White Adipose Tissue: Beyond Fat Storage

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Introduction

Adipose is a loose connective tissue that fills up space between organs and tissues and provides structural and metabolic support. In humans, adipose tissue is located beneath the skin (subcutaneous fat), around internal organs (visceral fat), in bone marrow (yellow bone marrow) and in the breast tissue. Apart from adipocytes, which comprise the highest percentage of cells within adipose tissue, other cell types are also present, such as preadipocytes, fibroblasts, adipose tissue macrophages, and endothelial cells. Adipose tissue contains many small blood vessels as well. In the skin it accumulates in the deepest level, the subcutaneous layer, providing insulation from heat and cold.

White adipocytes store lipids for release as free fatty acids during fasting periods; brown adipocytes burn glucose and lipids to maintain thermal homeostasis. A third type of adipocyte, the pink adipocyte, has recently been characterized in mouse subcutaneous fat depots during pregnancy and lactation [1].

Pink adipocytes are mammary gland alveolar epithelial cells whose role is to produce and secrete milk. Emerging evidence suggests that they are derived from the transdifferentiation of subcutaneous white adipocytes. All mammals possess both white and brown adipose tissues. White adipocytes contain a single large lipid droplet occupying about 90 % of the cell volume. The nucleus is squeezed to the cell periphery and the cytoplasm forms a very thin rim. The organelles are poorly developed; in particular mitochondria are small, elongated and have short, randomly organized cristae. Because of these ultrastructural characteristics, these cells are also called unilocular adipocytes [2].

Brown adipose fat cells are smaller in size and quantity and derive their color from the high concentration of mitochondria for energy production and vascularization of the tissue. These mitochondria contain a unique uncoupling protein 1 (UCP1), that supports the thermogenic function of brown adipocytes These cells are also called multilocular adipocytes [3].

The lipid in brown fat is burned to provide high levels of energy as heat in animals who hibernate and infants who may need additional thermal protection. The concept of white adipose tissue as an endocrine organ originated in 1995 with the discovery of leptin and its wide-ranging biological functions [4]. 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 fashion but also affect more than one metabolic pathway [5–7].

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To maintain normal body functions, each adipocyte secretes diverse cytokines and bioactive substances into the surrounding environment which act locally and distally through autocrine, paracrine and endocrine effects. Although each adipocyte produces a small quantity of adipocytokines, as adipose tissue is the largest organ in the human body, their total amount impacts on body functions. Furthermore, as adipose tissue is supplied by abundant blood stream adipocytokines released from adipocytes pour into the systemic circulation. In obesity the increased production of most adipokines impacts on multiple functions such as appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and haemostasis, all of which are linked with cardiovascular disease. Obesity, associated with unfavourable changes in adipokine expression such as increased levels of Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), resistin, Plasminogen Activator Inhibitor (PAI-1) and leptin, and reduced levels of adiponectin affect glycemic homeostasis, vascular endothelial function and the coagulation system, thus accelerating atherosclerosis. Adipokines and a 'low-grade inflammatory state' may be the link between the metabolic syndrome with its cluster of obesity and insulin resistance and cardiovascular disease.

Table 1.1 Important adipokines

Adipokines	Metabolic functions
Leptin	Improves insulin sensitivity, inhibits lipogenesis, increases lipolysis, satiety signals
Adiponectin	Improves insulin sensitivity, increases fatty acid oxidation, inhibits gluconeogenesis
Adipsin	Inhibits lipolysis, increases fatty acid re-esterification, triglyceride storage in adipose cells
IL-6	Impairs appetite, inflammation, insulin resistance, increases hepatic fatty acid synthesis
TNF	Inflammation, insulin resistance, reduces adiponectin synthesis
PAI-1	Inhibits activity of tissue type plasminogen activator
Resistin	Insulin resistance, endothelial dysfunction?
Angiotensinogen	Significantly correlated with hypertension
Aromatase	Driving fat to subcutaneous and breast tissues by converting androstenidione to estrone
11Beta HSD	Synthesizes cortisol from cortisone

Adipokines and Their Metabolic Function

See Table 1.1.

