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Impact of Increased Adipose Tissue Mass on Inflammation, Insulin Resistance, and Dyslipidemia

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Abstract

Obesity is associated with increased prevalence of metabolic disorders, such as inflammation, insulin resistance, and dyslipidemia, which can predispose an individual to develop diabetes and cardiovascular disease. Adipose tissue (AT) is now recognized as a metabolically active organ that controls plasma free fatty acid levels and contributes to systemic metabolic homeostasis by secreting adipokines. In obesity, the recruitment of immune cells, such as T-cells and macrophages, to AT causes inflammation, which is thought to contribute to local insulin resistance. This loss of insulin sensitivity within AT can lead to uncontrolled release of fatty acids, secretion of inflammatory cytokines, and alterations in the balance of adipokines, which ultimately impact lipoprotein metabolism and insulin sensitivity systemically. Thus, AT itself plays an important role in the increased risk of diabetes and cardiovascular disease that is associated with obesity.

Introduction

Obesity has become an epidemic affecting developed and developing countries. Current reports show that over 33% of adults in the United States are obese (defined as having a body mass index [BMI] ≥ 30.0 kg/m²). Even more concerning, the prevalence of obesity is on the rise in children and adolescents. Several health problems are associated with obesity, including sleep apnea, osteoarthritis, hypertension, cancer, dyslipidemia, insulin resistance (IR), type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD). In fact, the relative risk for the latter four listed is over threefold higher in obese compared with lean individuals. Because adipose tissue (AT) plays an important role in maintaining metabolic homeostasis, this article focuses on the mechanisms by which dysregulated AT function in obesity contributes to inflammation, IR, and dyslipidemia, which ultimately promote the development of T2DM and CVD.

AT and Inflammation

It has long been known that AT in obesity is in a heightened state of inflammation; however, it was not understood until recently that macrophage infiltration into AT is a primary source of this inflammation. Seminal studies published in 2003 clearly demonstrated that the presence of macrophages in AT increases in obesity [1,2]. Since the discovery of the link between obesity and an increased number of AT macrophages (ATMs), different genetic and diet-induced obese mouse models have been used to study the development of AT inflammation. These models share a common feature: increased macrophage-derived expression of proinflammatory genes,

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such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-1 α in AT. In addition, numerous studies have shown that AT in obese humans is also characterized by increased macrophage infiltration and inflammatory cytokine expression [3•,4,5]. Furthermore, human studies have found the upregulation of cytokine expression to be linked to IR and CVD [3•]. These findings in mice and humans have led to acceptance of the concept that macrophage infiltration into AT is a cardinal feature of adipose inflammation.

Mechanisms of macrophage recruitment to AT

Extensive research is being performed to understand the factors that initiate macrophage infiltration into AT. Many possible AT-specific cells and molecules contribute to macrophage infiltration of AT, including apoptotic adipocytes, chemokines, other immune cells, leptin, and preadipocytes.

Adipocyte apoptosis—During AT expansion, hypoxia can occur due to reduced delivery of oxygen to the hypertrophic adipocytes [6]. This hypoxia can cause an increase in inflammatory cytokine production from adipocytes and can also lead to adipocyte cell death [7]. As a part of their natural role in innate immunity, macrophages can be attracted to AT to phagocytose these dead adipocytes. Cinti et al. [8] and Strissel et al. [9] used electron microscopy and immunohistochemical techniques to show that the macrophages in AT are often localized to crown-like structures that surround dead adipocytes. These are thought to have increased inflammatory cytokine and chemokine secretion that may also contribute to further macrophage recruitment, as described below.

