The Link Between Abdominal Obesity and the Metabolic Syndrome

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The clustering of cardiovascular risk factors associated with abdominal obesity is well established. Although currently lacking a universal definition, the metabolic syndrome describes a constellation of metabolic abnormalities, including abdominal obesity, and was originally introduced to characterize a population at high cardiovascular risk. Adipose tissue is a dynamic endocrine organ that secretes several inflammatory and immune mediators known as adipokines. Dysregulation of adipokine secretion, free fatty acid toxicity, and the site-specific differences in abdominal (visceral) versus subcutaneous fat support abdominal obesity as a causal factor mediating the insulin resistance, increased risk of diabetes, and cardiovascular disease in the metabolic syndrome.

Introduction

The World Health Organization (WHO) estimates that more than 1 billion adults worldwide are overweight, 300 million of whom are obese. This obesity epidemic has now extended into the adolescent population, with health issues related to obesity across the globe accounting for up to 7% of total health care costs [1].

Vague [2] first described the relationship among "masculine" or "android" obesity and risk of metabolic dysfunction and cardiovascular disease. Subsequently, large epidemiologic studies confirmed this observation, initially with surrogate markers of visceral adiposity (eg, waist circumference and waist-hip ratio) and subsequently with imaging that enabled direct measurement of visceral fat [3]. The concept of the metabolic syndrome has been introduced to describe the increased cardiovascular risk seen in the presence of abdominal or visceral obesity and associated metabolic dysfunction [4,5]. A growing body of literature supports a causal relationship between visceral obesity and the metabolic syndrome.

The recognition of fat as an endocrine organ provided an important link between obesity and metabolic dysfunction [6]. The past decade has seen increased understanding of the mechanisms by which chronic inflammation mediates insulin resistance [7]. Adipose tissue secretes so-called adipokines with inflammatory and immune functions. In addition to promoting insulin resistance, these adipokines also mediate some cardiovascular complications of obesity (cardiometabolic risk). Although the adipocyte per se is an important source of chronic inflammation, other cell types within the adipose tissue—in particular, macrophages—are also significant [8,9]. Increasing evidence supports the importance of the site of excess adiposity. The inflammatory mediators and free fatty acids secreted from the visceral adipose tissue drain directly into the portal system, with potentially important ramifications for liver function and liver insulin sensitivity [3]. Furthermore, visceral fat has an increased sensitivity to lipolysis and an altered adipokine profile compared with that of subcutaneous adipose tissue [3]. Subcutaneous adipose tissue provides a nontoxic depot for storing esterified fatty acids. The importance of this safe depot is highlighted by the metabolic dysfunction seen in patients with lipodystrophy, in whom subcutaneous fat is absent.

This article reviews the link between adipokines and the metabolic syndrome, the detrimental effects of free fatty acids (or nonesterified fatty acids [NEFA]), and the depot-specific differences between visceral and subcutaneous adipose tissue. Finally, available and novel approaches to the treatment of visceral adiposity and the metabolic syndrome are outlined.

The Metabolic Syndrome

The recognition of clustering of cardiovascular risk factors is not controversial. However, the definition and utility of the "metabolic syndrome" have been debated. The concept that the constellation of features conveys a greater risk beyond the individual components has been

Table 1. Definitions of the metabolic syndrome

Parameters	NCEP-ATP III	IDF	WHO
Required		Waist circumference (Europoid population)[‡] ≥ 94 cm (men); ≥ 80 cm (women)	Insulin resistance,[§] impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes
Number of abnormalities	≥ 3	≥ 2	≥ 2
Obesity	Waist circumference[*] > 102 cm (men); > 88 cm (women)		WHR > 0.9 (men), > 0.85 (women); or BMI > 30 kg/m^2
Glucose	Fasting glucose > 5.6 mmol/L, or drug treatment for elevated glucose	Fasting glucose > 5.6 mmol/L; or diagnosis of diabetes	
HDL cholesterol	< 1.03 mmol/L (men); < 1.3 mmol/L (women); or drug treatment for low HDL cholesterol[†]	< 1.03 mmol/L (men); < 1.29 mmol/L (women); or drug treatment for low HDL cholesterol[†]	< 0.9 mmol/L (men); < 1.0 mmol/L (women)
TG	> 1.7 mmol/L; or treatment for elevated TG[†]	> 1.7 mmol/L; or treatment for elevated TG[†]	> 1.7 mmol/L
Hypertension	> 130/85 mm Hg; or drug treatment for hypertension	> 130/85 mm Hg; or drug treatment for hypertension	> 140/90 mm Hg
Other			Microalbuminuria[¶]