Leptin

Leptin, a 16-kDa adipocyte-derived cytokine is synthesized and released from fat cells in response to changes in body fat. It is encoded by a gene called *ob* (from obesity mice), and was named leptin from the Greek word meaning thin. Leptin circulates partially bound to plasma proteins and enters the CNS by diffusion through capillary junctures in the median eminence and by saturable receptor transport in the choroid plexus. In the hypothalamus, leptin binds to receptors that stimulate anorexigenic peptides such as proopiomelanocortin and cocaine- and amphetamine-regulated transcript and inhibits orexigenic peptides, e.g. neuropeptide Y and the agouti gene-related protein [8].

Leptin reduces intracellular lipid levels in skeletal muscle, liver and pancreatic beta cells, thereby improving insulin sensitivity. There is strong evidence showing that the dominant action of leptin is to act as a 'starvation signal'. Leptin declines rapidly during fasting, and triggers a rise in glucocorticoids, and reduction in thyroxine (T4), sex and growth hormones [9]. Moreover, the characteristic decrease in thermogenesis during fasting and postfast hyperphagia is mediated, at least in part, through a decline in leptin. Therefore, leptin deficiency could lead to hyperphagia, decreased metabolic rate and changes in hormone levels, designed to restore energy balance [10].

In patients with lipodystrophy and leptin deficiency, leptin replacement therapy improved glycemic control and decreased triglyceride levels. In a recent study, nine female patients (age range, 15–42 years; eight with diabetes mellitus) with lipodystrophy and serum leptin levels under 4 ng/ml (0·32 nmol/ml) received r-metHuLeptin (recombinant leptin) subcutaneously twice a day for 4 months at escalating doses, in order to achieve low, intermediate and high physiological leptin replacement levels. During treatment, serum leptin levels increased and glycosylated haemoglobin decreased in the eight patients with diabetes. Four months therapy reduced average triglyceride levels by 60 % and liver volume by a mean of 28 % in all nine patients and led to suspension of, or to a substantial reduction in, antidiabetes medication. Self-reported daily caloric intake and resting metabolic rate also decreased significantly [11]. Similar results were observed in three severely obese children with no functional leptin [12]. LEPR null humans are hyperphagic, morbidly obese and fail to undergo normal sexual maturation [13]. Furthermore, these patients did not respond to thyrotropin-releasing hormone and growth hormone releasing hormone testing, suggesting leptin also plays a critical role in neuroendocrine regulation [13].

Leptin Resistance Syndrome

The concept of 'leptin resistance' was introduced when increased adipose leptin production was observed in obese individuals who were not leptin-deficient. Apart from mutations in the leptin receptor gene, the molecular basis of leptin resistance has yet to be determined [14, 15].

A large prospective study – the West of Scotland Coronary Prevention Study (WOSCOPS) – showed, for the first time, that leptin might be an independent risk factor for coronary heart disease. At baseline, plasma leptin levels were significantly higher in 377 men (cases) who experienced a coronary event during the 5-year follow-up period than in 783 male controls, matched for age and smoking history who did not suffer a coronary event and who were representative of the entire WOSCOPS cohort [16].

Leptin and Neuroendocrine Functions

In addition to its effects on energy homeostasis, leptin regulates neuroendocrine function and traditional endocrine systems. Leptin deficiency in Lepob/Lepob mice is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and suppression of the hypothalamic-pituitary-thyroid and -gonadal axes. Leptin decreases hypercortisolemia in Lepob/Lepob mice, inhibits stress-induced secretion of hypothalamic CRH in mice, and inhibits cortisol secretion from rodent and human adrenocortical cells *in vitro*. The role of leptin in HPA activity in humans *in vivo* remains unclear. Leptin also normalizes suppressed thyroid hormone levels in leptin-deficient mice and humans, in part via stimulation of TRH expression and secretion from hypothalamic TRH neurons [14, 17]. Leptin replacement during fasting prevents starvation-induced changes in the hypothalamic-pituitary-gonadal and –thyroid axes in healthy men [18]. Leptin accelerates puberty in normal mice and restores normal gonadotropin secretion and reproductive function in leptin-deficient mice and humans as well has direct effects via peripheral leptin receptors in the ovary, testis, prostate, and placenta [19].

Several other important endocrine effects of leptin include regulation of immune function, hematopoiesis, angiogenesis, and bone development. Leptin normalizes the suppressed immune function associated with malnutrition and leptin deficiency [20].

