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Adipose tissue, adipokines, and inflammation

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White adipose tissue is no longer considered an inert tissue mainly devoted to energy storage but is emerging as an active participant in regulating physiologic and pathologic processes, including immunity and inflammation. Macrophages are components of adipose tissue and actively participate in its activities. Furthermore, cross-talk between lymphocytes and adipocytes can lead to immune regulation. Adipose tissue produces and releases a variety of proinflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines, such as TNF- α , IL-6, monocyte chemoattractant protein 1, and others. Proinflammatory molecules produced by adipose tissue have been implicated as active participants in the development of insulin resistance and the increased risk of cardiovascular disease associated with obesity. In contrast, reduced leptin levels might predispose to increased susceptibility to infection caused by reduced T-cell responses in malnourished individuals. Altered adipokine levels have been observed in a variety of inflammatory conditions, although their pathogenic role has not been completely clarified. (*J Allergy Clin Immunol* 2005;115:911-9.)

Key words: Obesity, inflammation, immunity, cytokines, adipokines, insulin resistance, adipose tissue

OBESITY, ADIPOSE TISSUE, AND INFLAMMATION

The incidence of obesity and associated comorbidities is dramatically increasing worldwide in both children and adults. The obese state is characterized by what has been called low-grade systemic inflammation. In fact, inflammatory markers, such as C-reactive protein (CRP) and IL-6, are increased in obese individuals compared with lean subjects, although not to the same extent observed

Abbreviations used

BMI:	Body mass index
CRP:	C-reactive protein
CVD:	Cardiovascular disease
FIZZ:	Found in inflammatory zone
IBD:	Inflammatory bowel disease
ICAM-1:	Intracellular adhesion molecule 1
MCP-1:	Monocyte chemoattractant protein 1
NF- κ B:	Nuclear factor κ B
PBEF:	Pre-B-cell colony-enhancing factor
RA:	Rheumatoid arthritis
RELM:	Resistin-like molecule
WAT:	White adipose tissue

in classic inflammatory conditions. The presence of systemic inflammation has been linked to the increased risk of development of cardiovascular disease (CVD) and type II diabetes in obesity, particularly in the case of visceral adiposity.¹ Epidemiologic evidence of this rising tide of obesity and associated pathologies has led, in the last decade, to a dramatic increase of research on the role of adipose tissue as an active participant in controlling the body's physiologic and pathologic processes. The current view of adipose tissue is that of an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism, and inflammation and immunity.

This review will focus on the role of adipose tissue and adipokines in modulating inflammation and immunity.

INTERACTIONS BETWEEN ADIPOCYTES AND IMMUNE-INFLAMMATORY CELLS

Macrophages are present in adipose tissue and increased in obesity

Adipose tissue can be divided into 2 major types: white adipose tissue (WAT) and brown adipose tissue. WAT represents the vast majority of adipose tissue in the organism and is the site of energy storage, whereas the main role of brown adipose tissue is nonshivering thermogenesis, particularly in small mammals and human neonates. WAT is composed of many cell types, adipocytes being the most abundant. The other cell types present in

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WAT are included in the stromovascular fraction, of which approximately 10% are CD14⁺CD31⁺ macrophages.² The number of macrophages present in WAT is directly correlated with adiposity and with adipocyte size in both human subjects and mice, with no significant differences present between subcutaneous and visceral WAT.²⁻⁴ Higher numbers of WAT macrophages are present in female than in male mice, but it is currently unknown whether the same holds true for human subjects.⁵

