

# Obesity as an inflammatory process

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## Abstract

Obesity is a major problem worldwide whose prevalence is increasing rapidly, with characteristics of a pandemic. In recent years it has become clear that obese patients present a low-grade chronic inflammation as a result of increased fat tissue and, consequently, an increased production of proinflammatory mediators by exogenous or endogenous stimuli. Fat tissue contains fibroblasts, preadipocytes, adipocytes and macrophages with the latter contributing to the systemic inflammatory process in the production of proinflammatory mediators. Thus, there is a highly coordinated and intimate association between inflammatory and metabolic pathways, highlighting the overlap between the functions of macrophages and adipocytes in obesity. Elucidating the links between obesity and inflammation is of primordial importance within the field of molecular biology of obesity, which implies the recognition of adipokines, molecules synthesized by adipocytes, which may lead to the discovery of new therapeutic targets related to metabolism and immunity. This may open the possibility to halt the development of inflammatory processes leading to degenerative diseases.

**Key words:** obesity, inflammation, cytokines, adipokines, immunity, degenerative diseases.

## Introduction

Obesity is a major global health problem because its prevalence is rapidly increasing, demonstrating characteristics of a pandemic. It has been predicted that during the coming years most of the population will be obese or overweight.<sup>1</sup>

Obesity is a complex chronic condition with a multifactorial etiology that results from an imbalance between ingested and expended energy, leading to an abnormal or excessive accumulation of energy

as fat in adipose tissue (AT).<sup>2</sup> Excess of energy is stored in adipocytes, which increase their size and/or numbers. This imbalance results from a combination of several physiological, psychological, metabolic, genetic, socioeconomic, cultural and emotional factors.<sup>3</sup> These factors lead to an increase in body weight, which differs among all persons and social groups.<sup>4</sup>

Obesity appears together with immune response alterations because a low-grade, chronic inflammatory process is generated that is also present in other associated degenerative diseases such as type 2 diabetes (T2D), hypertension, dyslipidemias, cardiac diseases, etc.<sup>5-7</sup> (Fig. 1). This chronic, inflammatory condition has also been associated with the development of insulin resistance.<sup>8</sup>

To control infections, the human body depends on its innate ability to repair damages and store

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energy until it is required. Metabolic and immune systems are essential to deal with this task because they are intimately bound and interdependent. Several hormones, cytokines, signaling proteins, transcription factors and lipids interact with both immune and metabolic systems.<sup>9</sup> Therefore, metabolic support plays an essential role because it can modify the body's immune ability to control infections during inflammatory response. In turn, inflammatory response modifies body metabolism, favoring or suppressing certain signaling pathways such as the insulin signaling pathway. The combination of immune response and an appropriate metabolic balance is beneficial to maintain an optimal health status. However, this optimal status may deteriorate according to certain metabolic alterations such as obesity.<sup>10</sup> There is evidence that supports the relationship between metabolism and immunity. Maintaining a healthy body weight leads to an immunity balance. On the other hand, malnutrition favors immunosuppression, whereas obesity generates a chronic inflammatory process.<sup>9</sup> In this review we analyze the relationship between obesity and inflammation, particularly that resulting from overexpression/deficiency of inflammatory cytokines and their signaling pathways, with the purpose of clarifying whether the inflammatory process is a consequence of obesity or vice versa.

## Materials and methods

A literature search was carried out in the following databases/publications: EBSCO, Elsevier, Free Medical Journals, PubMed, Scielo, Science Direct, Scopus and Springer Link, which provided articles related to the subject. We used the following key words: obesity, inflammation, fat tissue, macrophages and adipokines. We considered original publications between 2001 and 2008 in both Spanish and English, considering references from years 1982, 1985, 1994, 1996 and 1998. All articles were obtained *in extenso*. Once the most important literature sources were selected, they were reviewed. Information was classified by subject and we created abstracts where the most important themes from a given article were extracted to improve data organization. Data analysis was carried out using the already classified information. We obtained the most characteristic elements from obesity and inflammation. Likewise, we present results from our research regarding the close relationship between obesity and inflammation.