[*]Some residents of the United States of non-Asian origin (white, black, Hispanic) with marginally increased waist circumference—94 to 101 cm (men) or 80 to 87 cm (women)—may have strong genetic predisposition and benefit from changes in lifestyle habits. Lower waist circumference cut-offs for Asian Americans: ≥ 90 cm (men) and ≥ 80 cm (women).
[†]Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and low HDL. Patients on one or more of these drugs are presumed to have high TG and low HDL.
[‡]Ethnic-specific waist circumference: South Asian, Chinese, Ethnic South and Central American populations: > 90 cm (men), > 80 cm (women); Japanese populations: > 85 cm (men), > 90 cm (women); sub-Saharan African, Eastern Mediterranean, Middle Eastern populations: same cut-offs as for Europoid populations.
[§]Glucose uptake in lowest quartile for background population under investigation (hyperinsulinemic euglycemic clamp).
[¶]Albumin excretion rate ≥ 20 μg/min or albumin:creatinine ratio ≥ 30 mg/g.
BMI—body mass index: weight (kg)/height (m)^2; HDL—high-density lipoprotein; IDF—International Diabetes Federation; NCEP-ATP III—National Cholesterol Education Program Adult Treatment Panel III; TG—triglycerides; WHO—World Health Organization; WHR—waist-hip ratio.

challenged [10,11]. Although obesity and insulin resistance are important factors, no unifying pathogenetic explanation exists to underlie the metabolic syndrome [10]. The most frequently used definitions include the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), published in 2001 and updated in 2005 [5], the International Diabetes Federation Criteria (IDF) proposed in 2004 [4], and the WHO definition published in 1999 [12] (Table 1). Although these criteria overlap, there are differences. The IDF requires the presence of abdominal obesity, whereas abnormal glucose metabolism is a prerequisite to fulfil the WHO criteria. The WHO definition also includes microalbuminuria. Both the IDF and NCEP-ATP III definitions identify ethnic-specific waist circumference criteria. When applied to a US population, the NCEP-ATP III and IDF demonstrate an overlap of 93%; however, the IDF criteria identify a greater number of people with this syndrome [13]. Despite ongoing debate regarding the clinical utility of this entity, patients fulfilling criteria for the metabolic syndrome do have a significant cardiovascular risk, and these risk factors should be clinically targeted. Insights into the link between abdominal obesity and the associated metabolic dysfunction and cardiovascular risk may promote novel therapeutic targets.

Fat Tissue

Adipose tissue consists of adipocytes, vascular tissue, and immune cells [6]. Brown adipose tissue promotes thermogenesis through the uncoupling of oxidative phosphorylation; this is mediated through uncoupling protein-1, an integral inner membrane mitochondrial protein [14]. Although brown adipose tissue is present around the heart and great vessels in infancy, little remains in adulthood, and white adipose tissue predominates [14].

Abdominal fat can be divided into subcutaneous and intra-abdominal fat. Intra-abdominal fat can be further classified as retroperitoneal and intraperitoneal fat. The latter is also referred to as visceral fat and is composed of mesenteric and omental fat depots. Epidemiologic studies have confirmed the association between abdominal (particularly visceral) fat and insulin resistance and cardiovascular disease [3]. In times of energy surplus, ectopic fat

is deposited in liver, muscle, and visceral compartments, which can result in lipotoxicity and insulin resistance.

In addition to its role as an energy storage depot, adipose tissue is an important regulator of energy balance, appetite, glucose homeostasis, immune function, coagulation, and blood pressure through the effects of secreted adipokines [6]. Adipokines are numerous, and include leptin, adiponectin, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, angiotensinogen, plasminogen activator inhibitor (PAI)-1, monocyte chemoattractant protein (MCP)-1, resistin, visfatin, and omentin [6,14]. Adipokines act at both autocrine and paracrine levels, in addition to having peripheral and central effects.

Therefore, several potential pathophysiologic factors may contribute to the cardiometabolic consequences of abdominal obesity. These include dysregulation in adipokine secretion and the associated inflammatory state, in addition to the ramifications of ectopic fat deposition. The depot-specific differences directly implicating visceral fat in cardiometabolic risk are discussed below.

Adiponectin

Adiponectin, a 28-kd protein with 244 amino acids, circulates at high levels and constitutes 0.01% of total plasma protein [15,16]. In contradistinction to the other adipokines, adiponectin is believed to be an anti-inflammatory and insulin-sensitizing hormone whose levels are reduced in obesity [16].