Although clear similarities between macrophages and adipocytes have been reported and preadipocytes can differentiate into macrophages, these 2 cell types are actually distinct.⁶ In mice bone marrow chimeras experiments have demonstrated that WAT macrophages are bone marrow derived, indicating that macrophages present in adipose tissue do not derive *in situ* from differentiation of preadipocytes but rather from circulating monocytes infiltrating WAT.³ Incubation with adipocyte-conditioned medium increases expression of the adhesion molecules intracellular adhesion molecule 1 (ICAM-1) and platelet-endothelial cell adhesion molecule 1 in endothelial cells and induces adhesion and transmigration of blood monocytes, an effect mimicked by high doses of the adipokine leptin.² It is also possible that chemokines such as monocyte chemoattractant protein 1 (MCP-1), which is expressed by adipocytes and the levels of which correlate with adiposity, might contribute to monocyte recruitment into WAT.⁷ In obese mice WAT macrophages form multinucleated giant cells reminiscent of those present in granulomas, suggesting an activated phenotype.⁴

Circulating levels of TNF- α and IL-6 are directly correlated with adiposity and insulin resistance.⁸ Macrophages are the major source of TNF- α produced by WAT and contribute approximately 50% of WAT-derived IL-6.³

In summary, WAT of obese individuals contains an increased number of macrophages compared with that of lean persons, and these macrophages appear to be activated, both from a morphologic (giant cells) and a functional (cytokine production) standpoint (Fig 1).

Interactions between adipose tissue and lymphocytes

Although lymphocytes are not a constituent of WAT, there is often a close physical proximity between lymphocytes and WAT, particularly in lymph nodes, which are generally surrounded by pericapsular adipose tissue. Data indicate the presence of intriguing 2-way paracrine interactions between lymphocytes and adjacent adipocytes.⁹ The potential importance of evaluating the interactions between WAT and lymphocytes in the context of immunity is underlined by the observation that in mice protective immunization against *Helicobacter felis* is associated with adipokine upregulation, as well as the presence of (mostly T) lymphocytes in WAT surrounding the stomach.¹⁰ Despite these observations and the well-established demonstration that leptin is an important modulator of T-cell function, the evaluation of interactions

between lymphocytes and adipocytes has not yet received the full attention it deserves.

ADIPOKINES

Adipokines are proteins produced mainly by adipocytes. Although adipose tissue secretes a variety of factors, only leptin and adiponectin (and possibly resistin, adipisin, and visfatin) are primarily produced by adipocytes and can therefore be properly classified as adipokines.

Leptin

Leptin is a 16-kd protein encoded by the *ob* gene.¹¹ Adipocytes are the most important source of leptin, and circulating leptin levels directly correlate with adipose tissue mass.¹² Control of appetite is the primary role of leptin. In fact, mice with a mutation in the leptin (*ob/ob* mice) or leptin receptor (*db/db* mice) gene, as well as human subjects with mutations in the same genes, are massively obese. Excellent reviews have been published on the effects of leptin in regulating appetite and other physiologic functions.^{13,14}

Leptin's role in regulating immunity has been fueled by early observations of thymus atrophy in *db/db* mice. Since its cloning in 1994, many details of leptin's effects on the immune and inflammatory response have been clarified. Below, we briefly summarize these effects; for more details, the reader is referred to recent reviews that specifically deal with this topic.¹⁵⁻¹⁷ Leptin protects T lymphocytes from apoptosis and regulates T-cell proliferation and activation. Leptin also influences cytokine production from T lymphocytes, generally switching the phenotype toward a T_H1 response. Of note, cytokine production from T lymphocytes is suppressed in leptin-deficient children and restored by leptin administration.¹⁸ In addition to its effects on T lymphocytes, leptin also influences monocyte activation, phagocytosis, and cytokine production. Signal transduction pathways activated by leptin in immune cells include the Janus kinase-signal transducer and activator of transcription system (particularly signal transducer and activator of transcription 3), as well as phosphatidylinositol 3-kinase and mitogen-activated protein kinase. In endothelial cells leptin induces oxidative stress and upregulation of adhesion molecules.