## Innate immune response and obesity

Beginning with obesity, a low-grade inflammatory process appears with participation from a group of cells and molecules of the immune system. This is one of the most ancient and phylogenetically preserved systems in the human body.<sup>11</sup> In addition to its role as the first line of defense against infections from microorganisms and physical or chemical damage, the immune system is characterized by a specialized group of cells such as macrophages and dendritic cells whose main function is to recognize endogenous and exogenous ligands, which are well-preserved patterns from pathogens.<sup>12</sup> This recognition is carried out through receptors coded at the germinal line. The most studied receptors are "Toll-like receptors" (TLRs), which include a family of > 10 transmembrane proteins. Toll-like receptors were first identified in *Drosophila melanogaster* (common fruit fly).<sup>13</sup> TLRs cytoplasmic portion retains a great similarity with interleukin-1 receptor (IL-1) and is

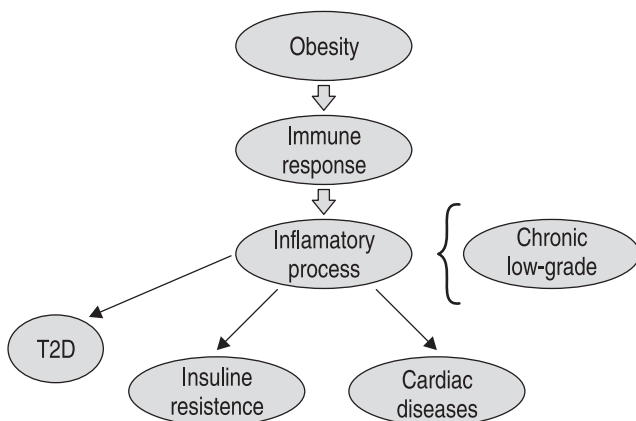


Figure 1. Obesity increases during chronic degenerative diseases.

named Toll/IL-1 receptor (TIR) domain; however, extracellular portions from both receptors are not homologous and TLRs have characteristic leucine-rich regions (LRRs). TLRs play an important role in specific recognition of pathogen microbial components including bacteria, fungi, virus and protozoa.

Toll-like receptor 4 (TLR-4) recognizes a lipopolysaccharide (LPS) from gram-negative bacteria associated with accessory molecules such as CD14 and MD-2. Likewise, it recognizes endogenous molecules such as fibronectin A region and heat shock proteins (HSP) HSP60 and HSP70. Their synthesis alerts the immune system of tissue damage. Toll-like receptor 2 (TLR-2) recognizes lipopeptides and lipoproteins from gram-positive bacteria as well as LPS from some nonenteric bacteria such as *Helicobacter pylori*. TLR-2 can form heterophilic dimers with other TLRs such as TLR6/TLR2 that recognizes diacylated peptides and TLR1/TLR2 that recognizes triacylated lipopeptides, thereby broadening their antigenic recognition spectrum.

TLRs activate common signaling pathways that end with translocation of nuclear factor kappa B (NF- $\kappa$ B) transcription, which is an essential protein involved in inflammatory cascade.<sup>14</sup> Then, inflammatory process is promoted by TLRs through cytokine production such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-1 beta (IL1- $\beta$ ). Although TLRs are expressed mostly in hematopoietic lineage cells, an increasing number of studies report their expression in other cell types such as adipose tissue and particularly in adipocytes.<sup>15,16</sup>

In patients with obesity and T2D, activation of proinflammatory cytokines is closely related with NF- $\kappa$ B. Adipocytes secrete adiponectin whose anti-inflammatory properties are executed through their action over NF- $\kappa$ B. On the other hand, adiponectin levels correlate inversely in patients with obesity and T2D.<sup>17</sup> A study reported that obesity-induced murine models (through a fatty diet) present overexpression of kappa-B kinase inhibitor (IKK $\beta$ ) of NF- $\kappa$ B in AT, which results in a high production of inflammatory cytokines and development of diabe-

tes.<sup>18</sup> In contrast, hepatocytes for IKK $\beta$  from knock-out mice (KO) show a reduced expression of proinflammatory cytokines and these models do not develop hepatic insulin and glucose resistances as happens in obesity-induced mice.<sup>19</sup>

