Visceral and Subcutaneous Adiposity: Are Both Potential Therapeutic Targets for Tackling the Metabolic Syndrome?

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Abstract: The metabolic syndrome represents a constellation of co-morbidities that include central adiposity, insulin resistance, dyslipidemia and hypertension, which results from an elevated prevalence of obesity. An increased abdominal adiposity is observed in upper-body obesity with preferential accumulation of fat in the visceral depot, which renders these individuals more prone to metabolic and cardiovascular problems. The pathophysiology of the metabolic syndrome seems to be closely associated to an elevated efflux of free fatty acids from the visceral fat compartment and a dysregulation of the expression of adipocyte tissue-derived factors (also termed “adipokines”). Weight reduction and increased physical activity represent the main approach to tackle the “diabesity” epidemic. Nonetheless, taking advantage of the different biochemical and molecular characteristics of visceral and subcutaneous adipose tissue may open up novel pharmacological strategies to combat the metabolic and cardiovascular derangements accompanying the metabolic syndrome.

REGIONAL FAT DISTRIBUTION AND THE METABOLIC SYNDROME

Obesity is closely associated to the development of insulin resistance, hypertension, and dyslipidemia, all well-documented risk factors for cardiovascular disease, which cluster together as the metabolic syndrome [1]. Interestingly, the notion that the regional fat distribution is key to the development of the metabolic syndrome as well as to the obesity-associated diseases has been firmly established [2, 3]. Upper body obesity (i.e. visceral or “android” obesity), as determined by an increased waist circumference and waist-to-hip ratio or an elevated intra-abdominal fat area by image analysis at the lumbosacral level, is associated to an increased incidence of metabolic disturbances, elevated risk of cardiovascular disease and premature death [4, 5]. In contrast, individuals with comparable amounts of adipose tissue stores located in the subcutaneous gluteo-femoral depots (characteristic of lower body or “gynoid” obesity) exhibit a lower morbidity and mortality risk than subjects with visceral obesity. Additionally, selective reduction of intra-abdominal visceral adiposity following a dietetic intervention and physical activity program is accompanied by improvements both in glucose and lipid metabolism [6].

Subcutaneous fat depots are predominantly accumulated in the gluteal and femoral regions, constituting the largest site of fat storage (approximately 80% of total body fat). Visceral fat is composed by the greater and lesser omentum (peritoneum that is attached to the stomach and links it with other abdominal organs) as well as by the mesenteric fat [7]. Quantitatively speaking visceral fat accounts for a small fraction of total body fat, representing approximately 20% of total body fat in men, while contributing to around 5-8% in women. Human omental adipose tissue displays a range of biochemical properties that distinguish it from fat depots of subcutaneous origin [8]. Insulin action is marked impaired in individuals with visceral obesity and epidemiological studies have shown that visceral fat accounts for most of the variability in insulin sensitivity. In this sense, it has been shown that an increased fat mass, particularly in the deep subcutaneous and visceral fat depots, is characterized by larger adipocytes that are resistant to insulin’s effects on lipolysis [9]. Furthermore, removal of visceral fat prevents insulin resistance and glucose intolerance, supporting the direct participation of visceral fat accumulation as one of the main elements of the metabolic syndrome [10]. Putative mechanisms for the role of visceral adipose tissue in the onset of the metabolic syndrome include an increased portal release of free fatty acids (FFA) together with an abnormal expression of adipose tissue-derived factors (also termed adipokines). Weight reduction and increased physical activity represent the initial approach to tackle the “diabesity” epidemic. Nonetheless, taking advantage of the different biochemical and molecular characteristics of visceral and subcutaneous adipose tissue may open up novel pharmacological strategies to combat the metabolic and cardiovascular derangements accompanying the metabolic syndrome.