In experimental animals inflammatory stimuli acutely induce leptin mRNA and increase serum leptin levels; however, this is not always true in human subjects.¹⁵ Most of the *in vivo* studies on the immune-modulating effects of leptin have been generated by using leptin-deficient *ob/ob* mice. In this setting leptin deficiency is associated with reduced inflammation in models of autoimmune disease but also with increased susceptibility to bacterial and viral infections.¹⁹⁻²⁴ These are likely consequences of the immune-activating effects of leptin. However, leptin deficiency is also associated with increased susceptibility to the toxicity of proinflammatory stimuli, such as endotoxin and TNF- α , an effect that might be mediated by leptin's activity on the kidney.²⁵⁻²⁷ Nevertheless, the general

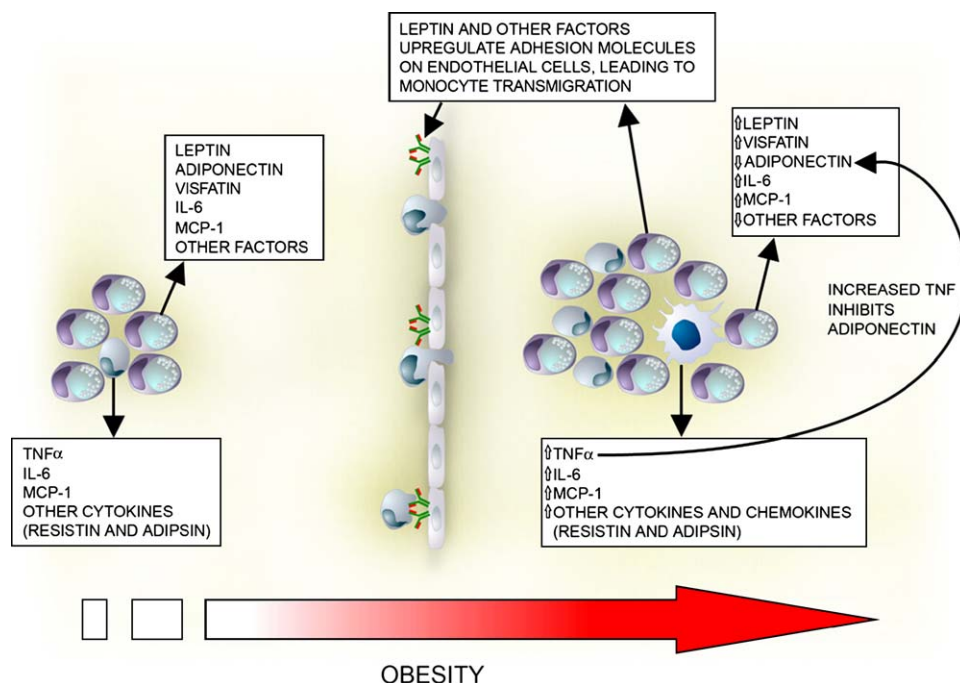


FIG 1. Adipose tissue: cellular components and molecules produced. Adipose tissue is composed of adipocytes and the stromovascular fraction, which includes macrophages. *Left*, Adipocytes produce leptin, adiponectin, visfatin, IL-6, MCP-1, and other factors. Macrophages produce TNF- α , IL-6, MCP-1, and other cytokines and chemokines. In human subjects the ultimate cellular source of adiponectin and resistin seems to be the macrophage. *Right*, In obesity leptin and possibly other factors produced by adipocytes, macrophages, or both upregulate adhesion molecules on endothelial cells, leading to transmigration of bone marrow–derived monocytes and thus an increase in WAT-resident macrophages, some of which fuse to generate giant multinucleated cells. Macrophages present in the WAT of obese individuals produce higher levels of TNF- α , IL-6, and chemokines compared with those in lean persons. At the same time, adiponectin production by adipocytes is reduced, possibly through upregulated local TNF- α levels.

consensus is that leptin exerts a proinflammatory role, while at the same time protecting against infections. Fig 2 summarizes the role of leptin in modulating immunity and inflammation.