Chemokines—Several groups have reported that MCP-1 and MCP-3 expression are upregulated in AT of genetically obese and diet-induced obese mice [10–12]. Furthermore, we have shown that western diet-fed Agouti yellow mice have a dramatic increase in MCP-1 and MIP-1 α expression in AT compared with lean controls [13]. Increased chemokine expression in AT in obesity is also found in humans. For example, Huber et al. [5] found an increase in the expression of MCP-1 and its receptor, CCR2, in AT of obese patients (BMI, 53.1 kg/m²) when compared with AT of individuals with an average BMI of 25.9 kg/m²; and that expression of two different chemokines, CCL3 and CCL5, positively correlated with fasting plasma insulin levels in obese individuals.

Evidence also exists that manipulating the chemokine system can alter ATM accumulation. Weisberg et al. [14] found that obese mice lacking CCR2 had reduced macrophage recruitment, decreased proinflammatory gene expression, and improved insulin sensitivity when compared with obese wild-type mice. Kanda et al. [10] tested three different conditions: overexpression of MCP-1 in AT, global disruption of the *MCP-1* gene, and expression of a dominant-negative MCP-1 mutant. Their results showed that MCP-1 overexpression increased macrophage infiltration and promoted IR, whereas silencing of the *MCP-1* gene or expression of a dominant-negative mutant reduced ATM recruitment and improved insulin sensitivity. Together, these data suggest that chemokine expression in AT plays an important role in macrophage recruitment to AT and the subsequent IR development. However, two other groups have reported that MCP-1-deficient mice have no difference in macrophage recruitment or systemic IR when compared with wild-type mice [15,16]. In addition, Chen et al. [12] found that CCR2 deficiency does not affect macrophage recruitment into AT. These opposing findings suggest that the role of MCP-1 and other chemokines in macrophage recruitment to AT is complicated and that many other factors may contribute to this process.

T lymphocytes—A different school of thought suggests that T-lymphocyte infiltration of AT precedes macrophage recruitment, inflammation, and IR. Kintscher et al. [17] used

immunohistochemical staining and quantitative reverse transcriptase-polymerase chain reaction to demonstrate that CD3-positive lymphocytes infiltrate AT during the first 5 weeks of high-fat diet feeding. These investigators also used insulin tolerance tests and demonstrated that the mice were already IR at this time point. Furthermore, they demonstrated that monocyte/macrophage recruitment did not occur until after 10 weeks of high-fat diet feeding, advocating that T-lymphocyte recruitment is a primary event in the development of AT inflammation and macrophage recruitment. Two other studies have also reported infiltration of T lymphocytes into AT, which was positively correlated with inflammation and IR development [18,19]. Taken together, these findings suggest that T lymphocytes may orchestrate macrophage recruitment to AT, inflammation, and IR development.

Leptin—An additional hypothesis suggests that the adipokine leptin may contribute to macrophage recruitment to AT. Increases in adiposity are positively correlated with plasma leptin levels and it is possible that leptin itself initiates ATM accumulation. As demonstrated by Curat et al. [20], leptin induces adhesion molecule expression on endothelial cells in a concentration-dependent manner, thereby contributing to monocyte diapedesis. In addition, our laboratory has shown that leptin is a potent monocyte chemoattractant in vitro at concentrations as low as 1 pg/mL [21]. More studies need to be performed to determine the relevance of these findings in vivo.

Preadipocyte transdifferentiation—A provocative hypothesis proposes the conversion of preadipocytes to macrophages. At least two studies have shown that activated preadipocytes share some functional and antigenic characteristics with macrophages [2,22]. Furthermore, Charriere et al. [22] demonstrated that preadipocytes acquired significant phagocytic activity when injected into the peritoneal cavity of mice, as well as in vitro, when cell-to-cell contacts were made between preadipocytes and peritoneal macrophages [22]. Moreover, they found that preadipocytes expressed at least five markers that are characteristic of macrophages: F4/80, Mac-1, CD80, CD86, and CD45. These findings give rise to the possibility that the first cells to initiate AT inflammation are preadipocytes with macrophage-like functions and macrophage-antigenic profiles. In disagreement with these findings, using bone marrow transplants studies of CD45.1 marrow into CD45.2 recipients, Weisberg et al. [1] demonstrated that approximately 85% of the F4/80-positive cells in AT were donor derived, whereas only 14% were recipient-derived, suggesting that most ATMs were immigrating to AT from the bone marrow [1]. It is now widely accepted that ATMs have a hematopoietic origin; however, the possibility of preadipocyte transdifferentiation contributing to initiation of recruitment of macrophages from the circulation cannot be disregarded until more comprehensive studies are performed.