It also promotes proliferation and differentiation of hematopoietic cells, alters cytokine production by immune cells, stimulates endothelial cell growth and angiogenesis, and accelerates wound healing [21, 22].

Adiponectin

Adiponectin is highly and specifically expressed in differentiated adipocytes and circulates at high levels in the bloodstream [23]. Its expression is higher in subcutaneous than visceral adipose tissue [24]. Adiponectin is an approximately

30-kDa polypeptide containing an Nterminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal globular domain [25–28]. It shares strong sequence homology with type VIII and X collagen and complement component C1q, termed adipocyte complement-related protein because of its homology to complement factor C1q. A strong and consistent inverse association between adiponectin and both insulin resistance and inflammatory states has been established [23, 29]. Plasma adiponectin declines before the onset of obesity and insulin resistance in nonhuman primates, suggesting that hypoadiponectinemia contributes to the pathogenesis of these conditions [30]. Adiponectin levels are low with insulin resistance due to either obesity or lipodystrophy, and administration of adiponectin improves metabolic parameters in these conditions [28, 31]. Conversely, adiponectin levels increase when insulin sensitivity improves, as occurs after weight reduction or treatment with insulin-sensitizing drugs [23, 29].

Several mechanisms for adiponectin's metabolic effects have been described. In the liver, adiponectin enhances insulin sensitivity, decreases influx of NEFAs, increases fatty acid oxidation, and reduces hepatic glucose output. In muscle, adiponectin stimulates glucose use and fatty acid oxidation. Within the vascular wall, adiponectin inhibits monocyte adhesion by decreasing expression of adhesion molecules, inhibits macrophage transformation to foam cells by inhibiting expression of scavenger receptors, and decreases proliferation of migrating smooth muscle cells in response to growth factors. In addition, adiponectin increases nitric oxide production in endothelial cells and stimulate angiogenesis. These effects are mediated via increased phosphorylation of the insulin receptor, activation of AMPactivated protein kinase, and modulation of the nuclear factor B pathway [23, 29]. Taken together, these studies suggest that adiponectin is a unique adipocyte-derived hormone with antidiabetic, anti-inflammatory, and anti-atherogenic effects. Adiponectin also has antiatherogenic properties, as shown *in vitro* by its inhibition of monocyte adhesion to endothelial cells, macrophage transformation to foam cells (through down-regulation of scavenger receptors and endothelial cell activation (through reduced production of adhesion molecules and inhibition of tumour necrosis factor α (TNF-α) and transcriptor factor nuclear factor kappa beta (NF-κβ) [32, 33]. Insulin resistance in lipoatrophic mice was fully reversed by a combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone [34]. This suggesting that adiponectin and leptin work together to sensitize peripheral tissues to insulin. However, because globular adiponectin improves insulin resistance but not obesity in *ob*/*ob* leptin-deficient mice, adiponectin and leptin appear to have distinct, albeit overlapping, functions [35]. Two receptors for adiponectin have been cloned. Adipo R1 and Adipo R2 are expressed predominantly in muscles and liver. Adiponectin-linked insulin sensitization is mediated, at least in part, by activation of AMPK in skeletal muscles and the liver, which increases fatty-acid oxidation and reduces hepatic glucose production [33]. Interleukin (IL) 6 and TNF-α are potent inhibitors of adiponectin expression and secretion in human white adipose tissue biopsies or cultured adipose cells [36, 37]. Unlike most adipokines, adiponectin expression and serum concentrations are reduced in obese and insulin-resistant states. *In vivo*, high plasma adiponectin levels are associated with reduced risk of myocardial infarction (MI) in men as demonstrated in a case control study that enrolled 18,225 subjects without cardiovascular disease who were followed up for 6 years [38]. Although further studies are needed to clarify whether adiponectin independently predicts coronary heart disease events, in men with Type 2 diabetes, increased adiponectin levels are associated with a moderately decreased risk of coronary heart disease. The association seems to be mediated in part by the effects of adiponectin on high-density lipoprotein (HDL) cholesterol, through parallel increases in both. Although many mechanisms have been hypothesized, exactly how adiponectin affects HDL cholesterol remains largely unknown. In American Indians, who are particularly at risk of obesity and diabetes, adiponectin does not correlate with the incidence of coronary heart disease [39, 40]. Two case control studies in

obesity-prone Pima Indians and in Caucasians suggest that individuals with high adiponectin concentrations are less likely to develop Type 2 diabetes than those with low concentrations [41, 42].