Adiponectin

Adiponectin is the adipokine that circulates at the highest levels (in the microgram per milliliter range versus nanograms per milliliter for leptin). This adipokine is best known for its role in the regulation of insulin sensitivity.²⁸ The adiponectin molecule is composed of a globular and a collagenous domain. Once synthesized, adiponectin forms trimers, which then oligomerize to form polymers composed of 4 to 6 trimers (Fig 3). Both trimers and oligomers, but not monomers, of adiponectin are present in the circulation. The globular domain of adiponectin presents close structural, though not sequence, similarities with TNF- α .²⁹ Both the full-length and the globular fractions have been used to evaluate the biologic activity of adiponectin, and a debate exists as to whether the 2 forms have the same activity. Leukocyte elastase cleaves adiponectin and generates the globular domain, which can then trimerize but does not further polymerize.^{29,30} Thus activated leukocytes might modulate adiponectin bioactivity in ways that are still not clear. A further level

of complexity is added by the glycosylation pattern of adiponectin, which appears to be necessary for full biologic activity.²⁹

Although adipocytes are the most important source of adiponectin, serum adiponectin levels do not increase with obesity as leptin levels do. On the contrary, there is a tendency for reduced adiponectin levels in obese subjects and increased levels in patients with anorexia nervosa.^{29,31} Adiponectin levels are significantly reduced in patients with type II diabetes (see below). The mechanism by which the insulin-resistant state is associated with low levels of adiponectin is not clear. However, TNF- α , which is increased in the WAT of obese subjects, might downregulate adiponectin production.^{27,32} On the other hand, adiponectin reduces the production and activity of TNF- α .³³ The anti-inflammatory activities of adiponectin extend to inhibition of IL-6 production accompanied by induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist.³⁴⁻³⁶ Inhibition of nuclear factor κ B (NF- κ B) by adiponectin might explain at least part of these effects.³⁶ Furthermore, adiponectin reduces induction of the endothelial adhesion molecules ICAM-1 and vascular cell adhesion molecule 1 by either TNF- α or resistin.^{37,38} *In vivo* overexpression of adiponectin in apolipoprotein E-deficient mice suppresses

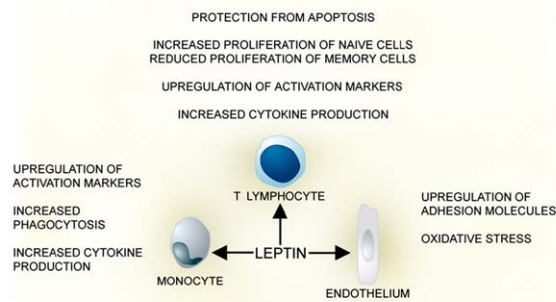


FIG 2. Effects of leptin on immunity and inflammation. Leptin is produced by adipocytes and acts on the long isoform of its receptor, which is expressed by many cell types, including lymphocytes, monocytes, and endothelial cells. Leptin protects T lymphocytes from apoptosis and modulates T-cell proliferation, increasing the proliferation of naive T cells while reducing the proliferation of memory T cells. Leptin modulates T cell–derived cytokine production and increases expression of the activation markers CD25 and CD71 in CD4⁺ and CD8⁺ cells. In monocytes leptin increases the expression of various activation markers and upregulates phagocytosis and cytokine production. In endothelial cells leptin upregulates the expression of adhesion molecules and induces oxidative stress. Many of the modulating activities of leptin in immune and inflammatory responses are observed only when a costimulus is present.

atherosclerosis, in part by downregulating adhesion molecules.³⁹ On the basis of all the above-mentioned effects, adiponectin appears to act as an anti-inflammatory molecule (Fig 3).

Resistin, adipsin, and visfatin

Resistin received its name from the original observation that it induced insulin resistance in mice.⁴⁰ Resistin belongs to the family of resistin-like molecules (RELMs), also known as “found in inflammatory zone” (FIZZ). As this latter name suggests, the FIZZ family of molecules has been implicated in the regulation of inflammation. In fact, the first member, FIZZ-1, was initially discovered in the bronchoalveolar lavage fluid of mice with allergic pulmonary inflammation and later found to be involved in other forms of lung inflammation.⁴¹ The FIZZ/RELM family consists of 4 members, each of which has a conserved 11-cysteine pattern at the C terminus. Resistin (FIZZ-3) was initially discovered in mice, in which it is predominantly expressed by adipocytes. In contrast, macrophages, rather than adipocytes, appear to be the most important source of resistin in human subjects.⁴² In rodents another member of the family, RELM γ , is expressed at high levels in hematopoietic tissues and WAT.⁴³ Although the function of RELM γ is currently unknown, this molecule might represent an additional interesting link between the immune system and WAT.