Characteristics of ATMs

AT resident macrophages have been classified into two primary phenotypes: M1 “classically activated” and M2 “alternatively activated.” M1 macrophages are polarized and activated in response to stimulation by bacterial lipopolysaccharide and by interferon- γ , which is secreted by Th1 cells, and they have a proinflammatory phenotype. M2 macrophages can be further subdivided into M2a (activated upon exposure to IL-4 or IL-13), M2b (activated through lipopolysaccharide or IL-1 β in complex with immune responses), and M2c (activated by IL-10, transforming growth factor- β , or glucocorticoids) and have an anti-inflammatory phenotype [23].

Lumeng et al. [24•,25] were among the first to propose a differential activation of macrophages depending on the degree of adiposity. They found that ATMs from lean and CCR2^{-/-} obese mice expressed many genes characteristic of M2 macrophages, including Ym1, arginase 1, and IL-10. Conversely, diet-induced obesity decreased the expression of these genes and increased

the expression of proinflammatory M1 genes, such as TNF- α , IL-6, and inducible nitric oxide synthase (iNOS). Thus, these authors concluded that diet-induced obesity leads to a shift in macrophage phenotype from an anti-inflammatory M2 type to a proinflammatory M1 type, and that CCR2 plays an important role in this phenotypic switch.

The role of M1 versus M2 ATMs in controlling inflammation and IR in AT has been supported by recent studies demonstrating that peroxisome proliferator-activated receptor (PPAR)- γ and PPAR- δ are integral for induction of M2 macrophages. First, an increase in M2 markers is induced upon the activation of PPAR- γ with rosiglitazone [26,27]. Second, macrophage deficiency of PPAR- γ or PPAR- δ results in a reduction of M2 macrophages in the AT, leading to an increase in IR possibly due to the reduced presence of protective M2 macrophages [26, 28••]. Taken together, these results indicate that a higher degree of adiposity is positively correlated with increased numbers of M1 macrophages and a heightened state of inflammation and IR, whereas a lower degree of adiposity is strongly correlated with an increased number of M2 macrophages and dampened inflammation leading to improved insulin sensitivity.

AT and IR

IR is characterized by decreased insulin sensitivity in the liver and peripheral tissues and individuals with IR have a high risk for developing T2DM. It has been known for some time that inflammation in AT can contribute to IR, and more recently, it has been shown that macrophage infiltration into AT is temporally associated with IR in mice [2]. Furthermore, recent studies in obese human patients demonstrated that ATM accumulation was associated with systemic hyperinsulinemia and IR [3••]. This inflammation is thought to contribute to IR by reducing insulin sensitivity locally in AT, as well as by exerting systemic effects on insulin sensitivity in other organs.

Local effect of AT inflammation on IR

Inflammatory cytokine inhibition of insulin signaling pathways—The elevated expression of proinflammatory molecules such as TNF- α in M1 macrophages has been shown to contribute to defects in insulin signaling. TNF- α can promote IR through at least two different mechanisms: induction of lipolysis and direct inhibition of insulin signaling pathways [29]. Souza et al. [30] found that the effects of TNF α are mediated through activation of the extracellular signal-related kinase (ERK) pathway and the N-terminal-c-Jun-kinase (JNK) pathway. Both TNF- α and saturated FFAs (products of lipolysis) can alter insulin signaling by promoting phosphorylation of serine residues on the insulin receptor substrate-1, inactivating it and blocking downstream signaling events [31,32]. The effect of TNF- α on lipolysis and insulin resistance can be reversed by treatment with PPAR- γ agonists [30]. In addition to TNF- α other cytokines commonly expressed by M1 macrophages, such as IL-6 and iNOS, also have been found to blunt insulin signaling and promote subsequent IR development [33,34].