Adiponectin has structural homology to both TNF-α and the complement factor C1q, and like the latter, it circulates in various multimeric structures [16]. Trimers and hexamers form the low-molecular-weight component of adiponectin, whereas the higher-order structures (12–18-mers) constitute the high-molecular-weight (HMW) fraction [16]. Studies suggest that HMW adiponectin is the most metabolically active multimer. The proportion of HMW adiponectin, rather than the total level, is associated with the beneficial effects of thiazolidinediones [16]. Furthermore, HMW adiponectin appears to modulate the antiatherogenic properties of adiponectin [16]. Adiponectin is subject to several posttranslational modifications; these appear to be important in the multimeric distribution and function of adiponectin [16,17]

Although secreted primarily by adipocytes, levels of this hormone are paradoxically reduced in obesity [16]. Adiponectin secretion is quite distinct from that of leptin; adiponectin has ultradian pulsatility and diurnal variation, with a decline in nocturnal levels of up to 30% [16]. The regulation of adiponectin secretion is incompletely understood. Glucocorticoids, IL-6, TNF-α, β-agonists, and chronic exposure to endothelin have been shown to reduce adiponectin gene expression [16]. The effect of insulin on adiponectin secretion is not clear, and likely depends on the chronicity of exposure [16]. Adiponectin levels are lower in men, likely mediated through the actions of testosterone [16].

Yamauchi et al. [18] described the adiponectin receptors adipoR1 and adipoR2. These receptors have reverse topology to G-protein–coupled receptors; adipoR2 has a greater affinity for HMW adiponectin, and is found predominantly in the liver, whereas adipoR1 is found predominantly in skeletal muscle [18]. Stimulation of adipoR1 and adipoR2 activate adenosine monophosphate–activated protein kinase (AMPK) and peroxisome proliferator–activated receptor (PPAR)-α [19]. Expression of adipoR1 and adipoR2 has been identified on pancreatic β-cells and islets, monocytes, endothelial cells, and osteoblasts, and in the central nervous system [16,20]. Other adiponectin receptors, T-cadherin [21] and calreticulin [22•], were described recently. T-cadherin has been proposed to act as a co-receptor for HMW adiponectin on endothelial and smooth muscle cells [21]. Calreticulin facilitates the clearance of apoptotic bodies by adiponectin, potentially affording protection against systemic inflammation. However, it appears that adipoR1 and adipoR2 are the most physiologically important receptors in vivo [23••].

The administration of adiponectin to rodents decreases fat mass through stimulation of fatty acid oxidation in muscle [15]. Overexpression of adiponectin in mice results in improved glycemic and lipid parameters, associated with increased AMPK activation in liver and PPARγ expression in white adipose tissue [16]. Results with adiponectin-knockout animal models have been somewhat conflicting, demonstrating varying levels of insulin resistance [15]. It has been suggested that the insulin resistance seen in these models is predominantly hepatic, associated with decreased PPAR activation [15].

Researchers have suggested that adiponectin has broad-ranging anti-inflammatory effects. Adiponectin has antiatherogenic properties, modulating both endothelial and macrophage function [16]. Recently, adiponectin's role in regulating appetite was reported [20]. In addition, low levels of adiponectin are seen in nonalcoholic steatohepatitis (NASH), a condition commonly seen in patients with the metabolic syndrome [16]. Administration of adiponectin to murine models of NASH ameliorates the steatosis and inflammation seen in this disease [24].

Adiponectin levels decrease in parallel with the progression of insulin resistance and type 2 diabetes in nonhuman primates [15]. Lower levels of adiponectin are seen in type 2 diabetes, and correlate with vascular dysfunction and coronary artery disease [16]. The *APM1* gene (chromosome 3q27), which encodes adiponectin, has been identified as a susceptibility locus for the metabolic syndrome and type 2 diabetes, further supporting the role of adiponectin as a "diabetogene" [16].

Leptin

Leptin, a 16-kd product of the *ob* gene, was the first adipokine described to modulate adipose tissue, and has therefore been studied extensively [6,14].

Leptin is secreted almost exclusively by adipocytes in proportion to fat mass and nutritional status [6]. However, leptin levels are also regulated by glucocorticoids, TNF-α, estrogens, and CCAAT/enhancer-binding protein-α (which increase leptin levels), and β3-adrenergic activity, androgens, free fatty acids, growth hormone, and PPARγ agonists (which decrease circulating leptin levels) [6]. Insulin promotes leptin secretion, whereas leptin inhibits insulin release, the "adipoinsular axis" [14]. Accordingly, increased basal insulin secretion and fasting hypoglycemia are observed following ablation of leptin receptors from pancreatic β-cells [25].