Tumor Necrosis Factor- α

TNF-α is a 26-kDa transmembrane protein that is cleaved into a 17-kDa biologically active protein that exerts its effects via type I and type II TNF-α receptors. Within adipose tissue, TNF α is expressed by adipocytes and stromovascular cells [24]. TNF-α, a multipotential cytokine with several immunologic functions, was initially described as a cause of tumour necrosis in septic animals and associated with cachexia-inducing states, such as cancer and infection [43]. In 1993 it was the first product from adipose secreted tissue to be proposed as a molecular link between obesity and insulin resistance [44–47]. Several potential mechanisms for TNF- α's metabolic effects have been described. First, TNF- α influences gene expression in metabolically important tissues such as adipose tissue and liver. In adipose tissue, TNF-α represses genes involved in uptake and storage of NEFAs and glucose, suppresses genes for transcription factors involved in adipogenesis and lipogenesis, and changes expression of several adipocyte secreted factors including adiponectin and IL-6. In liver, TNF-α suppresses expression of genes involved in glucose uptake and metabolism and fatty acid oxidation and increases expression of genes involved in *de novo* synthesis of cholesterol and fatty acids. Second, TNF α impairs insulin signaling. This effect is mediated by activation of serine kinases that increase serine phosphorylation of insulin receptor substrate-1 and −2, making them poor substrates for insulin receptor kinases and increasing their degradation [46]. TNF-α also impairs insulin signaling indirectly by increasing serum NEFAs, which have independently been shown to induce insulin resistance in multiple tissues [45].

A recent elegant hypothesis suggested that in obese rats TNF-α production from the fat cuff around the arteriole origin inhibits insulin-stimulated nitric oxide synthesis and results in unopposed vasoconstriction - a mechanism termed 'vasocrine' signalling [48]. These findings suggest a homology between vasoactive periarteriolar fat and visceral fat, which may explain relationships among visceral fat, insulin resistance and vascular disease. Several mechanisms could account for the effect of TNF-α on obesity-related insulin resistance such as increased release of FFA by adipocytes, reduced adiponectin synthesis and impaired insulin signalling. *In vitro* and *in vivo* studies show TNF-α inhibition of insulin action is, at least in part, antagonized by TZD, further supporting the role of TNF-α in insulin resistance [49]. Acute ischemia also increases TNF-α level. A nested case control study in the Cholesterol and Recurrent Events (CARE) trial compared TNF-α concentrations in case and control groups. Overall, TNF-α levels were significantly higher in cases than controls. The excess risk of recurrent coronary events after MI was predominantly seen among patients with the highest TNF-α levels [50].

Interleukin-6

IL-6, secreted by many cell types, including immune cells, fibroblasts, endothelial cells, skeletal muscle and adipose tissue, is another cytokine associated with obesity and insulin resistance [51]. However, only about 10 % of the total IL-6 appears to be produced exclusively by fat cells [52]. Omental fat produces threefold more IL-6 than subcutaneous adipose tissue, and adipocytes isolated from the omental depot also secrete more IL-6 than fat cells from the subcutaneous depot [53]. IL-6 circulates in multiple glycosylated forms ranging from 22 to 27-kDa in size. The IL-6 receptor (IL-6R) is homologous to the leptin receptor and exists as both an approximately 80-kDa membrane-bound form and an approximately 50-kDa soluble form. A complex consisting of the ligand-bound receptor and two homodimerized transmembrane gp130 molecules triggers intracellular signaling by IL-6. Within adipose tissue, IL-6 and IL-6R are expressed by adipocytes and adipose tissue matrix [24].