Cathecolamines

The sympathetic nervous system (SNS) plays a major role in the control of lipolysis in human adipose tissue. Cathecolamines (noradrenaline and adrenaline) stimulate lipolysis through lipolytic β-adrenoceptors (β₁, β₂ and β₃) and anti-lipolytic α₂-adrenoceptors [17, 18]. These receptors are linked to G-proteins and regulate the activity of adenylate cyclase in the cell membrane. The β₁, β₂ and β₃-adrenoceptors couple to G-proteins that activate adenylate cyclase, leading to an increase in cAMP production, which is followed by the activation of protein kinase A (PKA) that induces HSL phosphorylation, thereby increasing lipolysis. On the contrary, stimulation of G₁-coupled α₂-adrenoceptors inactivates the adeniny
late cyclase, leading to a decrease in intracellular cAMP levels and, subsequently, to a reduction in lipolysis.

It is well established that catecholamine action is markedly altered in obesity [19]. Interestingly, fat depot-related differences in catecholamine-mediated regulation of lipolysis have been reported in vitro in normal-weight and obese subjects [17, 18]. The lipolytic response to catecholamines is weaker in adipocytes isolated from the subcutaneous gluteal, femoral and abdominal locations compared to that of fat cells obtained from the visceral depot [17, 18]. Several mechanisms have been linked to this resistance in subcutaneous adipocytes: enhanced anti-lipolytic α2-adrenoceptor activity, decreased lipolytic β2-adrenoceptor responsiveness and reduced expression or function of HSL or proteins that interact with either HSL, such as adipocyte lipid binding protein (ALBP), or the lipid droplet, such as perilipin [18]. On the other hand, catecholamine-induced lipolysis is clearly increased in visceral fat cells, due to a decreased activity of α2-adrenoceptors and an increased activity of β1,2-adrenergic receptors, being the latter less relevant in humans [18]. In subjects with upper-body obesity the regional variations in the action of catecholamines on lipolysis are further enhanced. In addition, the impact of obesity on the catecholamine-mediated effects is more evident in men compared to women.

**Insulin**

Insulin constitutes a powerful inhibitor of lipolysis. It inhibits FFA efflux, increases fat storage by stimulating FFA re-esterification into TG and regulates glucose uptake [7]. When insulin binds to its receptors on adipocytes, the receptor is activated by phosphorylation on tyrosine residues, leading to tyrosine phosphorylation on insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) and to binding of the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) [20]. In addition, the serine kinase activity of PI3K autophosphorylates the p85 regulatory subunit and the p110 catalytic subunit. PI3K activation is followed by protein kinase B/Akt phosphorylation and, thereby, activation of phosphodiesterase 3B (PDE3B), the enzyme that catalyses the degradation of cAMP into...
5' AMP [21]. Reductions in intracellular cAMP levels result in inactivation of PKA and reduced phosphorylation of HSL.

Subcutaneous adipocytes are more responsive to the anti-lipolytic effects of insulin compared to visceral adipocytes [18]. Various depot-related differences have been identified at the level of the insulin receptor and the post-receptor insulin signaling cascade [22, 23]. A reduction in the anti-lipolytic action on visceral adipocytes can be explained by a reduced insulin receptor autophosphorylation and signal transduction via the IRS-1/PI3K pathway [22, 23]. Other components of the insulin signaling cascade such as PDE3B, which is responsible for the anti-lipolytic action of insulin, and protein tyrosine phosphatases (PTPases), which are involved in insulin receptor dephosphorylation, may also play a role in the control of FFA disposal by insulin. Increased PTPase 1B levels in visceral adipose tissue may contribute to the relative insulin resistance of this fat depot [24]. The regional differences in insulin action reported in isolated adipocytes also take place under in vivo circumstances. In fact, visceral adipose tissue is more resistant to the effects of insulin than the leg and non-visceral fat depots [25]. Nonetheless, the overall contribution of non-visceral versus visceral body fat as regards insulin-mediated effects on lipolysis merits further attention [7].