Levels of resistin have been reported to be either increased, unchanged, or decreased in murine and human obesity and type II diabetes, somewhat dampening the initial enthusiasm of resistin as a possible link between adiposity and

insulin resistance. However, recent data indicate that stimulation of macrophages *in vitro* with endotoxin or proinflammatory cytokines leads to a marked increase in resistin production.⁴⁴ Furthermore, administration of endotoxin to human volunteers is associated with dramatically increased circulating resistin levels.⁴⁴ Thus in human subjects resistin seems to act as a critical mediator of the insulin resistance associated with sepsis and possibly other inflammatory conditions. Only a few reports have investigated the effects of resistin in the modulation of inflammatory responses, showing that resistin upregulates expression of MCP-1, as well as vascular cell adhesion molecule 1 and ICAM-1, in endothelial cells.^{38,45} As mentioned above, the adhesion molecule-upregulating effects of resistin are antagonized by adiponectin.³⁸

Adipsin (which in human subjects corresponds to complement factor D⁴⁶) is the rate-limiting enzyme in the alternative pathway of complement activation.⁴⁷ Adipsin, together with several other components of both the classical and alternative complement cascade, is primarily expressed by adipocytes in mice and by both adipocytes and monocytes-macrophages in human subjects.^{47,48} Adipsin levels are reduced in murine models of obesity but either increased or unchanged in obese human subjects.⁴⁹

Visfatin is a recently discovered adipokine produced and secreted primarily by visceral WAT.⁵⁰ Visfatin binds to and activates the insulin receptor, exerting insulin-mimetic effects both *in vitro* and *in vivo*.⁵⁰ Visfatin is identical to pre-B-cell colony-enhancing factor (PBEF), a cytokine that is increased in the bronchoalveolar lavage fluid in animal models of acute lung injury and in neutrophils of septic patients.^{51,52} Interestingly, the presence of specific single nucleotide polymorphisms in the visfatin/PBEF gene, which decrease gene transcription rate, highly increases the risk of development of acute lung injury in septic patients.⁵¹ PBEF/visfatin is produced by endotoxin-stimulated neutrophils and inhibits neutrophil apoptosis through a caspase 3– and caspase 8–mediated mechanism.⁵² Although the connection between the insulin-mimetic and antiapoptotic effects of PBEF/visfatin still have to be investigated, this protein clearly represents an additional link between adipose tissue and inflammation.

CYTOKINES RELEASED BY ADIPOSE TISSUE IL-6 and TNF- α

IL-6 and TNF- α are the 2 best-studied cytokines in obesity and have been consistently found to be increased in the serum, WAT, or both of obese subjects.⁸

It has been estimated that WAT contributes about 30% of circulating IL-6, with visceral WAT producing higher levels of IL-6 compared with subcutaneous WAT.^{53,54} Both adipocytes and macrophages contribute to WAT-derived IL-6, although the ultimate stimulus for induction of IL-6 production in the presence of excess adiposity is currently unknown. The high levels of IL-6 are likely responsible for the increase in acute-phase proteins, such as CRP, observed in obese subjects.

