Metabolic alterations following visceral fat removal and expansion
Beyond anatomic location

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Increased visceral adiposity is a risk factor for metabolic disorders such as dyslipidemia, hypertension, insulin resistance and type 2 diabetes, whereas peripheral (subcutaneous) obesity is not. Though the specific mechanisms which contribute to these adipose depot differences are unknown, visceral fat accumulation is proposed to result in metabolic dysregulation because of increased effluent, e.g., fatty acids and/or adipokines/cytokines, to the liver via the hepatic portal vein. Pathological significance of visceral fat accumulation is also attributed to adipose depot/adipocyte-specific characteristics, specifically differences in structural, physiologic and metabolic characteristics compared with subcutaneous fat. Fat manipulations, such as removal or transplantation, have been utilized to identify location dependent or independent factors that play a role in metabolic dysregulation. Obesity-induced alterations in adipose tissue function/intrinsic characteristics, but not mass, appear to be responsible for obesity-induced metabolic dysregulation, thus “quality” is more important than “quantity.” This review summarizes the implications of obesity-induced metabolic dysfunction as it relates to anatomic site and inherent adipocyte characteristics.

Introduction

The distribution of accumulating adipose tissue varies among individuals but can generally be classified as lower body, abdominal subcutaneous (underneath the skin), overall coverage or visceral fat (located in the abdominal cavity among organs) (Fig. 1). Obesity-related adverse health consequences, however, are less related to total body fat deposition, and more strongly associated with a precise fat distribution. More specifically, lower body1 and abdominal subcutaneous2-4 fat accumulation are associated with reduced metabolic perturbations whereas upper body fat distribution and increased visceral fat,5-8 is associated with metabolic dysregulation. Metabolic disorders associated with upper body/visceral obesity include dyslipidemia,9 hypertension,10,11 insulin resistance and type 2 diabetes.12,13 Though the mechanisms for this connection remain to be elucidated the negative consequences of visceral fat are commonly attributed to fat mass, location and/or adipocyte specific physiology.

Adipose Tissue Location

Approximately 85% of total adipose tissue mass, in lean or obese humans, is subcutaneous while the remaining 15% constitutes intra-abdominal fat, including both visceral and retroperitoneal adipose depots.14 Visceral fat, encompassing mesenteric and omental adipose depots (Fig. 1), only constitutes ~10% of total body fat,14 yet has the highest associated risk for metabolic dysregulation. Visceral obesity is presumed to predispose individuals to adverse health consequences based on its anatomical site and venous drainage to the liver; i.e., insulin-sensitive hepatocytes are directly exposed to the metabolites and secretory products released by visceral adipocytes into the portal vein.15-17 Because substrate delivery is a major determinant of both hepatic gluconeogenesis and very low-density lipoprotein (VLDL) synthesis,18 an increased volume of visceral fat, and subsequent release of fatty acids, glycerol and lactate in addition to numerous adipokines and pro-inflammatory cytokines directly into the portal vein would be expected to have a major influence on these hepatic processes.

Chronic exposure of the liver to elevated free fatty acids promotes liver gluconeogenesis,17,18 reduces enzymes involved in fatty acid oxidation and increases fat storage and synthesis in the liver19,21 and insulin resistance.21 Elevated fatty acid flux to the liver also decreases hepatic insulin binding and degradation.22 This results in systemic hyperinsulinemia23 and additional attenuation of insulin suppression of hepatic glucose production (i.e., hepatic insulin resistance).24 In addition, fatty acids facilitate hepatic glucose production by providing a continuous source of energy and substrate.24 Overall, an excess lipid load to the liver can result in ectopic lipid accumulation and development or exacerbation of insulin resistance.23,25 The insulin resistance associated with these processes in turn amplifies the metabolic effects of obesity by increasing dyslipidemia.26

