasma HDL-cholesterol levels, the cholesterol:HDL-cholesterol ratio and insulin sensitivity in subjects who reduced their visceral fat to below 110 cm^2 compared with those who did not [46]. Furthermore, investigations that stratified subjects according to quantity of visceral fat reported that not all the metabolic alterations observed could be attributed to visceral fat accumulation [47–49].

The visceral to subcutaneous adipose tissue area ratio (V:S ratio) describes the relative accumulation of visceral and subcutaneous fat without defining absolute quantity of fat in either depot. Use of the ratio value to integrate the size, and hence the potential function of both adipose depots as correlates of systemic metabolism, may mirror the actual human physiology more closely. For example, a human cadaver dissection study on the relationships between visceral, trunk and whole-body adipose tissue weights showed that men and women possessed the same amount of visceral fat—3.00 kg in men vs 3.24 kg in women (p = 0.68) [40]—a result that is difficult to explain given the well-known differences between men and women in terms of adipose tissue distribution and metabolism. However, when the quantity of visceral fat was expressed as a percentage of total body fat in this same study, the difference became apparent: men had 16.8% of their body fat composed of visceral fat, while the corresponding value in women was only 12.9% (p=0.02) [40].

Calculation of the V:S ratio as an indicator of body fat distribution using adipose tissue measurements obtained by CT or MRI shows that fat deposition increases in all adipose tissue depots in obesity. However, this increase is not always proportional in the tissues, which results in the subtypes of visceral and subcutaneous, or central and peripheral, obesity. A common treatment regimen for obesity involves restricting daily energy intake and enhancing expenditure, which is normally achieved by prescribing a diet and an exercise programme. Although diet and exercise interventions generally cause more fat loss from the intra-abdominal than the subcutaneous adipose depot [2, 50], variations exist among individuals with regard to how much fat needs to be lost from the two fat depots before statistically significant improvements in insulin sensitivity, lipid profile and other metabolic parameters are observed (Table 2). For example, by comparing the V:S ratios measured before and after an intervention leading to improved systemic carbohydrate and lipid metabolism, it was found that the reduction in the V:S ratio after a given diet or exercise programme might range from ~3–20% (Table 2). In one study, a 10-week physical exercise programme prescribed to type 2 diabetic patients reduced the V:S ratio by more than 33%, and this was associated with significantly decreased triacylglycerol and increased dehydroepiandrosterone levels [51] (Table 2). In contrast, another study in which metformin was used to treat patients with polycystic ovary syndrome for 12 weeks at a dosage of 500 mg three times daily, showed that the decreased total cholesterol and LDL-cholesterol levels were not accompanied by any significant change in body fat distribution [52] (Table 2).

TZDs are agonists for the nuclear receptor PPARγ and are used to improve glycaemic control, lipid profile and insulin sensitivity. Because of the abundant expression of PPARγ in adipose tissue, it is generally thought that the induction of adipogenesis to recruit new small adipocytes, and thus to improve adipose tissue lipid accommodation and adiponectin secretion, accounts for most of the credible metabolic outcomes of TZD treatment. However, excessive body fat gain following long-term treatment may have detrimental health consequences, particularly in people who are overweight or obese prior to the treatment. Reduced dosages, or combination therapy with metformin, diet or exercise programme, have been reported to be beneficial. Similar to the change in the V:S ratio induced by diet and exercise interventions, variations in the extent of the reduction in the V:S ratio that accompanies improvements in systemic metabolism are also observed in TZD trials

Table 2 Abdominal fat redistribution by diet/exercise interventions or metformin treatment

