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REVIEW: Peroxisome Proliferator-Activated Receptor γ and Adipose Tissue—Understanding Obesity-Related Changes in Regulation of Lipid and Glucose Metabolism

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Context: Adipose tissue is a metabolically dynamic organ, serving as a buffer to control fatty acid flux and a regulator of endocrine function. In obese subjects, and those with type 2 diabetes or the metabolic syndrome, adipose tissue function is altered (*i.e.* adipocytes display morphological differences alongside aberrant endocrine and metabolic function and low-grade inflammation).

Evidence Acquisition: Articles on the role of peroxisome proliferator-activated receptor γ (PPARγ) in adipose tissue of healthy individuals and those with obesity, metabolic syndrome, or type 2 diabetes were sourced using MEDLINE (1990–2006).

Evidence Synthesis: Articles were assessed to provide a comprehensive overview of how PPARγ-activating ligands improve adipose tissue function, and how this links to improvements in insulin resistance and the progression to type 2 diabetes and atherosclerosis.

Conclusions: PPARγ is highly expressed in adipose tissue, where its activation with thiazolidinediones alters fat topography and adipocyte phenotype and up-regulates genes involved in fatty acid metabolism and triglyceride storage. Furthermore, PPARγ activation is associated with potentially beneficial effects on the expression and secretion of a range of factors, including adiponectin, resistin, IL-6, TNFα, plasminogen activator inhibitor-1, monocyte chemoattractant protein-1, and angiotensinogen, as well as a reduction in plasma nonesterified fatty acid supply. The effects of PPARγ also extend to macrophages, where they suppress production of inflammatory mediators. As such, PPARγ activation appears to have a beneficial effect on the relationship between the macrophage and adipocyte that is distorted in obesity. Thus, PPARγ-activating ligands improve adipose tissue function and may have a role in preventing progression of insulin resistance to diabetes and endothelial dysfunction to atherosclerosis. **(*J Clin Endocrinol Metab* 92: 386–395, 2007)**

OBESITY HAS STRONG associations with many factors that are constituents of type 2 diabetes and the cluster of cardiovascular disease risk factors referred to as the metabolic syndrome (1). Visceral obesity (where fat is associated with internal organs), in particular, appears to be the key component that determines cardiometabolic disease (2). Body fat is stored in white adipose tissue, a network of connective tissue specialized for this purpose. Adipose tissue is increasingly recognized as a key regulator of energy balance, playing an active role in lipid storage and buffering, and synthesizing and secreting a wide range of endocrine products that may be directly involved in the pathogenesis of the complications associated with obesity (1, 3–5).

The adipocyte has been described as presiding at the "crossroads" of energy homoeostasis, inflammation, and atherosclerosis, and a growing body of research into obesity and insulin-resistant states identifies visceral white adipose tissue as a key endocrine organ in this respect (5–7).

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Abbreviations: Apo, Apolipoprotein; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NEFA, nonesterified fatty acids; PAI, plasminogen activator inhibitor; PPARγ, peroxisome proliferator-activated receptor γ; RAS, renin-angiotensin system; TIMP, tissue inhibitor of metalloproteinase; VLDL, very low-density lipoprotein.

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Adipose tissue is a heterogeneous organ that includes multiple distinct sc, intra-abdominal, and intrathoracic depots (8). The endocrine function and lipid storage/buffering capacity of adipose tissue depends upon both fat depot location and adipocyte cell morphology. In particular, omental and mesenteric adipocytes, which are the main components of visceral abdominal fat, are more endocrinologically active than sc adipocytes (2, 9–11). As a person becomes overweight because of an inappropriate lifestyle, adipose tissue becomes dysfunctional, including alterations in adipocyte morphology and metabolic activity, with visceral adipocytes particularly affected (2, 12, 13). Under these conditions, obesity is associated with marked infiltration of adipose tissue by macrophages (14, 15). These changes impair the ability of adipose tissue to control plasma nonesterified fatty acids (NEFA) and contribute to aberrant endocrine function, with multiple potential consequences in terms of metabolic dysfunction, insulin resistance, and cardiovascular disease risk (10).

Peroxisome proliferator-activated receptor γ (PPARγ) is highly expressed in adipose tissue, where it plays a central role in adipose tissue function. Because of their insulin-sensitizing properties, activators of PPARγ (*i.e.* thiazolidinediones) are widely used in the treatment of type 2 diabetes, contributing to a wealth of information regarding PPARγ function in adipose tissue and elsewhere. This review discusses the emerging role of PPARγ in the regulation and control of adipose tissue function, and considers the impact

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of interventions that target PPARγ. Although genetic defects (*e.g.* in PPARγ or its cofactors) undoubtedly contribute to an individual's susceptibility for diabetes, we will focus exclusively on the modulation of adipose function resulting from lifestyle-induced acquired obesity by PPARγ activation. Moreover, the consequences and direct actions of PPARγ activators on vascular function and atherosclerosis (reviewed extensively in Ref. 16) will not be discussed.