Though visceral obesity is associated with an increase in post-prandial27 and post-absorptive28 systemic fatty acid concentration, and portal vein fatty acid concentration appears to increase proportionally with visceral fat accumulation29 (Fig. 2), some
suggested visceral obesity is not the principal initiator of metabolic dysfunction. Alternative observations propose obesity-induced pathophysiology of the liver may be due to the limited ability of subcutaneous adipose tissue to store excess energy. In obese humans it is estimated that the subcutaneous adipose depot supplies the majority of free fatty acids in the portal and systemic circulation. Indeed, some estimate that only 5–20% of the portal vein fatty acid concentration originates from visceral adipose tissue. While factors other than visceral fat are likely involved in obesity-related metabolic disturbances, these data imply that the strong association of visceral fat and metabolic dysfunction involves multiple secreted factors.

Adipokine/cytokine effluent to the hepatic portal vein is also proposed to play a role in the adverse health consequences resulting from visceral adipose tissue expansion. Common adipocytokines proposed to contribute to insulin resistance of the liver include adiponectin, leptin, resistin, tumor necrosis factor (TNF)-α and interleukin (IL)-6 (Fig. 2). Adiponectin is a modulator of numerous metabolic processes such as glucose regulation and fatty acid metabolism. It is considered an anti-diabetic, anti-atherogenic and anti-inflammatory peptide that is highly associated with systemic insulin sensitivity. Unlike the majority of adipokines, adiponectin secretion and receptor expression within the liver are inversely associated with increasing adipose tissue mass and non-alcoholic steatohepatitis. However, obesity-induced alterations in portal vein adiponectin do not appear to be different than arterial adiponectin as a marker of hepatic metabolic dysregulation. Although both leptin and resistin can induce insulin resistance, these effects do not appear to be due to differences in portal vein and systemic concentration.

Another consequence of expanding adipose tissue mass is increased production of proinflammatory molecules released from adipocytes and/or infiltrating macrophages. Obesity is characterized by elevations in several proinflammatory cytokines, including TNF-α and IL-6, and these cytokines have been linked to impairments in insulin action in liver, muscle and adipose tissue. Though systemic blood concentrations of TNF-α are increased in obesity, portal vein concentrations are not different than those measured in the peripheral artery. Some studies suggest, that TNF-α in blood of humans, unlike rodents, is not secreted at measurable levels. Instead of inducing alterations systemically, TNF-α modulates insulin sensitivity locally within adipocytes and stimulates expression of other adipocytokines like leptin and IL-6 and also increases the release of fatty acids. Though portal and systemic TNF-α concentration do not appear to be different, when detectable, TNF-α induced alterations in local adipose depot factors may contribute to portal vein increases in other adipocytokines. Alternatively, IL-6 in obese humans is ~50% higher in the portal vein than in the peripheral artery, thus is a potential mechanistic link between adipose depot anatomical site and obesity-induced adverse health consequences. Overall, further research is needed to clarify the direct effects of visceral fat pad expansion on hepatic and extra-hepatic metabolic regulation and the extent to which these effects are mediated by molecules secreted into the portal vein.