	Dumont et al. [96]	Janand-Delenne et al. [97]	Kanai et al. [98]	Miyatake et al. [99]	Okura et al. [100]	Shadid and Jensen [36]	Tanaka et al. [45]		Boudou et al.[b] [51]	Lord et al. [52]	
Pre-existing conditions at baseline	–	–	–	–	–	–	–		Type 2 diabetes	PCOS	PCOS
Baseline measurements											
No. of patients (men/women)	32/0	0/42	0/26	23/0	0/128	10/9	0/72	0/207	8/0	0/19	0/21
Age (years)	46 [6]	37.6 [12.5]	50 [13]	47.1 [6.9]	50 [7]	41 (2)	46.2 [8.0]	46.2 [8.0]	45.4 [7.2]	30.6 [4.8]	27.7 [4.9]
BMI (kg/m^2)	30.9 [3.0]	35.8 [3.4]	33.7 [3.1]	28.5 [1.7]	29.0 [2.8]	32.1 (0.7)	28.4 [2.9]	27.4 [3.0]	29.6 [4.6]	36.3 [7.4]	33.7 [6.7]
Visceral fat at L4–L5 (cm^2)	187 [55]	129 [52]	168 [12]	108.7 [49.1]	125 [43]	203 (29)	108.0 [54.3]	90.0 [43.3]	153.2 [38.5]	114.1 [43.2]	110.0 [56.9]
Subcutaneous fat at L4–L5 (cm^2)	320 [89]	378 [59]	332 [103]	147.7 [36.0]	281 [68]	259 (15)	260.3 [61.4]	252.7 [81.9]	241.5 [49.5]	402.5 [166.7]	313.0 [128.6]
V:S ratio	0.58[a]	0.34[a]	0.56 [0.33]	0.73[a]	0.47 [0.20]	0.80 (0.11)	0.43 [0.23]	0.37 [0.19]	0.63[a]	0.31 [0.11]	0.36 [0.16]
Intervention	6-month diet	5-week diet	12-week diet	5-month exercise	14-week diet/ exercise	18-20-week diet/ exercise	14-week diet	14-week diet/ exercise	10-week exercise	No intervention: 12 weeks' placebo	12 weeks' metformin (500 mg three times daily)
Measurements after intervention											
No. of patients (men/women)										0/16	0/16
Age (years)											
BMI (kg/m^2)	30.5 [3.1]	33.3 [3.8][c]	29.7 [2.7][c]	27.6 [1.8][c]	25.5 [2.8][c]	27.7 (0.8)[c]	25.4 [2.8][c]	24.0 [2.7][c]		35.2 [6.5]	34.6 [9.1]
Visceral fat at L4–L5 (cm^2)	164 [52][c]	100 [41][c]	124 [65][c]	85.9 [40.9][c]	84 [37][c]	123 (22)[c]	77.4 [46.6][c]	57.5 [28.0][c]	84.2 [21.3][c]	111.6 [43.3]	106.5 [51.3]
Subcutaneous fat at L4–L5 (cm^2)	311[91][c]	323 [64][c]	290 [81][c]	119.7 [43.0][c]	214 [69][c]	196 (18)[c]	206.1 [59.3][c]	181.9 [76.9][c]	198.0 [39.0][c]	378.3 [156.2]	298.0 [110.9]
V:S ratio	0.52[a]	0.31[a]	0.45 [0.27][c]	0.71[a]	0.41 [0.18][c]	0.66 (0.11)[c]	0.38 [0.23][c]	0.34 [0.16][c]	0.42[a]	0.31 [0.08]	0.36 [0.12]

Values are means±SD (in square brackets) or SEM (in parentheses). Measurements after intervention are not given for paired studies, in which the subjects serve as their own controls.

[a] Estimates from the given values.

[b] Abdominal fat distribution measured by MRI, other parameters measured by CT.

[c] Statistically significant change vs baseline.

PCOS polycystic ovary syndrome.