Expression and secretion of IL-6 are 2 to 3 times greater in visceral relative to sc adipose tissue [24, 54]. In contrast to TNF α, IL-6 circulates at high levels in the bloodstream, and as much as one third of circulating IL-6 originates from adipose tissue. Adipose tissue IL-6 expression and circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance. Both expression and circulating levels decrease with weight loss. Furthermore, plasma IL-6 concentrations predict the development of type 2 diabetes and cardiovascular disease and MI [55, 56]. Weight loss significantly reduces IL-6 levels in adipose tissue and serum. While as administration of IL-6 to healthy volunteers increased blood glucose in a dose-dependent manner probably by inducing resistance to insulin action [57].

Inhibition of insulin receptor signal transduction in hepatocytes might underlie the effects of IL-6 on insulin resistance. This could be mediated, at least in part, by suppression of cytokine signalling-3 (SOCS-3), increased circulating FFA (from adipose tissue) and reduced adiponectin secretion [58, 59].

It is interesting to note the central role of IL-6 in energy homeostasis. IL-6 levels in the CNS are negatively correlated with fat mass in overweight humans, suggesting central IL-6 deficiency in obesity. Central administration of IL-6 increases energy expenditure and decreases body fat in rodents. Furthermore, transgenic mice overexpressing IL-6 have a generalized defect in growth, which includes reduced body weight and decreased fat pad weights [60]. On the other hand, mice with a targeted deletion of IL-6 develop mature-onset obesity and associated metabolic abnormalities, which are reversed by IL-6 replacement, suggesting that IL-6 is involved in preventing rather than causing these conditions [61]. Hence, IL-6 has different effects on energy homeostasis in the periphery and the CNS.

Adipocyte Trypsin

Adipocyte trypsin (ADIPSIN) is a secreted serine protease related to complement factor D. In humans, adipose tissue also releases substantial amounts of acylation-stimulating protein (ASP), a protein derived from the interactions of ADIPSIN with complement C3 and factor B. Although ASP is known to stimulate triglyceride storage in adipose cells through stimulation of glucose transport, enhancement of fatty acid re-esterification and inhibition of lipolysis the receptor and signalling pathways mediating ASP effects have not yet been characterized [62]. ASP influences lipid and glucose metabolism via several mechanisms. ASP promotes fatty acid uptake by increasing lipoprotein lipase activity, promotes triglyceride synthesis by increasing the activity of diacylglycerol acyltransferase, and decreases lipolysis and release of NEFAs from adipocytes. ASP also increases glucose transport in adipocytes by increasing the translocation of glucose transporters and enhances glucose-stimulated insulin secretion from pancreatic β cells [63]. Most, but not all studies in humans report substantial increases in plasma ASP in obese subjects although it has still to be established whether these high circulating levels reflect increased ASP activity or resistance to ASP [64]. Resistance to ASP could redirect fatty acid flux away from adipose tissue towards the liver [63].

Resistin

Human resistin (resistance to insulin) is a dimeric protein containing 108 amino acids Holocomb et al. first described the gene family and its tissue-specific distribution, identifying a protein (FIZZ1) that was up-regulated in the asthmatic lung in bronchoalveolar lavages of mice with experimentally induced asthma [65]. Found in inflammatory zone 1, FIZZ1 is also known as resistin-like molecule a (RELMα). One of two homologues, FIZZ2, also known as RELMβ, was localized in proliferating epithelia at the base of intestinal crypt. A third homologue, FIZZ3, also known as 'resistin' or adipocyte-specific secretory factor was later identified. As TZD suppresses resistin production in 3 T3-L1 adipocytes, Steppan *et al*. suggested resistin could be a link between obesity and insulin resistance [66].

Initial studies suggested that resistin had significant effects on insulin action, potentially linking obesity with insulin resistance [67]. Treatment of cultured adipocytes with recombinant resistin impairs insulin-stimulated glucose uptake whereas antiresistin antibodies prevent this effect [66, 68]. In murine models, obesity is associated with rises in circulating resistin concentrations. Resistin increases blood glucose and insulin concentrations and impairs hypoglycaemic response to insulin infusion [69].

In obese mice, antiresistin antibodies decrease blood glucose and improve insulin sensitivity [70]. All these data support the hypothesis that in obese rodents, resistin induces insulin resistance and contributes to impaired insulin sensitivity.