Leptin

Leptin has been shown to stimulate lipolysis in white adipocytes both in vitro and in vivo [26-28]. It has been established that the lipolytic effect of leptin is located at the adenylate cyclase/Gi proteins and that the leptin-induced lipolysis opposes the tonic inhibition of endogenous adenosine [28]. Adenosine, via interaction with the A1 adenosine receptor, induces a potent inhibition of lipolysis in adipocytes. The A1 adenosine receptor is a typical transmembrane G coupled receptor, widely distributed in adipose tissue and known for its ability to inhibit adenylate cyclase [29]. Leptin opposes the anti-lipolytic effect of adenosine via the leptin receptor (OB-R), since no effects of leptin have been observed in adipocytes obtained from leptin receptor-deficient obese Zucker rats [28, 30].

Depot-specific differences in the lipolytic action of leptin in omental and subcutaneous adipose tissues have been also described [30]. Subcutaneous adipocytes are more sensitive to the lipolytic effect of leptin than fat cells obtained from the visceral location [30]. Thus, the decreased sensitivity to the lipolytic effect of leptin in omental adipocytes may underlie the association of visceral fat accumulation with increased co-morbidities.

Natriuretic Peptides

Natriuretic peptides (i.e. atrial and brain natriuretic peptides), well-known for their cardiovascular and renal effects, have also been shown to be powerful lipolytic agents both in vitro and in vivo [31]. The lipolytic effect of natriuretic peptides is mediated by natriuretic peptide receptor A, which possesses intrinsic guanylyl cyclase activity. Stimulation of natriuretic peptide receptor A is followed by an increase in cGMP levels and an activation of protein kinase G (PKG), which induces the phosphorylation and activation of HSL [32]. Fat depot-differences in the lipolytic effect of natriuretic peptides remain to be established.
Regional Differences in Adipokine Secretion

Adipose tissue was traditionally considered an energy storage organ, but over the last decade it has emerged as an endocrine organ. It is now recognized that adipose tissue produces multiple bioactive peptides, termed “adipokines”, which not only influence adipocyte function in an autocrine and paracrine manner but also affect multiple metabolic processes via an endocrine pathway [12]. In addition to adipocytes, which are the most abundant cell type, preadipocytes, endothelial cells, fibroblasts, leukocytes and, most importantly, macrophages, further contribute to the secretion of adipokytokines. Adipose tissue-secreted macromolecules derive from bone-marrow with the number of these cells in white adipose tissue being directly correlated with obesity [33]. The variety of molecules secreted by adipose tissue includes factors involved in glucose and lipid metabolism, such as LPL, apoE, CETP, glucocorticoids, sex steroids, prostaglandins, leptin, adiponectin and resistin, among others. A further relevant group of adipokytokines is represented by proinflammatory and proatherogenic factors, such as TNF-α, interleukin 6 (IL-6), angiotensinogen, C reactive protein (CRP), serum amyloid A (SAA), plasminogen activator inhibitor 1 (PAI-1) and complement factors (C3, factor B, adipsin, acylation stimulating protein). Several studies have reported a depot-related adipokine expression in human subcutaneous and omental adipose tissues [8, 34]. This fat depot-related difference has been viewed as an important mechanism by which adipose tissue exerts its effects for the modulation of insulin sensitivity, glucose homeostasis and lipid metabolism. Alterations in the secretion profile of adipokytokines play a key role in the pathogenesis of the metabolic syndrome and its accompanying cardiovascular complications [12].