Adipose Tissue—Integral in Metabolic Regulation

The importance of functional fat tissue in maintaining metabolic equilibrium is well illustrated by studies in lipoatrophic animal models and humans. Fatless mice are prone to insulin insensitivity, glucose intolerance, hyperphagia, weight gain, and fatty liver, and high triglyceride and NEFA levels; however, replacing the fat through transplantation can at least partially restore these metabolic deficits and reduce weight gain (17). White adipose tissue is involved in the storage of lipids, representing the most important and efficient energy store in the human body (4). This contrasts with brown adipose tissue, which is primarily involved in thermogenesis. However, white adipose tissue is not simply a passive lipid and energy depot, and it is now becoming increasingly clear that it is a metabolically dynamic organ.

There is good evidence to suggest that adipose tissue may serve as a dynamic buffer to control fatty acid flux by maintaining the balance between suppression of NEFA release and clearance of circulating triglycerides; this process is analogous to the roles of the liver and skeletal muscle in the tight control of glucose levels (18). Thus, in the fasting state, adipose tissue releases fatty acids (to be used as a substrate by other oxidative tissues), whereas, in the fed state, the adipocyte changes to "absorb" fatty acids from the circulation (mainly from circulating triglycerides). This capacity to absorb fatty acids from the circulation gives adipose tissue a special role in protecting other tissues from excessive fatty acid flux ("fat overflow"). There are marked regional differences in this process [*i.e.* hormone-induced release of NEFA is more pronounced in visceral adipose tissue (where the lipolytic effect of catecholamines is greater and the antilipolytic effect of insulin is less), whereas spontaneous (basal) release is more pronounced in the sc area] (19). This may be relevant to the hepatic delivery of NEFA and other adipose tissue-derived factors because only the visceral adipose tissue has direct access to the portal system.

In addition to a role as a lipid buffer, adipose tissue appears to have a major endocrine function by expressing and secreting a range of metabolically active hormones, such as adiponectin, resistin, and leptin; along with a diverse range of other secreted factors, these are collectively termed "adipocytokines" or, more accurately, "adipokines" (4, 5, 20, 21). To date, more than 100 such secreted factors have been identified (21) (selected examples are summarized in Fig. 1), with recent additions, such as the proatherogenic cytokine IL-18 and novel adipokine omentin (22, 23). Visceral white adipose tissue, in general, appears to be more involved in endocrine actions than sc white or brown fat tissue (24). Many adipokines, including IL-6, IL-8, plasminogen activator inhibitor (PAI)-1), and angiotensinogen, are found at higher levels in

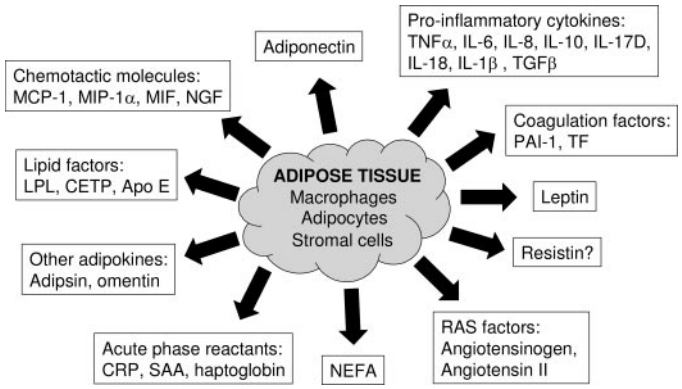

FIG. 1. Adipose tissue is a dynamic endocrine organ. Examples of secreted factors (Refs. 5 and 20–23). CETP, Cholesterol ester transfer protein; CRP, C-reactive protein; LPL, lipoprotein lipase; MIF, migration inhibitory factor; SAA, serum amyloid A; TF, tissue factor.

visceral adipose tissue (9, 25–28). However, adiponectin expression and leptin expression/release are generally higher in sc adipose tissue compared with visceral tissue (29–31). It is also worth noting that, with some exceptions, such as adiponectin and leptin, a large proportion of the release of many of these factors may be derived from cells other than adipocytes within the adipose tissue (32). Furthermore, with the exception of adiponectin (the major adipokine secreted by fat cells), all adipokines may, to varying degrees, also have nonadipose tissue sources.

The metabolically active molecules (adipokines and NEFA) released by adipose tissue may have effects on distant target tissues (*e.g.* liver, skeletal muscle, pancreas) and/or local paracrine effects in adipose tissue. They can affect immune/inflammatory processes (*e.g.* complement factors, haptoglobin, TNFα, IL-6), endocrine function (leptin, sex hormones, growth factors), metabolic function (NEFA, adiponectin, resistin), and cardiovascular function (NEFA, angiotensinogen, PAI-1, *etc.*) (3, 4, 11, 33) (Fig. 1). Adipose tissue possesses a functional renin-angiotensin system (RAS). Although a local role for angiotensinogen and angiotensin II in adipocyte development and metabolism is recognized, any possible impact of the adipose tissue RAS on blood pressure regulation remains unclear (34). Nevertheless, it does provide one potential mechanism that may underlie the link between obesity and hypertension.