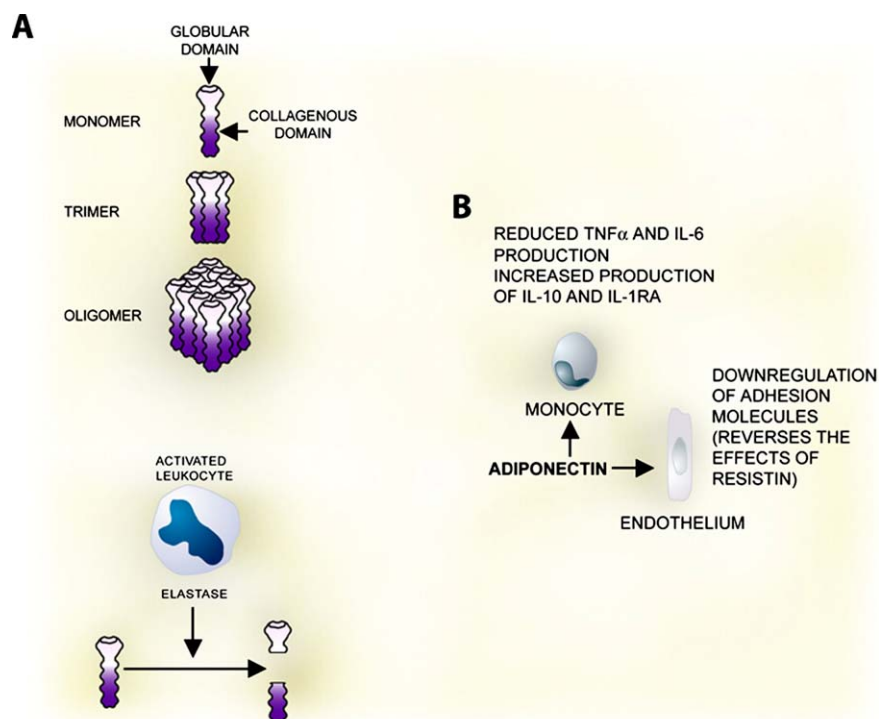


FIG 3. Adiponectin: structure and anti-inflammatory effects. *Left*, Adiponectin is composed of a collagenous and a globular domain. Adiponectin monomers trimerize through tight interactions in the collagenous domain. Trimers can then oligomerize. Both trimers and oligomers are present in the circulation and might have different effects on insulin sensitivity. Leukocyte elastase released by activated immune cells cleaves the globular domain of adiponectin, which might have activities distinct from those of the full-length molecule. *Right*, Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist in monocytes-macrophages, while inhibiting IL-6 and TNF- α levels. Adiponectin also inhibits the biologic activity of TNF- α . In endothelial cells adiponectin downregulates the expression of adhesion molecules, thus contrasting the effect of resistin.

Expression of TNF- α is increased in the WAT of obese subjects. Given that TNF- α was originally characterized as a factor inducing cachexia (hence its other name, cachectin), the high levels of this cytokine in obesity might appear paradoxical. However, it is important to note that both cachexia and obesity are inflammatory conditions, and therefore it should come as no surprise that the same mediators are involved in both processes. TNF- α can directly lead to insulin resistance by inducing serine phosphorylation of the insulin receptor, which inhibits insulin signaling.⁵⁵ Therefore TNF- α is considered a likely mediator of the insulin resistance and type II diabetes associated with high visceral adiposity. However, despite initial promising results in animal studies, neutralization of TNF- α activity has proved ineffective in ameliorating insulin sensitivity in diabetic patients.⁵⁶ Given the increased susceptibility to infection of diabetic patients and the association of TNF-neutralizing treatments with an increased risk of opportunistic infections, it does not seem advisable to further explore this avenue.

Other cytokines and chemokines

In addition to IL-6 and TNF- α , WAT expresses and releases a variety of other cytokines and chemokines.

WAT-derived IL-1 receptor antagonist is markedly increased in the serum of obese subjects, as is IL-18, although its ultimate source has not been identified.^{57,58} WAT also produces chemokines, including IL-8, MCP-1, and macrophage inflammatory protein 1.