Adipocyte-macrophage crosstalk—Several experiments by Toyoda et al. [35] and Suganami et al. [36,37] have established the existence of cross-talk between adipocytes and ATMs. In co-culture experiments with 3T3-L1 adipocytes and RAW264 macrophages, they detected an upregulation of proinflammatory cytokines and a downregulation of anti-inflammatory cytokines. RAW264 macrophage-derived TNF- α caused 3T3-L1 cells to release fatty acids; whereas the saturated free fatty acid, palmitate, increased the production of TNF- α in the macrophages. Thus, they hypothesized a paracrine loop between macrophages and adipocytes whereby macrophage-secreted cytokines increase the release of adipocyte-derived fatty acids, which in turn promotes further expression of inflammatory cytokines, creating a vicious feed-forward loop. Furthermore, they provided evidence that the toll-like receptor 4/nuclear factor- κ B pathway is involved in this inflammatory cycle, and that activation of PPAR- α ameliorates the inflammatory response. Thus, these results suggest that macrophages and

adipocytes interact in a way that promotes inflammatory responses in AT that ultimately influence insulin sensitivity.

Systemic effect of AT on IR

Although it is difficult to prove a causative role of AT inflammation in systemic IR, uncontrolled lipolysis of fatty acids from adipocytes likely contributes to this condition. These nonesterified fatty acids (NEFAs) can accumulate in liver, muscle, and pancreas leading to systemic IR. Adipokines such as leptin and adiponectin may also contribute to control of ectopic lipid homeostasis. For example, leptin can reduce lipid accumulation in muscle, liver, and pancreas by upregulating fatty acid oxidation and inhibiting endogenous lipogenic pathways [38]. Adiponectin, the expression of which is inversely correlated with AT mass, can also enhance muscle fat oxidation [39]. Thus, in obesity, the increase in plasma NEFA concentrations, the resistance to leptin, and the decrease in adiponectin levels can all contribute to ectopic lipid storage resulting in IR.

AT and Dyslipidemia

Obesity is known to be associated with an increased prevalence of dyslipidemia. This is primarily characterized by elevated plasma NEFAs, triglycerides (TGs), reduced high-density lipoproteins (HDL), and the presence of small dense low-density lipoprotein (LDL). The most likely contributing factor for obesity-related dyslipidemia is uncontrolled fatty acid lipolysis from visceral AT leading to increased delivery of fatty acids to the liver to act as a substrate for very low density lipoprotein (VLDL) synthesis. The size of the adipocytes, the specific AT bed that is expanded, and the number of ATMs may be important in determining the degree to which AT contributes to dyslipidemia. Aside from NEFAs, many other potential mediators of AT-related dyslipidemia exist; however, this article focuses on altered AT production of inflammatory molecules, such as TNF- α and serum amyloid A (SAA), and the adipokine adiponectin.

AT characteristics and dyslipidemia

Adipocyte size—Obesity is associated with an increase in adipocyte size; however, at some point, the adipocytes are unable to expand sufficiently for storage of excess lipids. This causes redirection of fatty acids to the liver, promoting TG synthesis, VLDL production, and dyslipidemia. Although small adipocytes store TGs more readily, large adipocytes are characterized by an increase in lipolytic activity [40]. This lipolysis further increases circulating NEFAs and their delivery to the liver to upregulate TG synthesis.