One key adipokine, adiponectin, appears to be important in glucose and lipid metabolism in skeletal muscle and the liver, and acts as an insulin sensitizer (35, 36). Recent evidence also suggests that adiponectin operates as a key autocrine regulator of adipocyte secretory function, reducing the release of IL-6 and IL-8, growth-regulated oncogene-α, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1α and -1β, and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 (37). TIMPs play an important role in extracellular matrix remodeling and, hence, may be essential for adipogenesis. Therefore, it has been suggested that, by decreasing the secretion of TIMPs, adiponectin may decrease adipocyte hypertrophy and fat accumulation, and, thus, directly contribute to adipose tissue remodeling by increasing the number of smaller adipocytes (37). How variations in this and other adipokines might be

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involved in the pathophysiological processes associated with obesity is highlighted below.

The Sick Fat Cell Syndrome

Alongside an obvious increase in adipose tissue mass and potential metabolic capacity, adipose tissue function is known to be altered in obese subjects with insulin resistance and features of the metabolic syndrome. It has long been established that adipocytes display morphological differences in obesity (*i.e.* increased sc abdominal adipocyte size is evident in subjects with obesity and these larger cells are less sensitive to insulin) (13, 38). These differences in fat cell size have significant clinical consequences; larger adipocytes are associated with hyperglycemia and predict the onset of type 2 diabetes, even after adjusting for insulin resistance and percent body fat (38) (Fig. 2). It has been suggested that an increased predominance of larger adipocytes reflects a failure of adipocyte proliferation/differentiation, leaving cells susceptible to hypertrophy under conditions of NEFA oversupply (13).

In addition to changes in adipocyte phenotype, aberrant adipose endocrine and metabolic function that is not simply a consequence of increased fat metabolic capacity is also evident in insulin-resistant obesity. First, there is insensitivity to insulin-induced inhibition of lipolysis, and a diminished effect of insulin in suppressing the rate of NEFA release in obese insulin-resistant subjects and those with type 2 diabetes (12). This and other mechanisms, such as inflammatory processes (see below), may contribute to diminished NEFA buffering capacity, leading to "fat overflow," despite increased adipose tissue (18). Increased delivery of NEFA from the omental fat depot to the liver (via the portal vein) has been implicated in the development of hepatic insulin resistance and fatty liver (steatosis) (10, 39). The situation is analogous to lipodystrophy, where an absolute deficiency of adipose tissue leads to a decrease in buffering capacity, and it is noteworthy that both adipose tissue deficiency (*e.g.* in lipodystrophy) and an excess of adipose tissue (obesity) are associated with insulin resistance. Interestingly, a number of morbidly obese individuals do not become "not" insulin resistant, suggesting that their adipose tissue depots display a higher flexibility to accommodate lipids without exceeding their buffering capacity.

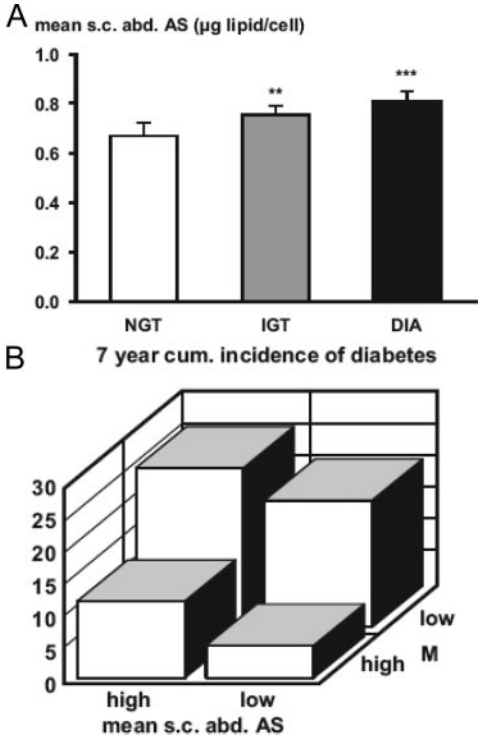

FIG. 2. Adipocyte size predicts type 2 diabetes (Ref. 38). A, Mean adipocyte diameter is higher in patients with impaired glucose tolerance and type 2 diabetes after adjusting for percent body fat. B, High baseline adipocyte diameter is associated with a higher 7-yr incidence of type 2 diabetes independent (at least in part) of baseline insulin sensitivity (M). cum, Cumulative; DIA, diabetes; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; s.c. abd AS, sc abdominal adipocyte size. [Reproduced with kind permission from Springer Science and Business Media. From Weyer C *et al.*: *Diabetologia* 43: 1498–1506, 2000, Figures 1B and 1D (38).]