CORRELATION BETWEEN ADIPOSITY AND IMMUNITY-INFLAMMATION

Obesity, particularly visceral adiposity, is associated with chronic low-grade inflammation, as indicated by increased levels of the inflammatory markers CRP and IL-6 in the circulation of obese subjects. Although not completely demonstrated, the current working hypothesis is that adipokines, cytokines, and other factors produced and released by WAT are responsible for the chronic inflammatory state of visceral obesity. The concomitance of inflammation, hypertension, and dyslipidemia increases the likelihood of development of type II diabetes and CVD.⁵⁹ However, the ultimate reason for increased production of proinflammatory factors by WAT in obesity has not been identified. Furthermore, visceral adiposity, rather than simply a high body mass index (BMI; in kilograms

TABLE I. Key concepts in the relation between adipose tissue and inflammation**Cells**

- Macrophages are a normal component of adipose tissue.
- Obesity is associated with increased numbers of macrophages in adipose tissue.
- Obesity is associated with the presence of activated macrophages in adipose tissue.
- There is a cross-talk between adipocytes and lymphocytes in lymph nodes.

Molecules

- Adipocytes produce many factors modulating immunity and inflammation.
- Leptin exerts mostly proinflammatory and immune-potentiating effects.
- Adiponectin exerts mostly anti-inflammatory effects.

Diseases

- Low adiponectin levels in type II diabetes are a possible link to insulin resistance.
- Obesity seems to be associated with asthma, but the mechanism is unknown.
- Several conditions are associated with altered adipokine levels, but the significance of this observation is unclear.

per meters squared), is correlated with increased risk of CVD and diabetes; however, more information is needed to understand the metabolic differences, inflammatory differences, or both between visceral versus subcutaneous WAT. It is possible that a direct access to the portal circulation by products of visceral but not subcutaneous WAT might account for most of the difference in the metabolic effects of the 2 depots. Despite the increased risk of type II diabetes and CVD with increasing BMI, it should be remembered that a high BMI is associated with increased survival rates in groups at high mortality risk, such as the elderly and patients with end-stage renal disease or chronic heart failure.⁶⁰

At the other end of the BMI spectrum, severe malnutrition has been associated with thymic atrophy, reduced T-cell function, and increased susceptibility to infection,⁶¹ alterations that are congruent with the sharp reduction in leptin levels observed at extremely low BMIs. However, a direct causal association between low leptin and reduced T-cell function seems to be negated by patients with anorexia nervosa, who also have BMIs and leptin levels at the low end of the spectrum, low enough that ovulation is generally impeded, but in whom immune function is usually well preserved, despite possible changes in T-cell subpopulations.⁶² Furthermore, although altered T-cell populations, reduced cytokine production, and possibly an increased susceptibility to infection have been observed in leptin-deficient children, these abnormalities are milder than observed in cases of severe malnutrition.¹⁸ Therefore it appears that other factors, such as the presence of poor hygienic conditions, lack of access to clean water, or concomitant chronic disease, which often accompany severe malnutrition but not anorexia nervosa or leptin deficiency, might play an important role.

INFLAMMATORY-AUTOIMMUNE DISORDERS AND ADIPOKINES

Altered systemic adipokine levels, local adipokine levels, or both have been reported in a variety of inflammatory-autoimmune conditions, with the majority of studies focusing on leptin. However, the pathogenic role played by adipokines in such disorders is far from understood, even for type II diabetes, a disease in which a potential role for adipokines has been studied in more detail. Below we summarize the data available for those conditions in which adipokine levels have been studied in more detail or an association with obesity has been reported.