Leptin receptors are members of the cytokine receptor class I superfamily, and although several splice variants have been described, the long form of the receptor mediates the majority of leptin's effects [6]. Leptin receptors are expressed centrally and peripherally; high levels of the receptor have been identified in the mediobasal hypothalamus, in particular the arcuate, ventromedial, and dorsomedial nuclei [6].

Leptin acts as a satiety signal, repressing food intake and promoting energy expenditure. Through effects at the level of the hypothalamus, leptin inhibits orexigenic pathways while inducing anorexigenic pathways [14].

In addition to its role in energy regulation, leptin is important in glucose homeostasis. The hyperglycemia seen in *ob/ob* mice is reversed with leptin treatment, prior to correction of obesity [14]. Leptin reduces intramyocellular lipid through activation of AMPK and similarly improves liver insulin sensitivity through reduction of intracellular triacylglycerol [14]. Leptin appears to be important in partitioning lipid into appropriate storage depots, limiting the detrimental effects of ectopic lipid deposition [14].

Human leptin deficiency is a rare cause of human obesity, which is reversed with leptin replacement [15]. However, levels of leptin are elevated in common human obesity, and due to leptin resistance, replacement strategies are ineffective [15]. The cause of leptin resistance is unknown. Recently, C-reactive protein has been proposed to mediate leptin resistance [26]; however, other investigators have questioned this [15,27].

Visfatin, Omentin, and Resistin

Visfatin is secreted from visceral adipocytes and promotes insulin sensitivity through direct binding to and activation of the insulin receptor [28]. This protein was originally identified from lymphocytes as pre–B-cell colony-enhancing factor, and also acts as an enzyme, catalyzing the rate-limiting step of mammalian nicotinamide adenine dinucleotide biosynthesis [14]. Therefore, visfatin is likely to be an important modulator of both immune and inflammatory pathways; however, its molecular and biochemical features are incompletely understood. Some groups have failed to replicate the visceral-specific production of this adipokine [29]. Furthermore, there have been conflicting reports regarding the association of visfatin with obesity, diabetes, and insulin resistance [30,31•]. Discrepancies may result from inconsistencies in immunoassays used in these studies [32].

Omentin, a recently described adipokine, is also secreted predominantly from visceral fat [33]; however, it appears to be produced by stromovascular cells rather than adipocytes [14]. Omentin is an insulin-sensitizing adipokine [33]. Reduced levels of omentin have been reported recently in obesity, and correlate with insulin resistance [34].

Resistin was first identified as a thiazolidinedione-suppressible gene secreted from mouse adipocytes [15]. It appears that stromal cells (eg, macrophages resident in adipose tissue) are the major source of this protein in humans [14]. Like adiponectin, resistin circulates in different multimeric forms [15]. Human resistin shares only 53% homology with murine resistin; although resistin is an inflammatory molecule with hyperglycemic effects in murine and rodent models, its role and physiologic relevance in humans have been debated [15].

PAI-1 and Visceral Adipose Tissue–derived Serine Protease Inhibitor

PAI-1, a member of the serine protease inhibitor (serpin) superfamily, is secreted primarily from visceral fat depots and inhibits fibrinolysis through its inhibition of plasminogen activator [6]. Mice lacking functional PAI-1 are protected from obesity and insulin resistance [35]. Plasma levels of PAI-1 are elevated in human obesity and insulin resistance [6]. TNF-α appears to be an important regulator of PAI-1 [6]. Treatment with metformin or thiazolidinediones results in reduced PAI-1, paralleling improved insulin sensitivity [15]. Visceral adipose tissue accumulation and obesity-related complications, including type 2 diabetes and cardiovascular disease, may be modulated by PAI-1, making it an attractive therapeutic target.

Visceral adipose tissue–derived serine protease inhibitor (vaspin) also belongs to the serpin superfamily [36]. Vaspin is expressed in both subcutaneous and visceral fat, and vaspin levels correlate with fat mass [15]. An insulin sensitizing role has been demonstrated in murine models [36]; however, a recent study failed to identify a correlation between vaspin levels and glucose and lipid metabolism in humans [37•].

Renin-Angiotensin System

The renin-angiotensin system (RAS) provides a potential link between adiposity and hypertension, cardiovascular disease, and diabetes [6]. Renin, angiotensinogen, angiotensin I and II, angiotensin receptor types 1 (AT1) and 2 (AT2), and angiotensin-converting enzyme (ACE) are all produced in adipose tissue [6].