TNF-α

The metabolic syndrome is associated with a pro-inflammatory state with increased adiposity being central to this condition [1]. The expanded adipose tissue constitutes an important source of circulating mediators of inflammation that participate in the mechanisms of vascular injury and atheromatous changes [12]. TNF-α was the first identified proinflammatory cytokine known to be secreted by adipose tissue [35]. The induction of TNF-α transcripts in adipose tissue can take place both in adipocytes and adipose tissue-resident macrophages, which act synergistically to stimulate the inflammatory activity of each other [36]. No differences in the level of TNF-α mRNA expression between subcutaneous and omental adipocytes have been established [8]. TNF-α has been implicated in the pathogenesis of insulin resistance and type 2 diabetes in mice and humans [37]. One of the mechanisms whereby TNF-α promotes insulin resistance constitutes the impairment of insulin signaling in adipocytes and skeletal muscle by interference at early steps with the insulin signalling cascade and, hence, impairment of insulin-stimulated glucose transport [38]. A second mechanism used by TNF-α to contribute to insulin resistance is through elevations in circulating FFA levels caused by the induction of lipolysis and the stimulation of hepatic lipogenesis [37]. Interestingly, several depot-specific differences have been recently reported regarding the effects of TNF-α as well as the expression of TNF-α and its receptors (TNFR1 and TNFR2) in omental and subcutaneous adipose tissue depots [39]. TNF only suppresses glucose uptake in insulin-stimulated subcutaneous adipose tissue, with this suppression being only observed in lean subjects. On the contrary, both TNF and TNFR2 expression are increased in obese individuals, while TNFR1 expression is higher in adipocytes of the omental depot compared to those obtained from the subcutaneous compartment.

IL-6

Subcutaneous adipose tissue accounts for approximately 30% of circulating IL-6 concentrations in humans with omental adipose tissue apparently exhibiting an even higher IL-6 release [33, 40]. The production of IL-6 augments with increasing adiposity; consequently, circulating IL-6 concentrations are highly correlated with the percentage of body fat. The proinflammatory role of IL-6 is based on the induction of the acute-phase reactant CRP in the liver, contributing to the low-grade, chronic inflammatory state linked to obesity [41]. Moreover, it has been suggested that IL-6 decreases LPL activity, which results in an increased lipid uptake by macrophages, favouring their conversion to foam cells [42]. In addition to its role as an inflammatory and atherogenic factor, IL-6 is linked to dyslipidemia, type 2 diabetes mellitus and the metabolic syndrome [43].

Leptin

Leptin is an adipocyte-derived protein that plays a major role in the control of body weight and energy expenditure [44]. In addition to its function as a satiety factor, leptin regulates several physiological processes, such as glucose and lipid metabolism, immunity, angiogenesis, reproduction and blood pressure homeostasis [12]. Human obesity is associated with increased circulating leptin concentrations, which are positively correlated to body mass index (BMI) and fat mass [45]. Leptin mRNA levels and leptin secretion rates are higher in subcutaneous than in visceral adipocytes with a strong correlation being evident between fat cell size and leptin secretion rate in these two fat depots [34, 46]. The subcutaneous fat depot is the main source of leptin owing to the combination of a mass effect (subcutaneous fat being quantitatively the predominant depot in men and women) together with the higher secretion rate of adipocytes of the subcutaneous location compared to those of the visceral origin [7]. Leptin resistance constitutes a hallmark of obesity, since obese subjects exhibit hyperleptinemia without the subsequent inhibition of food intake [45]. Thus, a better understanding of the onset of leptin resistance might be useful for the development of pharmacological tools to tackle the obesity epidemic and the accompanying increase in the incidence of the metabolic syndrome.