Table 3 Abdominal fat redistribution by TZD treatment

	Akazawa et al. [32]	Kawai et al. [33]		Mori et al. [34]		Nakamura et al. [35]		Shadid and Jensen [36]	Smith et al. [39]	Kelly et al.[b] [37]	Miyazaki et al. [b] [38]
Pre-existing conditions at baseline		–		–		–		–	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes
Treatment at baseline	Sulfonylurea	Diet	Sulfonylurea	Diet	Sulfonylurea	Diet + exercise	Diet + exercise			12 weeks' placebo	
Baseline measurements											
No. of patients (men/women)	7/13	10/0	7/0	7/11	6/6	5/5	6/5	10/10	9/12	8/2	9/4
Age (years)	63.5 (2.0)	53.5 (2.6)	57.1 (3.3)	59.7 [10.2]	64.6 [8.3]	54.8 (3.2)	53.3 (4.2)	36 (2)	56.2 [9.7]	58.6 [7.5]	52 (3)
BMI (kg/m^2)	24.6 (0.6)	22.7 (0.6)	22.2 (0.5)	26.0 [4.6]	25.4 [4.7]	28.7 (1.4)	29.9 (1.3)	33.4 (0.6)	32.1 [5.6]	28.6 [3.7]	29.0 (1.1)
Visceral fat at L4–L5 (cm^2)	121.0 (11.1)	132.8 (21.3)	139.7 (12.0)	118.3 [54.3]	108.1 [53.5]	155 (13)	166 (14)	154 (15)	230.4 [99.6]	2.41 [0.60] kg	144 (13)
Subcutaneous fat at L4–L5 (cm^2)	188.0 (15.6)	121.11 (13.5)	108.9 (13.1)	189.7 [93.3]	122.0 [44.6]	235 (33)	234 (32)	317 (18)	326.6 [143.2]	2.00 [0.91] kg	301 (44)
V:S ratio	0.72 (0.09)	1.09 (0.11)	1.44 (0.28)	0.74 [0.48]	0.91 [0.46]	0.71 (0.08)	0.80 (0.09)	0.50 (0.05)	0.7[a]	1.2[a]	0.59 (0.08)
Add-on TZD treatment	12 months' troglitazone	3 months' troglitazone	3 months' troglitazone	6 months' troglitazone	6 months' troglitazone	12 weeks' troglitazone (200 mg/day)	12 weeks' troglitazone (400 mg/day)	18–20 weeks' pioglitazone	24 weeks' pioglitazone	Type 2 diabetes/ 12 weeks' troglitazone	16 weeks' pioglitazone
Measurements after TZD											
No. of patients (men/women)										8/3	
Age (years)										58.0 [8.6]	
BMI (kg/m^2)	25.7 (0.6)[d]			27.2 [4.2][d]	26.7 [5.5][d]			34.0 (0.7)[d]		28.7 [3.9]	30.2 (1.1)[d]
Visceral fat at L4–L5 (cm^2)	125.3 (13.2)	122.6 (22.1)	132.6 (11.6)	101.0 [50.8][d]	112.5 [59.9][d]	153 (16)	155 (15)	154 (17)	220.2 [75.1]	2.36 [0.51] kg	131 (16)[d]
Subcutaneous fat at L4–L5 (cm^2)	217.6 (18.5)[d]	126.0 (17.4)	118.8 (17.0)	221.6 [101.6][d]	180.5 [143.5][d]	241 (37)[c]	253 (30)[c]	328 (23)	370.7 [182][d]	2.11 [1.0] kg	342 (44)[d]
V:S ratio	0.64 (0.07)[d]	0.94 (0.09)[d]	1.33 (0.27)	0.50 [0.32][d]	0.77 [0.44]	0.70 (0.09)	0.69 (0.11)	0.48 (0.05)	0.59[a]	1.1[a]	0.44 (0.06)[d]

Values are means ± SD (in square brackets) or SEM (in parentheses). Measurements after TZD are not given for paired studies, in which the subjects serve as their own controls.

[a] Estimates from the given values.

[b] Abdominal fat distribution measured by MRI, other parameters measured by CT.

[c] Trend increase vs baseline value.

[d] Statistically significant change vs baseline.

performed by different research groups in different ethnic populations (Table 3). For example, treatment with troglitazone or pioglitazone, either alone or in combination with a diet or exercise programme or with a sulfonylurea, reduced the V:S ratio of the subjects by ~1.5–32% of the values before the treatment (Table 3), which was associated with improved lipid profile and insulin sensitivity. However, in contrast to diet and exercise interventions, where the decreased V:S ratios are the result of mobilisation of the visceral fat (Table 2), the V:S ratio reduction induced by TZD treatment is the result of an increased subcutaneous depot mass with no significant change in visceral fat (Table 3). In one study, which reported a reduction in visceral fat mass after 3 months of treatment with troglitazone, the reduction might have resulted from the combined diet intervention [34] (Table 3). Thus, changing the quantitative relationship between visceral and subcutaneous depots, as indicated by a reduced V:S ratio, may improve systemic metabolism regardless of whether this is achieved through a reduction in visceral or an increase in subcutaneous fat mass. The variations in the size of the reduction in the V:S ratio after diet, exercise or TZD treatment may reflect the quantitative range of the adjustment of either fat depot, in terms of mass and function, required to restore the metabolic balance of the subjects across the studies.