Altered adipokine activity in insulin-resistant obesity

The release of adipokines is another aspect of adipose function that is altered in obesity and the abnormalities are more marked in those with abdominal visceral obesity compared with other obesity phenotypes (2). For instance, in obese states, there is a decrease in adipocyte-derived plasma adiponectin and an increase in leptin (albeit alongside leptin resistance); thus, increases in visceral adiposity alter two "insulin-sensitizing" mechanisms (7, 40). Adiponectin is the only adipokine known to be down-regulated in obesity, although hypoadiponectinemia has been more closely related to the degree of insulin resistance and hyperinsulinemia than the degree of adiposity (40). Thus, factors other than obesity *per se* (*e.g.* hyperinsulinemia and/or insulin resistance) might be major determinants of adiponectin levels. It has been suggested that the adipokine resistin, which is increased in obesity, could provide a crucial link between obesity and type 2 diabetes, with a role in the molecular mechanisms by which increased adiposity causes insulin resistance and type 2 diabetes. Treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action, while insulin-stimulated glucose uptake by adipocytes is enhanced by neutralization of resistin and is reduced by resistin treatment (41). Furthermore, resistin appears to influence adipocyte differentiation, although there are conflicting reports as to whether it inhibits or promotes this process (42, 43). Although the physiological role of resistin in humans remains unclear, a recent study shows that macrophages are the major source of this adipokine in human adipose tissue (44).

An increase in visceral adipose tissue-derived proinflammatory cytokines, such as TNFα and IL-6, in obesity is also implicated in insulin resistance, although their functions are poorly defined (7, 9, 20, 45). IL-6 appears to be released principally from visceral adipose tissue rather than sc fat (9). TNFα appears to act locally in adipose tissue, influencing the levels of other adipokines, such as PAI-1 and adiponectin (7). In addition, production of several adipocyte-derived acute phase reactants, with causal links to insulin resistance (*e.g.* serum amyloid proteins), increases in viscerally obese subjects, and, thus, they serve as indicators of systemic inflam-

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mation (5, 6, 46). Alterations in adipocyte production of factors, such as angiotensinogen, have implications for control of coagulation and normal regulation of blood pressure. Such factors, along with many of the other molecules secreted by adipose tissue (*e.g.* NEFA), may underlie the increased cardiovascular disease risk associated with increased adiposity (1, 3, 33).

This altered adipose endocrine function can also influence the circulating lipid profile. Adiponectin decreases the plasma concentration of very low-density lipoprotein (VLDL) apolipoprotein (Apo)-B in middle-aged men by increasing its rate of catabolism (47). This association is independent of the effect of insulin resistance on hepatic VLDL ApoB secretion and may result principally from the effect of adiponectin on lipid metabolism in skeletal muscle (47). This may explain why low plasma adiponectin levels are associated with atherogenic dyslipidemia [*i.e.* elevated triglycerides, low high-density lipoprotein cholesterol, and a preponderance of small dense low-density lipoprotein (LDL) particles] (47, 48).

Inflammation in obesity

The relationship between visceral adipocytes and the chronic inflammatory process of a corona of macrophages around the adipocytes may be linked to the alteration in cytokine production highlighted previously. It has become increasingly evident that there is an interrelationship between metabolic and inflammatory processes, and that obesity is linked to a state of chronic low-grade inflammation (48, 49). In particular, obesity is associated with significant infiltration of adipose tissue by macrophages (Refs. 14 and 15; for review, see Ref. 50). Many inflammation and macrophage-specific genes are dramatically and progressively up-regulated in white adipose in mouse models of obesity (15). The macrophage levels differ between fat depots, with the more metabolically active omental visceral adipose tissue containing a significantly greater number than sc adipose tissue in obese humans (51).

The precise mechanisms underlying increased macrophage infiltration into adipose tissue in obesity remain to be elucidated. Monocyte chemoattractant proteins such as MCP-1 (also known as C-C motif chemokine ligand-2) and their receptors may play a role. This protein, which is necessary for macrophage recruitment, is elevated in obesity, and mice deficient in this protein have decreases in food intake and obesity, and reduced macrophage content and inflammatory profile in adipose tissue (52). Furthermore, they exhibit increased adiponectin levels, decreased steatosis, and improved glucose homeostasis and insulin sensitivity. Furthermore, MCP-1 levels are higher in visceral adipose tissue compared with sc adipose tissue (53), and transgenic overexpression of MCP-1 in adipose tissue results in increased macrophage infiltration (54).

Adipose tissue macrophages constitute the major source of TNFα and MCP-1 in adipose tissue and express high levels of IL-6, as well as receptors for both leptin and adiponectin (50, 53). Macrophages and adipocytes share many characteristics. Both TNFα and IL-6 can induce an inflammatory phenotype in adipocytes (55), whereas adiponectin released by adipocytes may have antiinflammatory effects, such as inhibiting leptin-induced TNFα production (56). Some data also suggest that adiponectin may, in fact, have pro-inflammatory properties under some conditions, although prolonged exposure to adiponectin appears to render macrophages tolerant (57). As such, it has been predicted that cross talk is likely between macrophages and adipocytes, particularly in the more metabolically active visceral depots (58, 59). Thus, the colocalization of metabolically active adipocytes and other cell types in adipose tissue with macrophages provides an amplified paracrine environment, setting up a potential vicious cycle of inflammatory cell infiltration, cytokine production, and adipocyte dysfunction (48). One component of cross talk may involve a paracrine loop between NEFA and TNFα (60). A recent study using cocultures of adipocyte and macrophage cell lines showed that macrophage-derived TNFα increases the release of free fatty acids from adipocytes. This effect in turn induces inflammatory changes (*i.e.* an up-regulation of MCP-1, IL-6, and TNFα expression, and a down-regulation of adiponectin), at least partly through activation of MAPK (60).