In humans, the physiological role of resistin is far from clear and its role in obesity and insulin resistance and/or diabetes is controversial. In humans, as resistin is primarily produced in peripheral blood monocytes and its levels correlate with IL-6 concentrations, the question of its inflammatory role has been raised [68, 71, 72]. Four genes encode for resistin in the mouse and two in humans [73]. The human resistin gene is localized on chromosome 19. Some genetic case control studies demonstrated genetic variations in the resistin gene are associated with insulin resistance and obesity in humans [74–76].

Plasminogen Activating Inhibitor (PAI)-1

Plasminogen activating inhibitor (PAI)-1, synthesized in the liver and in adipose tissue, regulates thrombus formation by inhibiting the activity of tissue-type plasminogen activator, an anticlotting factor. PAI-1 serum concentrations increase with visceral adiposity decline with caloric restriction, exercise, and weight loss and metformin treatment [77]. Visceral tissues secrete significantly more PAI-1 than subcutaneous tissues from the same subject [78]. Plasma PAI-1 levels are elevated in obesity and insulin resistance, are positively correlated with features of the metabolic syndrome, and predict future risk for type 2 diabetes and cardiovascular disease [79, 80]. Plasma PAI-1 levels are strongly associated with visceral adiposity, which is independent of other variables including insulin sensitivity, total adipose tissue mass, or age. Weight loss and improvement in insulin sensitivity due to treatment with metformin or thiazolidinediones (TZDs) significantly reduce circulating PAI-1 levels.

Proteins of the Renin Angiotensin System (RAS)

Several proteins of the classic RAS are also produced in adipose tissue. These include renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin receptors type I (AT1) and type 2 (AT2), angiotensin-converting enzyme (ACE) etc. Expression of AGT, ACE, and AT1 receptors is higher in visceral compared with subcutaneous adipose tissue [81–83]. Angiotensin II mediates many of the well-documented effects of the RAS including increasing vascular tone, aldosterone secretion from the adrenal gland, and sodium and water reabsorption from the kidney, all of which contribute to blood pressure regulation. Thus, the adipose tissue RAS is a potential link between obesity and hypertension. Inhibition of the RAS, either by inhibition of ACE or antagonism of the AT1 receptor decreases weight and improves insulin sensitivity in rodents. Although several large randomized trials have shown that ACE inhibitors reduce the incidence of Type 2 diabetes, a direct effect of RAS inhibition on insulin sensitivity in humans has been observed in some studies but not others [84]. In addition to its well-known effects on blood pressure, the RAS influences adipose tissue development. Components of the RAS such as AGT and angiotensin II are induced during adipogenesis . Angiotensin II promotes adipocyte growth and differentiation, both directly by promoting lipogenesis and indirectly by stimulating prostaglandin synthesis [81]. Increased AGE production could also contribute to enhanced adipose mass because angiotensin II is believed to act locally as a trophic factor for new adipose cell formation. In human adipose tissue, aromatase

activity is principally expressed in mesenchymal cells with an undifferentiated preadipocyte phenotype [85].

Enzymes Involved in the Metabolism of Corticosteroids

Although the adrenal gland and gonads serve as the primary source of circulating steroid hormones, adipose tissue expresses a full arsenal of enzymes for activation, interconversion, and inactivation of steroid hormones [86, 87]. Several steroidogenic enzymes are expressed in adipose tissue including cytochrome P450-dependent aromatase, 3 β hydroxysteroid dehydrogenase (HSD), 3 α HSD, 11 β HSD1, 17 β HSD, 7 α hydroxylase, 17α hydroxylase, 5 α reductase, and UDP-glucuronosyltransferase 2B15.

Given the mass of adipose tissue, the relative contribution of adipose tissue to whole body steroid metabolism is quite significant, with adipose tissue contributing up to 100 % of circulating estrogen in postmenopausal women and 50 % of circulating testosterone in premenopausal women [86, 87]. The sexually dimorphic distribution of adipose tissue in humans has implicated sex steroids in the regulation of adiposity and body fat distribution. Premenopausal females tend to have increased lower body or subcutaneous adiposity, whereas males and postmenopausal females tend to have increased upper body or visceral adiposity. Expression of 17 β HSD is decreased relative to aromatase in subcutaneous adipose tissue but increased relative to aromatase in visceral adipose tissue. The ratio of 17 β HSD to aromatase is positively correlated with central adiposity, implicating increased local androgen production in visceral adipose tissue.