Type II diabetes

Type II diabetes has classically been considered a metabolic, rather than an inflammatory, disease. However, as data on adipokine and cytokine production by WAT are being generated, it appears that inflammatory mediators are involved in the development of insulin resistance. As mentioned above, TNF- α can reduce insulin sensitivity by influencing the phosphorylation state of the insulin receptor.⁵⁵ Signal transduction pathways linking inflammation and insulin resistance include NF- κ B, c-Jun N-terminal kinase, and endothelial reticulum stress.⁶³⁻⁶⁶ In type II diabetes leptin levels are correlated with BMI and therefore are generally increased, whereas adiponectin levels are significantly decreased in diabetic subjects and improve after treatment with insulin-sensitizing agents.²⁹ In contrast, amelioration of insulin sensitivity by exercise, with or without moderate weight loss, is not necessarily associated with increased adiponectin levels.^{67,68} However, as mentioned above, adiponectin is present in the circulation as both a trimer and a multimer; the ratio between these 2 molecular forms, rather than the absolute amount of circulating adiponectin, appears to be important in regulating insulin sensitivity.⁶⁹ Despite these uncertainties, adiponectin is one of the best candidates for a connection between adiposity and insulin resistance. In contrast, data on resistin levels in type II diabetes are at present inconclusive.⁴²

Asthma

An association between obesity and asthma incidence, asthma severity, or both has been reported in many studies, although considerable debate about the existence and meaning of the association still exists.^{70,71} Despite an abundant literature, the ultimate cause of the relationship between high BMI and asthma has not been identified. The majority of studies published on this topic are epidemiologic investigations; the paucity of basic research on the possible role of adipose tissue in modulating asthma susceptibility and symptoms is quite striking. The few reports available indicate the presence of altered T-cell responses, IFN- γ production, and mast cell numbers in the tracheas of obese mice sensitized to ovalbumin compared with those seen in lean control animals⁷² and the presence of increased airway hyperresponsiveness and

inflammation to ozone in obese mice.⁷³ Furthermore, administration of leptin increases airway hyperresponsiveness and T_H2 cytokine production in ovalbumin-sensitized mice.⁷⁴ Finally, high leptin levels have been observed in asthmatic children compared with in a control group with similar BMI.⁷⁵⁻⁷⁷ Although the possibility that factors produced by adipose tissue might indeed influence asthma severity has been suggested,⁷⁸ other causes have been proposed (ie, the higher prevalence of gastroesophageal reflux in obese individuals, increased perception of symptoms caused by mechanical stress on the respiratory system, dietary and environmental factors, and others).

Inflammatory bowel disease

Leptin-deficient mice are protected from inflammation in some, although not all, experimental models of inflammatory bowel disease (IBD),^{22,79} suggesting a possible involvement of leptin in maintaining high cytokine production and low rates of apoptosis in intestinal lymphocytes of patients with IBD. The likely participation of leptin in regulating intestinal inflammation is also highlighted by the observation that luminal leptin upregulates NF- κ B expression in colonic epithelial cells.⁸⁰ Serum leptin levels are not altered in IBD,⁸¹ although they might increase during acute stages of ulcerative colitis.⁸² Furthermore, leptin mRNA is upregulated in mesenteric adipose tissue of patients with IBD.⁸³

Rheumatoid arthritis

Similar to data obtained with IBD models, leptin-deficient mice have reduced inflammation in models of rheumatoid arthritis (RA), although the opposite results have been obtained when septic arthritis was studied.^{19,84} In patients with RA, serum leptin levels remain normally correlated with BMI rather than disease stage.⁸⁵ In addition, increased levels of adiponectin and resistin are observed in the synovial fluid of patients with RA compared with that seen in patients with osteoarthritis.⁸⁶

Multiple sclerosis

Leptin-deficient mice experience only mild disease in a model of multiple sclerosis, and leptin worsens disease severity in susceptible mice.^{21,87} Serum leptin levels are not significantly altered in patients with multiple sclerosis compared with healthy control subjects, although a sudden increase before relapses has been observed, which is in agreement with experimental data obtained in mice.^{88,89}

CONCLUSIONS

The recent interest in WAT as an active secretory organ and the observation of close links and similarities between adipocytes and immune-inflammatory cells have generated a sizeable amount of exciting data that have revolutionized our understanding of the role of WAT in physiologic and pathologic processes (Table I). However, the field is still too young to allow for therapeutic implications to be drawn at this point because we still

need to understand most of the details regarding adipokine and cytokine production by WAT, differences between visceral and subcutaneous WAT depots, and the exact role of WAT in modulating immunity and inflammation.

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