Regional AT differences—The degree of expansion of particular AT beds is an important factor in the development of dyslipidemia. Visceral AT has greater lipolytic activity than subcutaneous AT, and fatty acids are directly delivered to the liver from this region via the portal vein. This leads to increased delivery of lipids to the liver and worsening IR in the liver, promoting TG synthesis and exacerbating dyslipidemia. Sam et al. [41] found a significant link between visceral AT and dyslipidemia in patients with T2DM. Expansion of visceral AT was associated with a greater number of VLDL and LDL particles in the circulation, even when controlling for BMI and subcutaneous AT distribution. Patients with more visceral AT also had greater concentrations of the atherogenic type of lipoprotein particles: large TG-rich VLDL, small, dense LDL, and small HDL, which have a lower capacity to transfer cholesterol esters in reverse cholesterol transport [41]. Visceral AT is also associated with greater inflammatory cytokine production [42] and lower production of adiponectin [43] when compared with subcutaneous AT, aggravating the dyslipidemia associated with obesity, as explained in the sections below.

ATM contribution to dyslipidemia—Macrophage infiltration of AT increases expression of proinflammatory cytokines, promoting an elevation of circulating NEFAs and dyslipidemia. A direct link between ATMs and dyslipidemia has been demonstrated by two groups. Canello et al. [44] found that macrophage infiltration into omental AT negatively correlated with plasma HDL cholesterol, and positively correlated with circulating TGs in obese patients. Huber et al. [5] showed that macrophage infiltration into AT was significantly greater for obese patients when compared with their lean counterparts, and the macrophage infiltration into subcutaneous AT was found to positively correlate with plasma NEFAs, and negatively correlate with HDL cholesterol. Thus, some evidence exists that ATMs can influence plasma lipoprotein profiles in humans.

AT-secreted products and dyslipidemia

It is possible that an imbalance of AT secretion of proinflammatory molecules, such as TNF- α and SAA, and anti-inflammatory molecules, such as adiponectin, may lead to impaired insulin sensitivity in AT, thus increasing the concentration of circulating NEFAs and promoting dyslipidemia.

TNF- α —The elevation in TNF- α has major implications for dyslipidemia. A relationship has been shown between plasma TNF- α and VLDL-TG concentration in healthy humans and in those with CVD [45]. This may be due to the ability of TNF- α to upregulate lipolysis, leading to increases in circulating NEFAs and their subsequent delivery to the liver promoting TG synthesis and VLDL secretion.

The effects of TNF- α on lipoprotein metabolism are most likely not just a result of elevated circulating NEFAs; this cytokine also has been shown to affect apolipoprotein (apo) B metabolism. Studies using rat hepatocytes have shown an increase in apo B transcription and VLDL secretion with TNF- α treatment [46]. Furthermore, Qin et al. [47] subjected hamsters to TNF- α infusion and reported an increased secretion of large TG-rich particles. The authors speculated that IR prevented the inhibition of microsomal TG transfer protein expression by insulin, thereby increasing the incorporation of lipid into the growing apo B100 particle, enhancing its stability and promoting elevated VLDL secretion. Qin et al. [48] also reported increased serine phosphorylation of IRS-1 and elevated apo B48 production in the intestine of TNF- α -infused hamsters, which would further increase plasma TGs and exacerbate dyslipidemia associated with IR.

SAA—SAA is an acute-phase protein that is produced in response to inflammation primarily in the liver, but also in AT, intestinal epithelial cells, and macrophages, and is found to circulate in association with HDL [49]. SAA expression in AT is elevated with obesity, and elevated SAA expression in AT has been shown to be associated with greater concentrations in the plasma [50]. Elevated SAA expression has implications for promoting dyslipidemia by affecting the inflammatory nature of the AT environment and by directly impacting HDL structure and function. Chen et al. [51] demonstrated a reduction in PPAR- γ expression and an increase in TNF- α expression in porcine adipocytes treated with SAA. This could lead to an increase in lipolysis, creating an elevation in circulating NEFAs and contributing to dyslipidemia associated with obesity and IR. In addition to SAA's direct effects on AT, the SAA concentration on HDL can exceed that of apo A1, leading to various alterations in HDL function. These include interfering with cholesterol delivery from HDL to the liver [52] and increasing retention of HDL on vascular proteoglycans [53]—thus inhibiting their ability to promote reverse cholesterol transport.