The origin of stimuli that persist during the low-grade inflammatory process in obesity is yet to be fully known. However, we know that obesity, T2D and metabolic syndrome are characterized by a systemic increase in fatty acid levels. They increase TNF- $\alpha$  synthesis in adipocytes of murine cell line 3T3-L1 through TLR-2.<sup>15</sup> Another study found that the expression of TLR-2/TLR4 in cultured human adipose tissue is induced through stimulation using LPS and Pam3SCK4 (a TLR antagonist), which activates NF- $\kappa$ B nuclear translocation and the synthesis of proinflammatory cytokines. Therefore, fat deposits contribute to maintain a chronic inflammatory condition promoting the synthesis of cytokines through TLRs; the origin of this activation may be related with mechanisms of cardiometabolic dysfunction.<sup>16</sup>

Another explanation of the constant antigenic stimulation through the innate immune system during obesity is that, because of hyperinsulinemia, there is a reduction in the immunocompetent capacity of Kupffer cells in clearing LPS that pass through the gastrointestinal tract.<sup>20</sup> Some studies have demonstrated that endotoxemia can aggravate hyperinsulinemia because there is a direct relationship between a systemic LPS increment and insulin levels.<sup>21</sup> This activates a positive feedback mechanism that begins with insulin resistance and increased synthesis of insulin and its secretion, leading to an inflammatory process.<sup>17</sup>

## Inflammation and obesity

Inflammatory response starts with a signaling recognition that may have an infectious or inflammatory origin, which produces cellular activation and protein synthesis, modifying the effectors response in immune cells. During the immune response triggered by infections, these mediators produce the

recruitment of adjacent cells through a paracrine process. When mediators release exceeds local borders, they disseminate and distribute through the blood, producing an endocrine-type generalized cellular activation that matches systematic inflammatory response syndrome (SIRS). SIRS is a host defense mechanism and is part of a tissue repair process. To effectively initiate this defense mechanism, cytokines with a proinflammatory function are required such as TNF- $\alpha$ , IL-1 $\beta$ , interleukin-12 (IL-12), interferon- $\gamma$  (IFN- $\gamma$ ) and possibly IL-6.<sup>22</sup> The initial inflammatory response is controlled by immunoregulating molecules such as specific inhibitors and soluble receptors of cytokines. The main anti-inflammatory cytokines are antagonists of IL-1 receptor (IL-1RA), transforming growth factor beta (TGF- $\beta$ ) and interleukins 4, 6, 10, 11 and 13. Specific receptors for IL-1, TNF- $\alpha$  and interleukin-18 (IL-18) act as inhibitors of their own proinflammatory cytokines. Under physiological conditions all these molecules act as immunomodulators and therefore limit the potentially harmful effect of the inflammatory response. However, during obesity the anti-inflammatory response may be inadequate to neutralize the inflammatory activity and this would explain a chronic low-grade inflammatory process expressed in this pathology. Whereas at a first stage proinflammatory mediators prevail, later stages show a prevalence of anti-inflammatory mediators. This means that cytokine action depends on the time they are released, the location where they act upon and the presence of other competitive or synergistic elements on receptor density and response from a particular tissue to each cytokine.<sup>22</sup>

Adipocytes stimulated by infectious or inflammatory signals secrete acute phase reactants and inflammatory mediators. Inflammatory factors expressed by adipocytes include TNF- $\alpha$ , IL-6, plasminogen activator inhibitor (PAI-1), monocyte chemoattractant protein-1 (MCP1), IL-1 $\beta$ , IL-8, 10, 15, leukemia inhibitor factor (LIF), hepatocyte growth factor (HGF), apolipoprotein A3 (SAA3), macrophage migration inhibitory factor (MIF), potent inflammatory modulators such as leptin, adi-

ponectin and resistin, as well as C-reactive protein (CRP).<sup>6,23,24</sup>

The relationship between obesity and inflammation is confirmed because weight loss in obese women after a 1-year diet, exercise and liposuction surgery has been associated with a reduction of IL-6 and TNF- $\alpha$  circulating levels.<sup>25</sup> A similar situation has been observed after gastric bypass in patients with morbid obesity because weight loss observed in these subjects has been associated with a reduction in CRP and IL-6 levels. These patients also present an improvement in insulin sensitivity.<sup>26</sup>

### Adipose tissue, macrophages and inflammation

Cytokines synthesized in AT (adipokines) are involved in inflammation and their levels are modified during obesity. Therefore, obesity may favor or alter the evolution of inflammatory processes. A low-grade, slow-progression inflammatory response is presented during obesity and increases the risk for multiple organ damage including those involved in glucose homeostasis.