Recently, several attempts have been made to improve the metabolic profile of obese subjects by surgically removing certain quantities of subcutaneous or omental fat [53–58]. However, the outcomes of these studies have been inconsistent. Removal of a large volume of abdominal subcutaneous fat has yielded improved [54–56], unchanged [57] or deteriorated [58] carbohydrate and lipid metabolism. Although promising long-term improvements in fasting plasma glucose and insulin, glucose tolerance and insulin sensitivity have been reported by a study that combined omentectomy with adjustable gastric banding, the metabolic benefits that may have been provided by the reduction of visceral fat may be complemented by the potential reduction in average adipose cell size and, hence the fat mass of all the depots, through the gastric banding [53, 59]. Comparing these studies with the adipose tissue redistribution data from the diet, exercise and TZD studies, the inconsistent metabolic outcomes resulting from the surgical procedures may reflect inter-patient variation in terms of the quantity of fat that needs to be removed (or lost) in order to obtain a best-fit ratio of V:S volume and function.

Adipose tissue redistribution induced by diet, exercise or treatment with TZDs is associated with an increased number of small adipocytes in the adipose tissue, leading to improved adipose tissue cell composition and function. The reduction in average adipose cell size in given depots results from adipocyte lipid depletion by restricting energy intake or enhancing energy expenditure in a diet or an exercise programme. With TZD treatment, this may be achieved by adipose cell recruitment through activation of PPARγ [60]. Although the changes in adipocyte size distribution following TZD treatment vary in human studies [36, 61, 62], it has been reported that the proportion of small adipocytes increases and the proportion of very large adipocytes decreases after pioglitazone treatment in type 2 diabetic patients [61]. It is conceivable that the surgical removal of adipose tissue may reduce the total release of lipolytic products and inflammatory cytokines from the adipose tissue by reducing the number of hypertrophic adipose cells in obesity. However, in theory, this does not improve the cell composition of the remaining adipose tissue unless the procedure triggers adipogenesis. In this context, the metabolic improvements in the omentectomy/gastric banding study [53] illustrate the significance of comprehensive adjustment of adipose tissue volume and function [53, 59].

Summarising all the studies, if one factor is to be sought to integrate the situations, as Occam's Razor would have argued for, it may be suggested that human adipose tissue in different anatomic locations does not work in isolation, and that, for any given individual, there exists a best-fit relationship in terms of volume and function among different fat depots that needs to be met to maintain the systemic energy balance and prevent the complications related to obesity. Thus, the carbohydrate and lipid metabolism of MHO subjects would remain normal provided their subcutaneous adipose tissue functionally matches the metabolic rate of their visceral adipose tissue, i.e. their subcutaneous tissue is able to take up NEFAs to compensate for the increased visceral lipolysis, while MONW subjects may obtain an improved metabolic profile if the functional relationship between the two depots is properly adjusted.

Human adipose tissue in different anatomic locations does not work in isolation. There is a best-fit relation of volume and function among different fat depots to be met in order to maintain the systemic energy balance and to prevent complications related to obesity

Conclusion

There have been many discussions about the role of visceral or subcutaneous adipose tissue in the pathogenesis of chronic metabolic diseases. Hypotheses claiming either of the depots to be more causative than the other have been proposed, and are supported by ample clinical and laboratory data. However, in practice, treatments based on either of these hypotheses do not always produce the expected metabolic outcomes, which is particularly evident

in several recent attempts using surgical procedures to reduce subcutaneous or visceral fat.

Adipose tissue distribution data from the TZD trials, when compared with the data from diet and exercise intervention studies, ascertain that adipose tissue biology in relation to the regulation of systemic metabolism should be considered in integrity; different adipose tissue depots may function differently, yet both co-operatively and compensatorily. Therefore, when contemplating pathogenic mechanisms of obesity-related metabolic disease or prescribing a treatment for the obesity-related syndrome, consciously aiming at an individualized ratio of visceral to subcutaneous adipose tissue volume and functional activity, in addition to general body fat reduction, may prove to be beneficial to obtain intended outcomes.

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