Adiponectin

Adiponectin, also known as Acrp30, AdipoQ, apM1 and gelatin-binding protein 28, is mainly expressed in adipocytes and can be found in three oligomeric forms, namely as trimer, hexamer and high-molecular-weight molecules [47, 48]. Adiponectin acts as an antidiabetic, antiinflammatory and antiatherogenic adipokine, being reduced in patients with obesity, type 2 diabetes mellitus and coronary artery disease [49-51]. The reduced adiponectin synthesis in subcutaneous adipocytes underlies the lower serum adiponectin concentrations observed in obesity and type 2 diabetes mellitus [52, 53]. Two adiponectin receptors (AdipoR1 and AdipoR2) have been described and it has been shown that both mediate direct effects on insulin sensitivity in liver and skeletal muscle [54]. A recent study has shown that AdipoR1 is highly expressed in human adipose tissue, suggesting that adiponectin may exert biological effects in an autocrine/paracrine manner [55]. Depot-specific differences have been established with AdipoR1 expression being significantly reduced in omental adipose tissue compared to subcutaneous fat. Moreover, the expression of AdipoR1 and AdipoR2 is reduced in obese subjects, while weight loss is followed by an increase in AdipoR1 expression [55, 56]. Therefore, low AdipoR1 expression levels in the omental depot of obese subjects may further contribute to the negative metabolic effects characterising the obese state.

Resistin

Resistin, also known as FIZZ3, is a member of a gene family that includes resistin-like molecule a (RELM-α), RELM-β and RELM-γ [57]. In humans resistin is markedly expressed in adipose tissue-embedded macrophages and, to a lesser extent, in adipocytes [58]. Initially, resistin was proposed as a relevant factor involved in obesity-associated insulin resistance. Administration of recombinant resistin caused insulin resistance in mice, which was improved by either anti-resistin antibodies or thiazolidinediones (TZDs) [57]. In spite of the hyperresistinemia observed in obese mice, the asso-
cation between circulating resistin concentrations and obesity in humans remains controversial. Several groups have described increased concentrations of resistin in obesity [59, 60], while others report no differences at all [61, 62]. Studies on the association of plasma resistin levels with insulin resistance and type 2 diabetes mellitus have also been inconsistent. Nonetheless, growing evidence links resistin with inflammation and cardiovascular disease [63]. A significant association between resistin concentrations and markers of inflammation has been established in subjects with severe inflammation and coronary atherosclerosis [64, 65]. Macrophages infiltrating human atherosclerotic aneurysms have been shown to secrete resistin [66]. In turn, resistin stimulates the synthesis of proinflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-12 through a nuclear factor κB (NF-κB) dependent pathway, upregulates the expression of adhesion molecules (VCAM1 and ICAM1) and promotes the release of endothelin-1 in human endothelial cells [67]. Interestingly, resistin also stimulates the synthesis of monocyte chemoattractant protein-1 (MCP-1) in the endothelium, which contributes to the perpetuation of the vicious circle of macrophage recruitment and production of proinflammatory cytokines.

Visfatin

Visfatin, which was initially identified as pre-B-cell-colony-enhancing factor, is a novel adipokine mainly produced by visceral adipose tissue of both mice and humans [68]. Visfatin binds insulin receptors at a different site to that of insulin, thereby exhibiting insulin-mimetic properties, such as the stimulation of glucose uptake and lipogenesis in 3T3-L1 adipocytes or L6 myocytes, as well as the suppression of the glucose production by cultured hepatocytes. Contrarily to what would be expected according to its name, plasma concentrations of visfatin and visceral visfatin mRNA expression have been reported to correlate with measures of obesity, but not with visceral fat mass or waist-to-hip ratio. Moreover, no differences in visfatin mRNA expression between the visceral and subcutaneous fat depots have been observed [69]. A twofold increase in circulating concentrations of visfatin in patients with type 2 diabetes mellitus has been recently reported [70]. However, the independent association between visfatin and type 2 diabetes mellitus disappeared after adjustment for body mass index and waist-to-hip ratio. Up to date the pathophysiological relevance of visfatin remains unclear. Visfatin may enhance fat accumulation in the intra-abdominal depot, as a feedback control preventing the detrimental effects of increased visceral fat on insulin sensitivity or merely embody an epiphenomenon with potential useful application as a surrogate marker of increased omental adipose tissue.