Angiotensinogen, ACE, and AT1 expression are higher in visceral compared with subcutaneous fat. In addition to the well-characterized effects on blood pressure and the cardiovascular system, components of the RAS are important in adipose tissue development [6].

Mice with deletion of angiotensinogen have decreased blood pressure and reduced adipose tissue mass; overexpression of angiotensinogen in fat tissue results in hypertension and increased adiposity [6]. In humans, plasma angiotensinogen, ACE, and adipose tissue angiotensinogen expression correlate with adiposity [6]. A reduced incidence of diabetes has been noted in several large, randomized, controlled trials evaluating ACE inhibition; however, the evidence that the RAS has direct effects on insulin sensitivity has been conflicting [6].

TNF-α and IL-6

TNF-α, a 26-kd transmembrane protein, is cleaved into a 17-kd product that acts via type I and type II TNF-α receptors [6]. TNF-α secretion is greater in subcutaneous compared with visceral fat; adipocytes express both types of TNF-α receptors [6].

TNF-α expression in adipose tissue is up-regulated in obese rodents, and infusion of neutralizing soluble TNF-α receptors improves insulin sensitivity [7]. Although adipose tissue expression of TNF-α is correlated with obesity in humans, TNF-α blockade does not ameliorate insulin resistance [38•]. TNF-α stimulates leptin and inhibits adiponectin secretion, down-regulates adipogenesis, promotes lipolysis, and induces apoptosis of adipocytes, and thus has been proposed as an "adipostat," limiting adiposity in times of energy excess [3,6].

Unlike TNF-α, IL-6 circulates in high levels [6]. Several glycosylated forms of IL-6 exist, ranging in size from 22 to 27 kd [6]. The IL-6 receptor is expressed in adipocytes, and like the leptin receptor, it has both membrane-bound and soluble forms [6]. Adipose tissue secretes up to one third of the circulating IL-6, and visceral fat expression of this cytokine is threefold higher compared with that found in the subcutaneous compartment [15].

Administration of IL-6 to rodents induces insulin resistance in the liver and skeletal muscle, whereas antagonism improves hepatic insulin sensitivity in murine models of obesity [6]. Levels of IL-6 are increased in obesity and insulin-resistant states, and predict the development of type 2 diabetes and cardiovascular disease [6]. However, evidence exists that IL-6 may have differential effects in the central nervous system, regulating appetite and promoting weight loss [6].

TNF-α, IL-6, and other cytokines/adipokines may decrease insulin sensitivity through several pathways; however, the molecular etiology underscoring the insulin resistance associated with inflammation remains incompletely understood. Both TNF-α and IL-6 down-regulate genes involved in adipogenesis, and reduce adiponectin secretion [6]. Additional mechanisms include c-Jun-N-terminal kinase 1–mediated serine phosphorylation of insulin receptor substrate-1, induction of suppressor of cytokine signaling 3, IκB kinase–mediated nuclear factor-κB (NF-κB) activation, and production of reactive oxygen species [7].

Macrophages and MCP-1

Obesity is associated with macrophage infiltration of adipose tissue [8]. Activated macrophages secrete cytokines, including TNF-α and IL-6, which are likely to be important in regulating insulin sensitivity [6]. Circulating monocytes have been implicated in modulating systemic insulin sensitivity through NF-κB–related pathways [39••].

MCP-1 is secreted by adipose tissue and mediates macrophage recruitment to sites of inflammation [6]. Levels of systemic and adipose tissue MCP-1 are elevated in rodent obesity [6]. Targeted ablation of MCP-1 or its receptor reduces adipose tissue macrophage infiltration, and improves insulin sensitivity without inducing weight loss [40,41]. Conversely, insulin resistance and increased adipose tissue macrophages are observed in models of MCP-1 overexpression [41].

Glucocorticoids

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) converts inactive cortisone to active cortisol in adipose tissue [6]. The enzyme is highly expressed in adipose tissue, and is up-regulated in both subcutaneous and visceral adipose tissue in obesity [42]. Although systemic cortisol levels are not significantly affected by 11βHSD1 activity, paracrine effects are important. Dysregulation of this enzyme has been implicated in obesity, type 2 diabetes, hypertension, and cardiovascular disease [6]. Therapeutic modulation of this enzyme is the focus of ongoing research.