White adipose tissue also plays a role in glucocorticoid metabolism [88, 89].

This tissue specific glucocorticoid metabolism is primarily determined by the enzyme 11 β HSD1, which catalyzes the conversion of hormonally inactive 11 β ketoglucocorticoid metabolites (cortisone in humans and 11-dehydrocorticosterone in mice) to hormonally active 11 β hydroxylated metabolites (cortisol in humans and corticosterone in mice).

Although 11 β HSD1 amplifies local glucocorticoid concentrations within adipose tissue, it does not contribute significantly to systemic glucocorticoid concentrations. Tissue-specific dysregulation of glucocorticoid metabolism by 11 β HSD1 has been implicated in a variety of common medical conditions including obesity, diabetes, hypertension, dyslipidemia, hypertension, cardiovascular disease, and polycystic ovarian syndrome [88, 89]. In human idiopathic obesity, 11 β HSD1 expression and activity are also decreased in liver and increased in adipose tissue and are highly correlated with total and regional adiposity. Finally, pharmacological inhibition of 11 β HSD1 in humans increases insulin sensitivity suggesting a potential therapeutic role for 11 β HSD1 inhibition in the treatment of obesity and insulin resistance [90, 91].

Adipokines and Atherosclerosis

Adipokines play a significant role in the pathogenesis of atherosclerosis. TNF-α activates the transcription factor nuclear factor-κβ, with subsequent inflammatory changes in vascular tissue. These include increased expression of intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, which enhances monocyte adhesion to the vessel wall, greater production of MCP-1 and M-CSF from endothelial cells and vascular smooth muscle cells and up-regulated macrophage expression of inducible nitric oxide (NO) synthase, interleukins, superoxide dismutase, etc. [92–97]. Leptin, especially in the presence of high glucose, stimulates macrophages to accumulate cholesterol [98]. IL-6 exerts proinflammatory activity in itself and by increasing IL-1 and TNF-α. Importantly, IL-6 also stimulates liver production of C-reactive protein, which is considered a predictor of atherosclerosis. IL-6 may also influence glucose tolerance by regulation of visfatin. Visfatin, a newly discovered adipocytokine in the human visceral fat, exerts insulin-mimetic effects in cultured cells and lowers plasma glucose levels in mice through activation of the insulin receptor [97]. PAI-1 concentrations,

which are regulated by the transcription factor nuclear factor-κβ, are abnormally high in hyperglycaemia, obesity and hypertriglyceridaemia, because of the increased PAI-1 gene expression [99]. PAI-1 inhibits fibrin clot breakdown, thereby favouring thrombus formation upon ruptured atherosclerotic plaques [100]. In humans, circulating PAI-1 levels correlate with atherosclerotic events and mortality, and some studies suggest PAI-1 is an independent risk factor for coronary artery disease [101]. Angiotensinogen is a precursor of angiotensin II (AngII), which stimulates ICAM-1, VCAM-1, MCP-1 and M-CSF expression in vessel wall cells [102]. AngII also reduces NO bioavailability with loss of vasodilator capacity and with increased platelet adhesion to the vessel wall [103]. Furthermore, endothelial dysfunction is indicative of the preclinical stages of atherosclerosis and is prognostic of future cardiovascular events [104, 105]. Therefore, high concentrations of proinflammatory adipokines may contribute to development of endothelial dysfunction and accelerate the process of atherosclerosis.

Conclusion

The traditional role attributed to white adipose tissue is energy storage. Now it is proven that the white adipose tissue is a major secretory and endocrine organ involved in a range of functions beyond simple fat storage. Adipose tissues secrete adipokines which perform various functions. However, the metabolic effects of adipokines are a challenging and an emerging area of research and in-depth understanding of their pathophysiology and molecular actions will undoubtedly lead to the discovery of effective therapeutic interventions. Reducing adipose tissue mass will prevent the metabolic syndrome, atherosclerosis and cardiovascular events. Despite the new findings in the field of adipokines, researchers are still led to focus back on obesity as an essential primary target in the continued effort to reduce the risk of developing the metabolic syndrome and Type 2 diabetes, challenges of this millennium, with its associated cardiovascular complications.

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