Figure 1. Description of body fat distribution in humans. Lower body: fat storage around the buttocks, hips and thighs. Abdominal subcutaneous: subcutaneous fat storage around the stomach and chest. Overall coverage: fat accumulation in the arms, breast, thighs, buttocks, lower back and breast. Visceral: intra-abdominal fat deposition among organs such as the intestines, stomach, liver and pancreas. Fat distributed within the visceral cavity is highly associated with obesity-related health consequences whereas other fat distribution is not.
Adipose tissue depots display distinct structural, physiologic and metabolic characteristics. Thus, it has been proposed that distinct biologic properties of native adipocytes contribute to the association between visceral fat and metabolic dysregulation. Since adipose tissue has been recognized as an endocrine organ that secretes numerous proteins that modify metabolism, much of the research has focused on depot-specific differences in adipocyte cytokine release. Because the production of most adipocyte cytokines is increased in the adipose tissue of obese individuals, it has been proposed that differential protein secretion accounts for the divergent metabolic consequences of visceral vs. subcutaneous fat. Obesity increases many adipocyte cytokines, but only a few have been demonstrated to be consistently different between adipose depots (Fig. 2). For example, leptin and adiponectin gene expression and release appear to be higher in subcutaneous adipose tissue compared with visceral. Conversely, cytokine expression, specifically IL-6, IL-8, PAI-1, MCP-1 and Visfatin, appears to be greater in visceral fat compared with subcutaneous (for a review see ref. 51). Metabolic characteristics also differ between visceral and subcutaneous adipose tissue depots (Fig. 2). For example, human studies have demonstrated a higher turnover of triglyceride in the upper body compartment compared with lower body fat. These differences are presumably due to higher triglyceride/fatty acid turnover in visceral adipocytes compared with subcutaneous fat due, at least in part, to a combination of increased lipolysis and decreased sensitivity to the antilipolytic effects of insulin. Consistent with this observation are studies that have examined the metabolic properties of isolated visceral adipocytes. In comparison with subcutaneous adipocytes, adipocytes isolated from visceral fat were characterized by higher rates of catecholamine-induced lipolysis, increased expression of β-1, -2 and -3 adrenergic receptors, and reduced responsiveness to the cAMP-lowering effects of α-adrenergic agonists. Consequently, although obesity appears to be associated with reduced expression of hormone-sensitive lipase and increased expression of lipoprotein lipase and fatty acid synthase, these proteins are all higher in visceral adipose tissue when compared with subcutaneous. In addition, in obese humans there is a direct inverse correlation between the antilipolytic effect of insulin
and the amount of visceral adipose tissue, but not with subcutaneous adipose tissue or waist-hip-ratio (WHR), suggesting that antilipolytic signaling mechanisms are less active in visceral fat cells. In humans, local infusion of insulin into the visceral region suppresses lipolysis, but only at a higher concentration than is effective in non-visceral adipose tissue.\textsuperscript{63} In vitro studies confirm that visceral adipocytes are less responsive to the antilipolytic effect of insulin than are subcutaneous adipocytes.\textsuperscript{64,65} Visceral fat has a lower binding affinity for insulin\textsuperscript{66} and reduced insulin receptor substrate (IRS)-1 protein expression compared with subcutaneous adipocytes.\textsuperscript{65}

Other intrinsic and extrinsic differences between adipose tissue depots may also modify gene expression and metabolism in adipocytes. Some proposed intrinsic influences include mean adipocyte size, adipocyte expansion capacity and cell heterogeneity. Increased visceral adipocyte size is linked to adipose tissue dysfunction, inflammation, adipocyte apoptosis, systemic lipotoxicity and subsequent decline in metabolic parameters\textsuperscript{67-69} whereas an increase in adipocyte size in subcutaneous adipose tissue is not.\textsuperscript{70} Visceral fat is also characterized by a reduced capacity for differentiation\textsuperscript{71} and increased susceptibility to apoptotic stimuli\textsuperscript{69} compared with subcutaneous fat. Other factors currently receiving attention include variations in connective tissue, macrophages, immune cells and stromovascular cells.\textsuperscript{72,73} Extrinsic factors which may play a role in the metabolic complications associated with increased visceral fat mass include angiogenic capacity and innervation.\textsuperscript{74,75} Overall, current research demonstrates that visceral adipose tissue is morphologically and functionally different than subcutaneous. The precise mechanisms responsible for adverse health consequences of expanding visceral fat, however, still remain unclear.