Nonesterified Fatty Acids

NEFA have been implicated in obesity-related insulin resistance. Levels of NEFA are elevated in obesity and type 2 diabetes and are associated with insulin resistance [3]. Excessive NEFA levels inhibit muscle glucose uptake, promote liver gluconeogenesis, impair pancreatic β-cell function, and increase hepatic production of very low-density lipoprotein (VLDL) triglycerides [3]. The mechanisms through which NEFA mediate effects on insulin sensitivity include increased ceramide formation, protein kinase C (PKC) activation, and oxidative stress induction [14]. Recently, fatty acids have been shown to activate the innate immune system through interaction with Toll-like receptor 4, providing an important link between fatty acid metabolism, diet, and insulin resistance [43••].

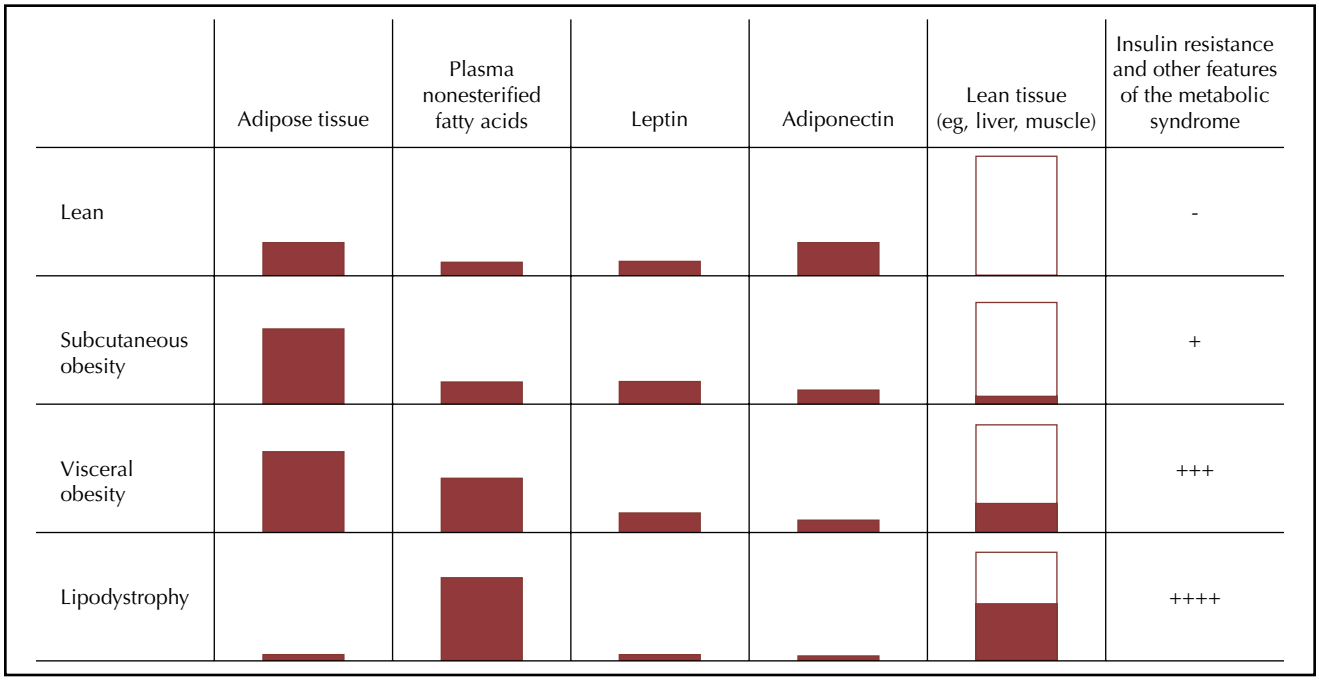

Figure 1. Adipose tissue distribution and insulin resistance in lean subjects, subcutaneous obesity, visceral obesity, and lipodystrophy, demonstrating the importance of both a "safe" storage for esterified lipids and appropriate adipokine regulation in promoting glucose homeostasis.

Insulin inhibits lipolysis; therefore insulin resistance can increase NEFA levels. Chronically increased fatty acids can impair insulin secretion at the pancreatic β-cell level, compounding the insulin resistance [14].

The portal drainage of visceral fat to the liver has been proposed as an important factor linking visceral adiposity and insulin resistance [3]. However, recent work suggests that NEFA derived from visceral fat constitute a relatively small proportion of portal NEFA (5% and 20% in lean and obese subjects, respectively) [44]. Similarly, visceral adipose tissue–derived NEFAs have a minimal contribution to systemic free fatty acid exposure (6% in lean and 14% in obese subjects) [44]. Therefore, whereas visceral fat–derived NEFA may modulate hepatic insulin sensitivity, effects on skeletal or systemic insulin resistance appear to be minimal [44].