Adipose tissue contains adipocytes, fibroblasts, preadipocytes and macrophages. Macrophages contribute importantly to a generalized systemic inflammatory process. They have been associated with the development and maintenance of obesity-induced inflammation in AT and contribute with the secretion of several proinflammatory molecules produced in adipose tissue. There is an intimate, highly coordinated association between inflammatory and metabolic pathways, with a remarkable coincidence in function between macrophages and adipocytes in obesity.<sup>10</sup> Genetic expression of both cell types is similar. Macrophages express most proteinaceous products from adipocyte such as fatty acid binding proteins (FABP-aP2) and peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), whereas adipocytes can express several proinflammatory proteins that may be considered as exclusive of macrophages such as TNF- $\alpha$  and IL-6. The functional ability of these two cell types matches and overlaps. Macrophages can attract, include and

store lipids to become atherosclerotic foam cells. Also, under certain conditions (inflammatory processes), preadipocytes may present phagocytic and antimicrobial properties. They have the ability to differentiate into macrophages in an appropriate environment, which suggests that adipocytes have a potential immunological role.<sup>10,27</sup> It has been documented that macrophages and adipocytes are very similar when there is excessive AT, which is characteristic during obesity. This is related with the origin of the obesity and its strong relationship with inflammatory processes, which occur simultaneously in adipose tissue and macrophages to promote insulin resistance.<sup>10</sup>

The origin of inflammatory markers can be diverse and includes, besides AT, the liver, macrophages, endothelium and other tissues. This scenario may be more complex when there is interaction between producing tissues. Therefore, circulating CRP production that proceeds mostly from the liver is regulated by IL-6 synthesized in AT.<sup>8</sup> It has also been observed that CRP production in AT may contribute to circulating levels of this factor in obese patients,<sup>28</sup> although the total contribution from each tissue has not yet been established.

The correlation between resident macrophages in AT and obesity has been observed in several murine obesity models as well as in human subcutaneous adipose tissue.<sup>29,30</sup> Infiltration of circulating

monocytes into tissues is a complex phenomenon that involves several stages including the activation of capillary endothelium, increased expression of adhesion molecules (intercellular adhesion molecule-1, ICAM-1), circulating monocyte adhesion followed by their migration through endothelium and final differentiation as macrophages. Human adipocytes produce soluble factors that stimulate diapedesis of blood monocytes. Diapedesis is related with the activation of capillary endothelial cells from AT, increasing the expression of ICAM-1 and platelet endothelial cell adhesion molecule-1 (PECAM-1). Overweight and obese individuals present high plasma concentrations of cell adhesion molecules such as E-selectin, vascular cell-adhesion molecule-1 (VCAM-1), ICAM-1 and von Willebrand factor (VWF), which suggests that body fat increase is associated with an early systemic endothelial activation.<sup>31</sup> Factors derived from adipocytes released into systemic circulation play an important role in the activation of endothelial cells,<sup>32,33</sup> promoting macrophage infiltration into AT and therefore generating an inflammatory process due to uncontrolled pro- and anti-inflammatory cytokines as shown in Table 1.

### Adipokines and autoimmune disorders

A great variety of inflammatory conditions have been documented where adipokine levels are altered both

**Table 1. Actions from cytokines involved in inflammation associated with obesity**

Molecule response	Synthesized at	Main effects	Obesity
TNF- $\alpha$	• Adipocyte • Macrophage	Contributes to insulin resistance	Increases
Leptin	• Adipocyte	Suppresses appetite and promotes energy expense	Increases
Visfatin	• Adipocyte • Macrophage	Hypoglycemic action similar to insulin	Increases
Resistin	• Adipocyte	Participates in insulin resistance	Increases
IL-6	• Macrophage • Adipocyte	Favors insulin resistance	Increases
PAI-1	• Adipocyte • Macrophage	Intervenes in insulin resistance onset	Increases
Adiponectin	• Adipocyte	Improves insulin sensitivity and reduces glycemia	Decreases

at systemic and local levels. However, we have yet to understand the role of adipokines in pathological dysfunctions even in T2D where the participation of these molecules has been extensively studied. Therefore, it is of utmost importance to understand the mechanisms through which obesity is produced and be able to attack diseases with chronic degenerative inflammatory processes such as asthma, arthritis, cardiac diseases, etc., all of them having a close relationship with obesity.