**Identifying the Link between Visceral Fat and Deleterious Metabolic Outcomes through Fat Manipulation**

**Lipectomy (fat removal) studies.** Selective reduction in intra-abdominal adipose tissue improves metabolic profile. More specifically, intra-abdominal lipectomy reverses insulin resistance and glucose intolerance in obese, aged and young rodents.\textsuperscript{76-81} Though controversial in humans,\textsuperscript{82,83} omental fat removal improves insulin action,\textsuperscript{84,85} whereas removal of non-visceral fat has no effect.\textsuperscript{86} Conflicting results among human omentectomy studies likely occur because outcome measurements are not consistent or sensitive enough to detect metabolic improvements. In addition, if omentectomy is combined with gastric bypass, the accelerated weight loss due to bypass could mask the beneficial effects of omental fat removal. While several studies have investigated lipectomy-induced alterations in insulin action, glucose tolerance and even adipokines, mechanisms by which these improvements occur remain unclear. Research suggests, however, that alterations in free fatty acids and adipocyte/cytokines may play prominent roles in fat removal-induced improvements in insulin signaling and glucose homeostasis.\textsuperscript{76-81}

There is another, often forgotten or overlooked, consequence of lipectomy. In both humans and rodents there are fat removal-induced compensatory increases in non-excised adipose tissue depots. There is evidence that human liposuction increases body fat in non-excised areas\textsuperscript{87,88} and there is a preponderance of evidence that lipectomy induces compensatory increases in rodents.\textsuperscript{89-97} Several studies have found that compensatory increases in fat mass result from both larger mean fat cell size and increased adipocyte number.\textsuperscript{90,91,97} Hence, enhanced insulin sensitivity following fat removal may not be dictated by fat removal alone and may be based in part on compensatory increases of non-excised fat depots. Further, lipectomy results in decreased norepinephrine turnover in non-excised adipose tissue pads,\textsuperscript{100} implying that decreased sympathetic tone may contribute to lipectomy-induced compensatory increases of fat mass by means of promoting lipid accretion through decreased basal lipolysis. Independent studies indicate that a reduction of norepinephrine release to adipose tissues results in increased fat accumulation in adipocytes.\textsuperscript{98,101} Sensory innervation is hypothesized to initiate compensatory lipid increases via informing the brain of alterations in lipid reserves and consequently adjusting lipid storage (for a review see ref. 102).

Previous lipectomy studies in rodents are somewhat limited in that there is an ambiguity as to whether excised fat was in fact attached to the portal drainage to the liver. As an example, epididymal white adipose tissue (EWAT) is in an intra-abdominal location in rats and mice that allows for fast and simple removal, thus many researchers have considered epididymal fat to be a visceral depot. However, because of its drainage into the systemic circulation, EWAT should not be considered a visceral depot.\textsuperscript{103} In addition, EWAT has no human equivalent, making it more appropriate to conduct lipectomy studies that manipulate actual visceral adipose tissue such as mesenteric and omental WAT (MWAT and OWAT).

**Transplantation studies.** Recent studies have begun to investigate metabolic alterations following transplantation of adipose tissue. Investigation of morphological and physiological changes in the transplanted adipocytes between lean and genetically obese mice revealed that abnormalities of obese-derived adipose tissue are due to extrinsic and not intrinsic factors.\textsuperscript{104} That report, however, was limited in that the actual effects of adipose tissue transplantation on overall physiology were negated due to small tissue-sample size. Additional studies later demonstrated that physiological changes can be revealed after transplantation using larger amounts of adipose tissue. The ability of larger amounts of adipose tissue to survive after removal and insertion to another site has been repeatedly demonstrated in humans by reconstructive and plastic surgeries termed autologous fat transplantation.\textsuperscript{105} Only recently have the effects of added body fat been scrutinized.\textsuperscript{106} Successful transplantation of physiologically meaningful amounts of subcutaneous adipose tissue in mice and Siberian hamsters is associated with revascularization and normal appearance both macro- and microscopically.\textsuperscript{107-110} Fat transplantation has not been observed to lead to compensatory decreases in total body fat suggesting that body fat regulation is a system biased toward rectifying decreases but not increases in lipid storage capacity.\textsuperscript{109,110}
A seminal study utilizing adipose tissue transplantation to define the role adipose tissue physiology plays in insulin resistance and type 2 diabetes used a paradoxical approach via a lipoatrophic (low fat mass) recipient. This study demonstrated that the addition of normal subcutaneous adipose tissue to lipoatrophic mice reversed hyperphagia, insulin resistance, hepatic steatosis and hypoleptinemia, suggesting that lack of adipose tissue caused the metabolic abnormalities. The mechanisms leading to these improvements, however, are unknown but may involve enhanced free fatty acid uptake by adipocytes and muscle and increased circulating leptin.