Visceral Fat and the Lipid Sink

A significant amount of work has focused on defining inherent differences between subcutaneous and visceral fat to explain the apparent pathogenicity of visceral adiposity. Indeed, the portal drainage of visceral fat discussed previously has potential implications for all adipokines secreted by this depot.

Visceral fat is more lipolytic than subcutaneous fat and is resistant to the insulin-mediated inhibition of lipolysis [3]. Compared with subcutaneous fat, visceral fat expresses several adipokines to a greater degree, including IL-6, PAI-1, visfatin, omentin, angiotensinogen, and ACE [3]. Leptin and TNF-α are expressed to a greater extent in subcutaneous tissue [3]. Levels of adiponectin secretion from visceral and subcutaneous depots are comparable; however, due to greater volume, the majority of circulating hormone is derived from subcutaneous fat [45].

The concept of the "lipid sink" followed the observation of profound metabolic dysfunction in patients with lipodystrophy who lacked subcutaneous fat [14]. The ectopic hepatic, muscle, and pancreatic β-cell lipid deposition, and increased visceral adiposity seen in partial lipodystrophy promote insulin resistance, likely mediated through inflammation as a result of lipotoxicity. In addition to highlighting the importance of having a "safe" storage depot for esterified lipid (ie, subcutaneous fat), the beneficial effects seen with leptin and adiponectin replacement therapy in patients with lipodystrophy support an important role for adipokines in regulating metabolic function [14]. In the more common problem of obesity, intramyocellular, hepatic, and visceral fat may be considered "ectopic," overflowing from replete subcutaneous stores. A combination of increased portal NEFA and dysregulation of adipokines may then result in metabolic dysfunction [14] (Fig. 1).

Treatment

Weight loss is an effective, though often elusive, strategy for addressing obesity-related metabolic dysfunction. Diet and lifestyle modifications are the most effective approach; however, without an expensive, rigorous follow-up, success is poor [46].

Evidence is currently insufficient to promote drug therapy for treatment of the metabolic syndrome. However, available antiobesity medications and surgical procedures are used to manage obesity. Sibutramine (an appetite suppressant) and orlistat (an inhibitor of fat absorption in the gut) are mainstays of available drug therapy for weight loss. These agents generally achieve 5% to 10% weight loss [46]. Rimonabant, a selective inhibitor of the endocannabinoid receptor 1, has central and peripheral effects on appetite and weight regulation [46], and demonstrates beneficial effects on weight and metabolic parameters [46]. Although not available as obesity treatment per se, several drug treatments for diabetes are also associated with weight loss, including metformin and the newer incretin-based therapies, exenatide and pramlintide [46]. Surgical approaches to restrict oral intake and/or reduce nutrient absorption have proved the most effective approach to achieve clinically significant sustained weight loss [46]. Surgical approaches to removing visceral fat have demonstrated metabolic benefits in animal studies [47], though they are unlikely to be adopted in humans. Further supporting the metabolic relevance of visceral fat, liposuction (removal of subcutaneous adipose tissue) does not improve metabolic parameters [48].

Increasing basal metabolic rate by manipulating white adipose tissue to adopt features of brown adipose tissue has been suggested as a novel therapeutic approach to treat the metabolic syndrome [14]. Sirtuin-based therapies have recently been proposed as a potential treatment target for the metabolic syndrome. In contradistinction to the obesity associated with overnutrition, caloric restriction is associated with increased longevity in several animal models, possibly including primates [49]. This finding has recently been linked to the activity of sirtuins, which regulate pathways relevant for both aging and glucose and lipid metabolism [49]. Therefore, "calorie restriction mimetics" may be a potential therapeutic target [49]. The acknowledgment of adipose tissue as an important endocrine organ raises the prospect of adipokine-based therapies.

The mechanisms of action of thiazolidinediones are incompletely understood. These PPARγ agonists mediate some of their insulin sensitizing and anti-inflammatory effects through an increase in adiponectin levels, particularly HMW adiponectin [16]. PPARγ agonists also decrease circulating NEFAs and promote redistribution of ectopic fat in liver and muscle to adipose tissue. Treatment does not promote weight loss, and this class of medication is currently used only to treat type 2 diabetes. Leptin resistance precludes replacement as a successful strategy in common obesity, though other treatment approaches that manipulate adiponectin, particularly HMW adiponectin, are appealing. As mentioned previously, therapies based on PAI-1 and RAS are under investigation. Preliminary proof-of-concept animal studies have demonstrated the effectiveness of the 11βHSD inhibitor carbenoxolone in attenuating manifestations of obesity-related metabolic syndrome [50]. Although targeted inhibition of inflammatory cytokines (TNF-α) was ineffective [38•], other anti-inflammatory approaches may prove more successful.