Thus, macrophage infiltration into adipose tissue is observed in obesity, and many of the factors secreted by macrophages can induce inflammation in adipose tissue. Although direct evidence linking macrophages with inflammation and insulin insensitivity *per se* has been lacking, recently it has been shown directly that macrophage-secreted factors can induce inflammatory responses in adipocytes and also induce insulin insensitivity in adipocytes (*i.e.* increased lipolysis and reduced suppression of lipolysis by insulin) (61). Although the mechanisms by which inflammatory cytokines reduce insulin responsiveness are unclear, this effect is associated with increased nuclear factor κB activity (61), induction of suppressor of cytokine signaling expression (62), and stimulation of inactivating IRS-1 phosphorylation (63).

PPARγ Receptors—A Pivotal Role in Adipose Tissue Function

PPARs are nuclear receptors that function as transcriptional regulators. Although PPARγ is found in a wide variety of human tissues, it is most highly expressed in adipose tissue (64). More specifically, both the PPARγ1 and γ2 isoforms, which are derived from the same gene by alternative promoter usage and splicing, are expressed at high levels in adipocytes and macrophages (64–66). Although several lipid metabolites have been shown to activate PPARγ, their role as endogenous ligands remains unclear (67). However, the use of PPARγ agonists (thiazolidinediones) for the treatment of insulin resistance and type 2 diabetes has provided the tools and stimulus for further investigation of PPARγ function.

Clinical studies involving thiazolidinediones suggest that the direct effects of these glucose-lowering agents on adipose tissue can contribute to improvements in hepatic and peripheral insulin sensitivity, and hepatic steatosis in patients with type 2 diabetes (68–72).

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PPARγ, adipocyte morphology, and fat distribution

Based on data from *ex vivo* studies, activation of PPARγ in adipose tissue may cause apoptosis of large fat cells in visceral and/or sc fat depots from rodents and induce the differentiation of preadipocytes into mature fat cells in sc (but not visceral) fat depots from humans (73, 74), along with the up-regulation of key genes involved in lipogenesis and triglyceride storage (75, 76). *Ex vivo* studies in rats also show that thiazolidinediones induce a phenotypic change, remodeling visceral adipocytes to a smaller size with higher lipid storage potential (77) (Fig. 3). A further effect of PPARγ activation, shown *in vitro*, may also be to promote a shift to the brown *vs.* white adipose tissue phenotype (24).

At a superficial level, thiazolidinedione treatment can often be associated with some weight gain, which is most likely a combination of both increased adipocyte formation and fluid retention (78). However, this obscures the true picture, and more detailed observations reveal changes in both fat topography and adipocyte phenotype with thiazolidinedione treatment. In humans, thiazolidinediones have caused a shift of fat distribution from visceral to sc adipose depots, which is associated with improvements in both hepatic and peripheral tissue sensitivity to insulin (79, 80). Furthermore, thiazolidinediones reduce liver fat, an effect not seen with the nonthiazolidinedione insulin sensitizer, metformin (72, 81, 82). Excess liver fat may be a key factor in the development of hepatic insulin resistance and type 2 diabetes, as well as a contributor to dyslipidemia and increased cardiovascular risk (39). It has been suggested that hepatic insulin resistance could play a role in hepatic VLDL overproduction and hypertriglyceridemia; although NEFA oversupply is believed to be the main cause, it may not be sufficient to explain the high VLDL production rates seen in insulin resistance and type 2 diabetes (12). Furthermore, the metabolic dysregulation in the fatty liver results in the overproduction of a wide range of factors that may contribute to increased cardiovascular risk (glucose, lipids, PAI-1, C-reactive protein, fibrinogen, *etc.*) (39). In subjects with impaired glucose tolerance, pioglitazone, in contrast to metformin, has also been shown to reduce intramyocellular lipid accumulation, a factor that is associated with insulin resistance (83). This reduction in intramyocellular lipid was not caused by an increase in muscle lipid oxidation, but by a diversion of lipid from ectopic sites into sc adipose tissue. Thus, PPARγ activation appears to promote a shift toward more, but "better quality," fat tissue, such that, despite weight gain, there are improvements in insulin sensitivity and glycemic control, and, in the case of pioglitazone, in triglyceride levels (80). However, differential effects among different thiazolidinediones on triglyceride levels (see below) suggest that factors other than PPARγ activation may be involved.