### Signaling pathways in inflammation and obesity

What triggers the inflammatory response during obesity? Is it caused by AT, macrophages or both? These are currently the most relevant questions. It seems possible that the inflammatory response begins in adipocytes (the first cell type involved in obesity) and further macrophage recruitment takes place, aggravating the inflammatory condition. Activation of inflammatory pathways from stress in the endoplasmic reticulum (ER) seems to be an important mechanism. Obesity generates conditions that increase the demand in ER and overloads its functional capacity.<sup>34</sup> This is particularly important in AT that experiences dramatic changes in its architecture, increasing the synthesis of proteins and lipids and disturbing intracellular nutrient and energy flow. Cultures and intact animal analyses demonstrate that ER triggers the activation of c-Jun NH<sub>2</sub>-terminal kinase (JNK) and kinase inhibitor of NF- $\kappa$ B (IKK); in turn they activate NF- $\kappa$ B. The latter is an inducible transcription factor that participates in immune and inflammatory responses, activating a large number of proinflammatory cytokines and suppressing others such as adiponectin and glucose transporters type-4 (GLUT-4). This has suggested that the inflammatory process is closely associated with obesity and contributes to insulin resistance.<sup>35</sup>

Oxidative stress is another mechanism that may be relevant at the beginning of the inflammatory process as a result of obesity. The increased glucose uptake by AT endothelial cells during hyperglycemia produces an excess of reactive oxygen spe-

cies in mitochondria that conditions oxidative damage and activates inflammation signals within endothelial cells.<sup>36</sup> Endothelial damage in AT produces macrophage chemotaxis and exacerbates local inflammatory response. Hyperglycemia also stimulates the generation of reactive oxygen species in adipocytes, which increases the production of proinflammatory cytokines.<sup>37</sup>

A third mechanism is associated with the fact that, in most obese persons, the main defect in insulin action is located at a postreceptor level.<sup>38</sup> Insulin action at a postreceptor level is altered by the increased TNF- $\alpha$  and free fatty acids (FFA) levels that inhibit phosphorylation of insulin receptor substrate-1 (IRS-1) in serine residues.<sup>39</sup> In turn, lack of serine activation of IRS-1 reduces tyrosine phosphorylation of IRS-1 as a response to insulin, thus suppressing the appropriate cytosolic molecular signaling for this hormone, causing its resistance. Several mediators responsible for these alterations have been investigated and this has expanded our knowledge on critical intracellular signaling that determines insulin resistance. There are several serine/threonine kinases activated by inflammatory or stress stimuli that contribute to inhibit insulin signaling. These include kinases JNK, IKK and protein kinase C- $\theta$  (PKC- $\theta$ ). Activation of these inflammatory kinases in obesity and their role in insulin actions illustrate the close relationship between metabolic and immune pathways. Particularly, kinases JNK and IKK control the most important inflammatory response pathways and they are activated through a wide variety of stress signals and regulate innate immune response.<sup>10</sup> Both JNK and IKK are essential and their constant activation and genetic expression are required so that TNF- $\alpha$  induces insulin resistance. Suppression of one or the other increases sensitivity to insulin actions.<sup>40</sup> These three enzymes (JNK, IKK and PKC- $\theta$ ) are able to increase phosphorylation of serine-IRS-1 and alter deleterious profiles of inflammatory genetic expression (Fig. 2).<sup>19</sup>

Lipid synthesis increases by increasing energy intake. Therefore, a larger fat accumulation occurs in adipocytes, increasing their number. The con-

sequence is the lack of oxygen in adipocytes farther from the vascularization area, which leads to ER stress because of lack of oxygen, also known as hypoxic stress. This stress generates free radicals and oxidative damage, which will end in cellular death from necrosis. This process triggers damage alerts including the secretion of proinflammatory cytokines by neighboring adipocytes and recruited macrophages as a response to the alert, therefore establishing the typical inflammatory obesity profile.