Conclusions

Obesity-related diseases are a significant global problem. The metabolic syndrome has been proposed to conceptualize the increased cardiometabolic risk associated with visceral obesity. There is no universally accepted definition, and contention exists regarding its usefulness in defining increased cardiovascular risk. The recognition of adipose tissue as a dynamic endocrine organ, and the site-specific differences between visceral and subcutaneous fat, suggest that visceral adiposity is more than a marker of metabolic dysfunction. In addition to secreting adipokines and NEFAs, adipose tissue has an important role as a "safe" storage site for esterified fatty acids, preventing the lipotoxicity and insulin resistance seen with ectopic fat deposition.

Our armamentarium against the obesity epidemic is limited. Closely supervised diet and lifestyle programs are effective, though difficult to maintain due to logistics and high costs. Currently available drug therapy is suboptimal; however, the manipulation of adipose cell biology provides the potential for exploration of novel therapeutic avenues.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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This study identifies a new receptor for adiponectin and demonstrates another facet of adiponectin's anti-inflammatory actions. Because hypoadiponectinemia is associated with the chronic inflammation of obesity, and adiponectin has homology to the complement factor C1q, the researchers proposed that adiponectin may control systemic inflammation through clearance of apoptotic bodies. Adiponectin knockout mice demonstrated a reduced ability to clear apoptotic cells, which was mitigated by adenovirus-mediated overexpression of adiponectin. Adiponectin was also shown to opsonize apoptotic cells, mediated by binding adiponectin to calreticulin on the macrophage surface.

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This group cloned the adiponectin receptors adipoR1 and adipoR2 in 2003. This recent work suggests these are the predominant receptors for adiponectin in vivo. *Db-db* mice (a murine model of obesity) have reduced adipoR1 and adipoR2 expression in the liver. Adenoviral overexpression of these receptors dose-dependently improved glucose and lipid parameters (R1 mediated through activation of AMPK and R2 predominantly through PPARα pathways). These observations were corroborated with knockout models.

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Data are conflicting regarding the association between the novel adipokine visfatin and cardiovascular risk, in addition to debate regarding tissue specificity of expression. This cross-sectional, community-based study assessed 374 subjects from the Framingham third-generation cohort. Visfatin levels were not correlated with diabetes or obesity. The authors note that their cohort was modest in size and included a low prevalence of type 2 diabetes (6%), and that insulin sensitivity was not measured directly. Furthermore, serum levels may not be predictive of tissue expression and activity. Further studies are required to elucidate the potential role of visfatin in the metabolic syndrome.

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The first study to evaluate the relationship between vaspin and components of the metabolic syndrome. The investigators identified significantly higher levels of vaspin in women; however, no correlation was found between vaspin, body mass index, waist-to-hip ratio, or measures of insulin sensitivity. Unlike some other adipokines, vaspin does not appear to be renally cleared or regulated.

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In a seminal 1993 paper, Hotamisligil et al. defined a link between TNF-α–associated chronic inflammation, obesity, and insulin resistance. TNF-α was overexpressed in adipose tissue of obese mice, and inhibition of TNF-α restored insulin sensitivity. Subsequently,

TNF-α was found to be overexpressed in human adipose tissue, but initial studies assessing response to TNF-α blockade were disappointing. In their study, Bernstein et al. assessed the effects of treatment with etanercept (a TNF-α antagonist) on markers of inflammation, body composition, and insulin sensitivity in 56 obese subjects with the metabolic syndrome. In this randomized, double-blind, placebo-controlled trial, etanercept treatment was associated with a significant decrease of C-reactive protein and fibrinogen and an increase in adiponectin. No effect was seen on body composition or change in insulin sensitivity. The study duration was relatively short; however, the lack of insulin-sensitizing effects in this insulin-resistant population raised the possibility of a dissociation of TNF-α's effects on insulin sensitivity and inflammation in humans.

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This group identified a further link between chronic inflammation and insulin resistance. IκB kinase-β (IKK-β) is an enzyme that coordinates the NF-κB inflammatory response. Mice lacking hepatic expression of IKK-β retained liver insulin sensitivity, but demonstrated insulin resistance in the periphery in response to high-fat diet challenge. Decreased systemic insulin sensitivity was seen in mice in which myeloid IKK-β was absent. This novel observation highlights the importance of myeloid cells in modulating global insulin sensitivity.

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