Retinol Binding Protein 4

Retinol binding protein 4 (RBP4) is the only specific transport protein for retinol in the blood and its main function is to deliver retinol to tissues [70, 71]. It has been shown recently that this adipokine may contribute to the pathogenesis of type 2 diabetes mellitus. Transgenic overexpression of human RBP4 or injection of RBP4 to normal mice causes insulin resistance, whereas genetic deletion of Rbp4 enhances insulin sensitivity [72]. These observations have been extended to humans [73], where RBP4 has been found to be elevated in subjects with impaired fasting glucose tolerance or type 2 diabetes mellitus and to be independently related to sex and fasting plasma glucose concentrations, clinical variables with known association to insulin resistance [74]. However, other researchers have pointed out profound differences between rodents and humans as regards the regulation of adipose and circulating RBP4 [75]. In fact, RBP4 was found to be highly expressed in isolated and mature human fat cells at the same time as being secreted by differentiating human adipocytes. In contrast to the seminal observations in mice, RBP4 mRNA was shown to be downregulated in white adipose tissue of obese women with similar circulating RBP4 concentrations in normal weight, overweight and obese patients [75]. RBP4 was observed to correlate positively with GLUT4 expression in WAT independently of other obesity-associated variables. Additionally, a modest weight loss of 5% slightly decreased adipose RBP4 expression, but was not accompanied by significant changes in circulating concentrations [75]. These findings challenge the notion that glucose uptake by adipocytes plays a dominant role in the regulation of RBP4 in humans.

VISCERAL AND SUBCUTANEOUS ADIPOSE TISSUE AS POTENTIAL THERAPEUTIC TARGETS OF THE METABOLIC SYNDROME

It is well characterized that visceral obesity is associated with an increased risk of incident metabolic syndrome with weight loss improving all risk factors associated with this syndrome. Effective weight loss can be achieved by behavioural changes oriented towards reducing food intake and increasing physical activity in order to attain a negative energy balance [76]. Weight loss drugs, such as orlistat and sibutramine, have been shown to reduce visceral obesity and improve the derangements of the metabolic syndrome [77, 78]. Rimonabant, a selective cannabinoid type 1 receptor blocker, has been also shown to reduce body weight and improve cardiovascular and metabolic risk factors in overweight and obese patients with type 2 diabetes mellitus [79]. On the other hand, bariatric surgery has become an effective alternative for morbid obese patients with previous failure to conventional treatment [80]. Noteworthy, the effectiveness of the surgical approach in improving glucose metabolism and other features of the metabolic syndrome is remarkable both in the short- and long-term [81]. On the other hand, it has been speculated that high expression levels of α2-adrenoceptors in subcutaneous adipose tissue of subjects with lower body obesity may exert a marked contribution to the resistance of subcutaneous fat loss during very-low-calorie diets and during slimming programs including physical activity [82, 83]. The physiological stimulation of α2-adrenoceptors during exercise-induced sympathetic nervous system activation contributes to the blunted lipolysis observed in the subcutaneous depot of obese subjects [84]. Thus, locally acting or orally administered α2-adrenoceptor antagonists (i.e. phenolamine or yohimbine) have been considered as a plausible strategy to optimize lipid mobilization in subjects with lower body obesity that are following low-calorie diets combined with exercise regimens [13, 82].

The dysregulation of the expression profile of adipokines merits further investigation to design novel pharmacological approaches to combat the metabolic syndrome [85]. For example, an increased adiponectin production or action should be supposedly beneficial in the treatment of insulin resistance and atherosclerosis. In this sense, TZDs [oral antidiabetic agents that increase insulin-sensitivity via the stimulation of peroxisome proliferator activating receptor γ (PPARγ)], have been shown to increase adiponectin expression in human visceral adipose tissue [86]. Pharmacological modulation of adipocyte function including upregulation of adiponectin and down-regulation of proinflammatory factors, such as IL-6, TNF-α or leptin, might also represent promising strategies for the treatment of the metabolic syndrome. Undoubtedly, adipose tissue represents a primary target for pharmacological and life-style intervention approaches to ameliorate the metabolic syndrome.

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