Adiponectin—Elevated adiponectin levels are associated with improvements in lipoprotein metabolism. Cnop et al. [54] demonstrated an inverse relationship between adiponectin and

plasma TG levels and small, dense LDL, and a positive relationship with plasma HDL cholesterol independent of abdominal fat and degree of IR. Many of the positive effects of adiponectin on insulin sensitivity and lipoprotein metabolism occur via an upregulation of adenosine 5'triphosphate-activated protein kinase (AMPK) in the liver and skeletal muscle [55]. Adiponectin activates AMPK, which inhibits acetyl coenzyme A carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis. ACC inhibition lowers the concentration of malonyl CoA, the product of this reaction. Malonyl CoA is an inhibitor of carnitine palmityl transferase 1, the rate-limiting enzyme in fatty acid β oxidation. Therefore, reduced concentration of malonyl CoA by AMPK increases fatty acid oxidation.

The increased activation of AMPK in tissues as a result of the actions of adiponectin and the subsequent reduction of circulating NEFAs has important implications for VLDL and TG metabolism. Greater skeletal muscle fatty acid oxidation decreases NEFA delivery to the liver which, along with the actions of AMPK in the liver, causes a reduction in liver TG synthesis and VLDL secretion. Adiponectin also increases lipoprotein lipase, thereby enhancing VLDL clearance and reducing plasma TG levels [56].

Adiponectin is unique from other adipokines in that AT production and plasma concentrations of adiponectin are decreased with obesity. Direct evidence for the potential of AT to impact dyslipidemia via reduced adiponectin levels derives from what is known about lipoprotein metabolism in hypoadiponectinemia. Larger, TG-rich VLDL particles, present as a result of increased TG synthesis and reduced fatty acid oxidation in hypoadiponectinemia, are lipolyzed to LDL particles that also have elevated TG content [56]. Hepatic lipase has greater affinity for these LDL particles, creating atherogenic small, dense LDL particles that are more easily oxidized and taken up by the arterial wall. Given the vast benefits of adiponectin on lipoprotein metabolism, hypoadiponectinemia that occurs with AT expansion has many negative implications.

AT as a Potential Target for Treating T2DM and CVD

Several mechanisms by which AT can contribute to the inflammation, IR, and dyslipidemia associated with obesity have been discussed. Because these three metabolic processes all can promote T2DM and CVD, AT is an ideal target for treating these devastating diseases. Some of the therapies currently used for treating IR and dyslipidemia may have their beneficial effects partially via influencing AT function. With regard to dietary intervention, fish oil supplementation is known to effectively reduce plasma TG levels. This may be in part due to its effects on reducing AT lipolysis and preventing ectopic lipid accumulation [57]. PPAR- γ agonists have long been used for treating IR, and it is possible that part of their insulin-sensitizing effects may be due to improving lipid storage in subcutaneous AT or by promoting the "alternative" activation of macrophages. In addition to these therapies already in use, potential treatments to reduce ATM accumulation are an appealing alternative. Some possibilities are 1) increasing vascularization of the growing AT to prevent adipocyte apoptosis due to hypoxia; 2) disrupting chemokine signaling pathways to delay the recruitment of new macrophages; 3) promoting emigration of macrophages from AT; or 4) inducing a phenotypic switch of the ATMs to an M2 phenotype. Thus, research into using AT as a therapeutic target for metabolic diseases holds much promise.

Conclusions

AT had long been thought to be an inert organ that simply stored excess energy. However, we now know that it plays an important role in instigating many of the metabolic consequences of obesity. In this article, we highlighted AT's role in inflammation, IR, and dyslipidemia. Although many different organ systems interact in the pathophysiology of T2DM and CVD,

increasing our knowledge of how AT contributes to these processes will enable future research to focus on AT as a therapeutic target.

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