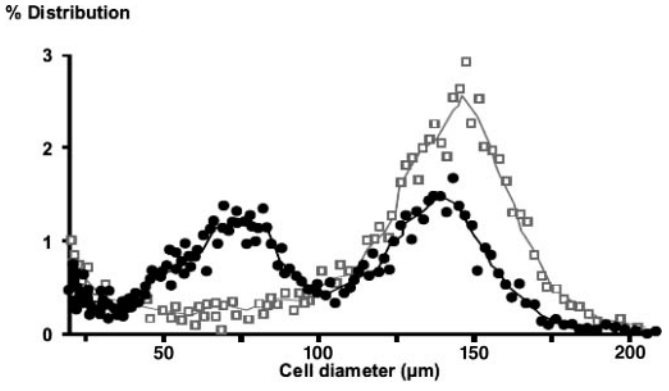

FIG. 3. Pioglitazone remodeling of visceral adipocytes to a smaller size. White adipocyte cell size in ovarian visceral fat from Zucker rats after 14-d treatment with pioglitazone (*black circles*) or vehicle (*white squares*) (Ref. 77). [Reprinted with permission from the American Diabetes Association. Copyright © American Diabetes Assocation. From de Souza CJ *et al.*: *Diabetes* 50: 1863–1871, 2001 (77).]

PPARγ and adipose-derived factors

The impact of PPARγ in adipose tissue also extends to another main area of dysfunction associated with obesity and insulin resistance, that of altered adipokine release. PPARγ activation is associated with potentially beneficial effects on the expression and secretion of a whole range of adipokines, including adiponectin, resistin, leptin, IL-6, TNFα, PAI-1, MCP-1, and angiotensinogen (84–87).

The up-regulation of adiponectin in response to PPARγ activation exposure may be a key factor. Adiponectin appears to be an important mediator of PPARγ agonist-mediated improvements in insulin sensitivity, particularly with respect to improving hepatic insulin sensitivity (88). The increase in plasma adiponectin concentration observed after thiazolidinedione therapy is strongly associated with a decrease in hepatic fat content, and improvements in both hepatic and peripheral insulin sensitivity (82) (Fig. 4). In particular, an increase in the ratio of high molecular weight to low molecular weight adiponectin strongly correlates with improvements in hepatic insulin sensitivity in response to thiazolidinedione treatment (89). Recent studies in obese adiponectin-deficient knockout mice suggest that thiazolidinedione-induced amelioration of hepatic insulin resistance is mediated via an adiponectin-dependent mechanism that involves activation of AMP-activated protein kinase (90, 91). Therefore, increases in adiponectin caused by PPARγ activation may play an important role in reversing the abnormality in hepatic fat mobilization and hepatic/muscle insulin insensitivity in people with type 2 diabetes (68, 82). Although thiazolidinediones appear to have differential effects on lipid profiles (*e.g.* pioglitazone is associated with significant improvements in triglycerides, high-density lipoprotein cholesterol, LDL particle concentration, and LDL particle size compared with rosiglitazone) (92), their impact on adiponectin levels may contribute to improvements in atherogenic lipid profile in patients with type 2 diabetes.

Therapeutic use of thiazolidinediones in patients with type 2 diabetes has also resulted in a significant decrease in plasma resistin concentration, which, in turn, positively correlates with a decrease in hepatic fat content and an improvement in hepatic insulin sensitivity (72) (Fig. 4). However, the primary origin of the circulating resistin affected by thiazolidinedione treatment in this study was not firmly established and may have included nonadipose sources. Leptin levels, on the other hand, do not appear to be influenced by thiazolidinedione treatment in patients with type 2

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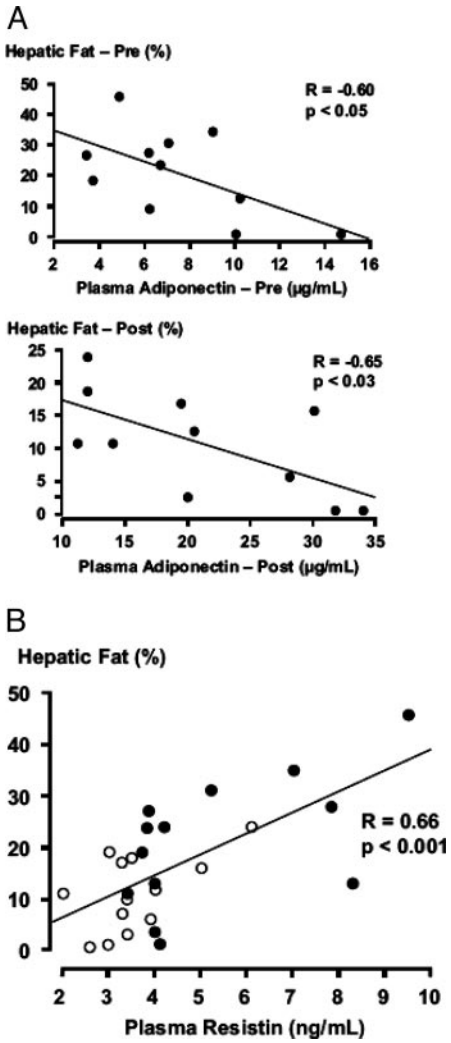

FIG. 4. Pioglitazone-induced changes in adipokines are associated with decreased hepatic fat. Increases in adiponectin (A) and decreases in resistin (B) are associated with decreased hepatic fat after 16-wk treatment with pioglitazone in patients with type 2 diabetes. A, The relationship between hepatic fat content and plasma adiponectin concentration before and after pioglitazone treatment (Ref. 82). [Reproduced with permission from The Endocrine Society © 2004. From Bajaj M *et al.*: *J Clin Endocrinol Metab* 89: 200–206, 2004.] B, The relationship between hepatic fat content and plasma resistin concentration before (*black circles*) and after (*white circles*) pioglitazone treatment (Ref. 72). [Reproduced with permission from Macmillan Publishers Ltd. From Bajaj M *et al.*: *Int J Obes Relat Metab Disord* 28: 783–789, 2004.]

diabetes (73), despite effects on leptin expression in adipocytes (86).