The connection among increased visceral fat mass, insulin resistance and type 2 diabetes is well documented. However, the contribution of increased intra-abdominal fat mass vs. obesity-induced functional modifications in adipose tissue metabolism is currently being defined. Transplantation of adipose tissue from lean donor rodents to the intra-abdominal cavity of a lean recipient, thus mimicking visceral obesity, is a standard model used to characterize these differences. Although human data predicts that increased visceral fat mass is a fundamental problem in obesity-related metabolic disorders, data from rodent studies support an alternative view. Intra-abdominal transplantation of adipose tissue of non-visceral origin in most cases has beneficial effects on metabolism. In addition, implantation of specific fat depots produces cell-autonomous distinctive changes in glucose tolerance and insulin sensitivity. Mechanisms for these beneficial improvements are uncertain but do not appear to involve changes in inflammatory cytokines, adipokines (e.g., adiponectin, leptin or resistin) or free fatty acids. Only one of the previous studies placed the transplanted tissue in a manner that allowed for maximal revascularization proximal to the portal vein. The others sutured transplants to the visceral side of the peritoneum on the anterior abdominal wall, with a high probability that revascularization would occur through the abdominal wall and thus the systemic circulation. All previous studies drew blood from the systemic circulation. Therefore, future studies should utilize approaches that result in transplanted tissue that is vascularized by vessels that deliver blood directly into the hepatic portal drainage and blood sampling from both the portal vein and systemic circulation. In support of such an approach, recent studies have demonstrated that transplantation of non-visceral (e.g., subcutaneous) fat into the visceral cavity improves glucose tolerance and enhances hepatic insulin sensitivity, in part, via decreased portal vein lipid concentrations and consequently reduced liver fat storage. However, at least one study, using similar techniques, observed impaired glucose tolerance and hepatic insulin resistance, implicating IL-6 as the mechanism for dysregulation. Overall, these data suggest that visceral fat mass per se is not the mechanism linking visceral fat to obesity-related metabolic disorders. The link between visceral fat and insulin resistance likely involves inherent differences in the metabolic behavior of visceral fat. This suggests that the “quality” of fat plays a larger role than the “quantity” in the development of obesity-related metabolic diseases.

Conclusions

Increased visceral adiposity is an associated risk factor of metabolic disorders; research also suggests it is the origin. Metabolic improvement following decreases in visceral adipose tissue mass, but not peripheral (subcutaneous) demonstrates a direct relationship between central obesity and metabolic dysregulation. The connection, however, cannot exclusively be attributed to location providing visceral adipose depot adipocytes structure, physiologic and metabolic characteristics are different than subcutaneous adipose depot. Fat addition mimicking visceral obesity, via transplantation, does not impair metabolic function, but rather improves it, thus implies specific obesity-induced dysfunction of visceral adipocytes. Indeed, intrinsic properties of adipocytes, regardless of location, are responsible for metabolic dysregulation. In accord, obesity-induced alterations in adipose tissue function rather than mass are responsible for the adverse metabolic consequences of obesity. Hence, increased intra-abdominal fat mass is not necessary for the development of insulin resistance. In addition, to completely understand how adipocyte intrinsic characteristics regulate obesity-induced metabolic dysregulation the role of extrinsic factors (i.e., hormones, growth factors, vasculature, sympathetic/sensory innervation and cross-talk with associated organs) should be investigated as well. Alterations in the extrinsic environment following fat removal or transplantation have yet to be investigated, though fat manipulation causes great changes between adipocytes, vasculature and nerves. Overall, identification of regionally secreted or extrinsic factors may provide targets for treatments to prevent or reverse co-morbidities associated with obesity.

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