However, we have yet to understand what triggers AT to produce inflammatory cytokines and proteins during acute phase. A possible explanation is that the origin of this process is intrinsic to AT with hypoxia as triggering factor.<sup>35</sup> Hypoxia would take place with the excessive AT growth during the development of obesity. Under such conditions, initiation of an inflammatory process is induced by groups of hypoxic adipocytes that would allow the stimulation of angiogenesis and the increase in blood supply. This proposal is based on studies where AT has proven sensitive to angiogenesis inhibitors,<sup>41</sup> and there are others that

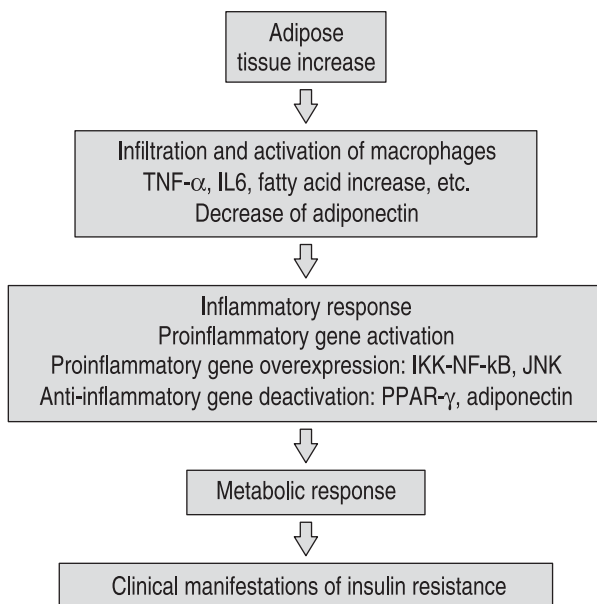
show that AT is able to produce angiogenesis stimulating factors such as vascular endothelial growth factor (VEGF), PAI-1 and leptin.<sup>5</sup> During this process, hypoxia-inducible factor-1 (HIF-1) plays a central role. This is a transcription factor stimulated by adipocyte hypoxia and shows an increased production in obese mice.<sup>41</sup> This factor is also stimulated by cytokines and regulates production of VEGF and PAI-1.<sup>42</sup>

### Therapeutic targets

We are aware that obesity depends on environmental and genetic factors and that it has consequences in altering the expression and function of several proteins. Therefore, it would be important to find key molecules as therapeutic targets to develop useful treatments to decrease the inflammatory process.

Adipocytes, in addition to storing energy, synthesize and secrete a large variety of bioactive molecules called adipokines, such as leptin that reduces food intake and increases energy expenditure,<sup>43</sup> as well as other inflammatory adipokines that express in larger quantities during obesity. Although metabolic diseases associated with obesity are treated with specific medications (sibutramine, orlistat), recent investigations are trying to find alternatives to reduce inflammatory processes characteristic of obesity, such as weight loss through gastric band surgery or diet.

Among therapeutic alternatives seeking to reduce proinflammatory profile, we found that the use of glycine. *in vitro* and *in vivo*, as well as in humans, reduces the expression of proinflammatory cytokines such as TNF- $\alpha$ , IL-6 and resistin, increasing the expression of adiponectin (an anti-inflammatory cytokine) and its regulator (PPAR- $\gamma$ ).<sup>44,45</sup> In conclusion, adipocytes and macrophages present in AT synthesize similar molecules that contribute to establish an inflammatory process characteristic of obesity. Obese individuals who have excessive amounts of adipocytes and macrophages present an increase in circulating levels of proinflammatory cytokines (TNF- $\alpha$ , IL-6, etc.), which sig-



**Figure 2.** Responses during obesity associated with a chronic low-grade inflammatory state.

nificantly favor a low-grade inflammatory process characteristic in obesity. It seems possible that the inflammatory state in obesity is a consequence of the increased fat in adipose tissue and hypoxia is therefore generated.

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