As expected with PPARγ activation, a reduction in plasma NEFA is a consistent observation across many large-scale thiazolidinedione clinical trials (93). This reduction in plasma NEFA also provides a potential mechanism to improve insulin sensitivity in the liver and periphery, as well as reducing lipotoxicity in the pancreatic β-cell and improving insulin secretory function (12). Accordingly, thiazolidinedione-induced decreases in NEFA correlate with improvements in both muscle and hepatic insulin sensitivity in patients with type 2 diabetes (71). A study in PPARγ± mice showed that PPARγ indirectly protects pancreatic islets from lipotoxicity by regulating triglyceride partitioning among tissues (reducing net influx of NEFA into the islets) and that thiazolidinediones can restore insulin secretion impaired by lipotoxicity (94). It is possible that β-cell protective effects of thiazolidinediones may also be mediated indirectly through reduced β-cell stress resulting from the amelioration of insulin resistance. However, based on studies in isolated human islets, there is also evidence that PPARγ activation can have direct effects on β-cell function (95–97).

The adipose tissue-related improvements seen in circulating levels of inflammatory factors, such as IL-6, TNFα, and PAI-1, with PPARγ activation may also have indirect anti-inflammatory and anticoagulant effects on the liver and vasculature, in addition to the direct effects of thiazolidinediones in those tissues (98, 99) (Fig. 5). Furthermore, the effects of thiazolidinediones on the RAS may contribute to their long-term antihypertensive effects (87), but could also have implications for vascular leakage and edema.

PPARγ, macrophages, and inflammation

PPARγ activation in macrophages inhibits the expression of a number of proinflammatory genes (14, 15, 100). These findings suggest that PPARγ functions as a negative regulator of macrophage activation (100). Thus, PPARγ activation may have beneficial effects on the relationship between the stromal macrophage and visceral adipocyte that is distorted in obesity (Fig. 6). Furthermore, as well as increasing adiponectin release from adipocytes and the ratio of high molecular weight to total adiponectin, PPARγ activation also induces the expression of the AdipoR2 adiponectin receptor in both adipocytes and macrophages (101, 102).

Thiazolidinediones and other PPARγ agonists suppress macrophage production of TNFα, IL-6, inducible nitric oxide synthase, and IL-1β induced by lipopolysaccharide and interferonα via down-regulation of their respective genes (14, 15). Although thiazolidinediones have been shown to reduce plasma TNFα levels in patients with type 2 diabetes, the exact source of this factor is unclear, and the changes do not correlate with improvements in hepatic or peripheral insulin

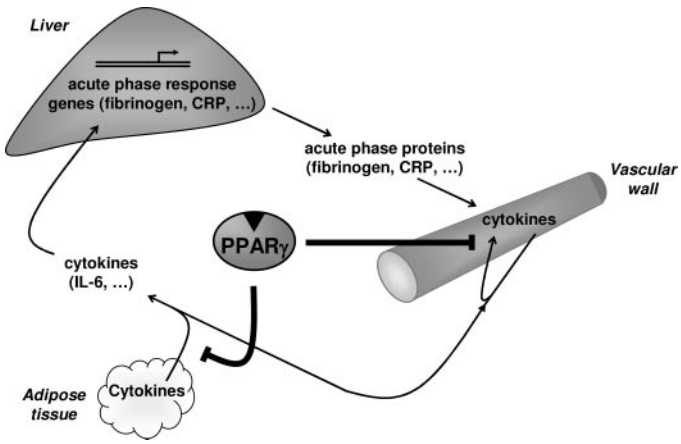

FIG. 5. PPARγ activation in adipose tissue may have indirect anti-inflammatory effects in liver and the vasculature. CRP, C-reactive protein.

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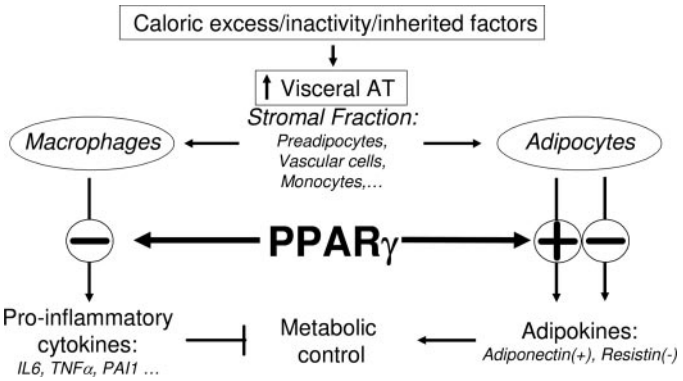

FIG. 6. PPARγ activation. Beneficial effects on both macrophages and visceral adipocytes in adipose tissue (Refs. 14, 15, 32). AT, Adipose tissue.

sensitivity (71), although this does not exclude the possibility of local effects within the adipose tissue.

In adipose tissue cultures, MCP-1 is correlated with specific macrophage markers, adiposity, and adipose tissue localization (with higher levels in visceral adipose tissue relative to sc tissue), and the relationship seems to be related to the number of adipose-resident macrophages (53). Thiazolidinediones decrease MCP-1 levels in these cultures, and similar effects are observed in clinical studies. Indeed, pioglitazone has been shown to reduce MCP-1 levels in patients with type 2 diabetes (103). Moreover, in subjects with impaired glucose tolerance, pioglitazone treatment, but not metformin, reduces expression of CD68 (a macrophage marker) and MCP-1 in adipose tissue, apparently by reducing macrophage numbers, resulting in reduced inflammatory cytokine production and improvement in insulin sensitivity (85).

Insights from animals lacking adipose PPARγ

Several innovative studies involving targeted deletion ("knockout") of these receptors in experimental animal models have assisted in understanding the function of PPARγ specifically in adipose tissue and skeletal muscle, and the secondary effects in other organs, including the liver and pancreas (both of which express low levels of PPARγ) (39, 104–108).

Targeted deletion of PPARγ in fat tissue resulted in marked reduction in the number of adipocytes, alongside a compensatory hypertrophy of the remaining cells and the appearance of a population of small adipocyte-like cells (105). In addition, it resulted in elevated levels of plasma NEFA and triglycerides, and decreased levels of plasma leptin and adiponectin. These mice were also significantly more susceptible to high-fat diet-induced steatosis (fatty liver), hyperinsulinemia, and insulin insensitivity (in fat and liver, but not muscle). Thiazolidinediones failed to reduce plasma NEFA in these animals, unlike their effect in mice with intact fat PPARγ. Similar effects on adipocyte-derived factors and steatosis were also observed in a different adipose PPARγ-deficient model (109), albeit with some differences in the effects on overall insulin sensitivity.

On the other hand, targeted deletion of muscle PPARγ suggests that muscle PPARγ is not required for the glucose-lowering effects of thiazolidinediones but, nevertheless, may play a role in the maintenance of normal adiposity, whole-body insulin sensitivity, and hepatic insulin action, a process that may involve altered lipid metabolism in muscle (106). Similarly, thiazolidinediones remained effective in nonlipoatrophic mice lacking liver PPARγ, suggesting that adipose tissue is the major site of thiazolidinedione action in typical mice with adipose tissue (104), although in the absence of adipose tissue, the liver may become a primary site of thiazolidinedione action because of the induction of PPARγ expression in this organ.

Conclusions

A combination of caloric excess, inactivity, and inherited factors are likely to contribute to changes in adipose tissue, leading to alterations in its normal function as an energy store, lipid buffer, and as a dynamic endocrine organ vital to normal metabolic homeostasis. In addition to alterations in fat metabolism, a number of adipokines (fat-derived humoral mediators of metabolic homeostasis) and inflammatory processes are altered in insulin-resistant obesity states. This inability of adipose tissue to function normally may lead to lipid accumulation and endocrine effects in other tissues, reducing their ability to function and respond normally (6), most notably with respect to insulin insensitivity in the liver and periphery.

PPARγ has emerged as a key regulator of adipocyte and macrophage function in adipose tissue. Direct effects of PPARγ activation on adipose tissue lipid metabolism and endocrine function may be linked with secondary benefits in liver and muscle lipid metabolism and insulin signaling, and suggest that PPARγ is an important target for pharmacotherapy to tackle the metabolic syndrome and obesity related insulin resistance (110, 111). Furthermore, activation of PPARγ in adipose tissue may also have positive effects on pancreatic β-cell function and vascular inflammation, and help to minimize the aggravated paracrine relationship between adipocytes and macrophages seen in obesity.

Thus, adipose PPARγ appears to be an essential mediator for the maintenance of whole body insulin sensitivity; adipose PPARγ protects nonadipose tissue against lipid overload and guarantees appropriate production of adipokines, such as adiponectin and leptin from adipocytes (108, 110). PPARγ ligands promote the restoration of normal levels of adipose-derived substances, including NEFA, TNFα, leptin, adiponectin, and PAI-1. Thus, PPARγ ligands reverse major defects of the insulin resistance syndrome and have important effects that inhibit atherosclerosis, improve endothelial cell function, and attenuate inflammation.

An excess of visceral adipose tissue increases the risk for a number of conditions, including coronary artery disease, hypertension, dyslipidemia, and type 2 diabetes. Although more research is needed, current data suggest that PPARγ activating ligands improve adipose tissue function, and may prevent the progression of both insulin resistance to diabetes and endothelial dysfunction to atherosclerosis.

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