Obesity leptin and the immune system

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ABSTRACT

The increasing prevalence of obesity in developed and developing countries raises a major health concern due to the fact that obesity and nutrition are associated with impaired immune responses. Overconsumption of nutrients alters several functions of the immune defence mechanisms leading to severe infection and chronic diseases. The hormone leptin, known to regulate energy balance has been proved to activate several components of signalling pathways having thus immunoregulatory activity. The aim of this paper is to present the connections between obesity, immune system mechanisms and the role of the adipocyte hormone leptin.

Key words: Obesity, immune system, leptin, overconsumption, health concern.
Παχυσαρκία, λεπτίνη και το ανοσοποιητικό σύστημα

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ΠΕΡΙΛΗΨΗ
Η αυξανόμενη επικράτηση της παχυσαρκίας στις αναπτυγμένες και τις αναπτυσσόμενες χώρες προκαλεί μια σημαντική ανησυχία για την υγεία λόγω του ότι η παχυσαρκία και η διατροφή συσχετίζονται με μειωμένη ανοσολογική απόκριση. Η υπερκατανάλωση θρεπτικών ουσιών αλλάζει πολλές λειτουργίες του ανοσοποιητικού συστήματος αδημοίητως σε σοβαρές λοιμώξεις και χρόνιες παθήσεις. Η ορμόνη λεπτίνη, που είναι γνωστή για τη ρύθμιση του ενεργειακού ισοζυγίου έχει αποδειχθεί ότι ενεργοποιεί διάφορα μονοπατιατικά σήματα έχοντας με αυτόν τον τρόπο ανοσορυθμιστικές ιδιότητες. Ο σκοπός αυτής της εργασίας είναι να παρουσιάσει τις συνδέσεις μεταξύ της παχυσαρκίας, των μηχανισμών του ανοσοποιητικού συστήματος και του ρόλου της ορμόνης των λιποκυττάρων λεπτίνης.

Λέξεις κλειδιά: παχυσαρκία, ανοσοποιητικό σύστημα, λεπτίνη, υπερκατανάλωση, πρόβλημα υγείας

INTRODUCTION
The increasing prevalence of obesity, in developed and developing countries, is a major health concern due to the high risk factor that overweight and obesity represent in a number of chronic diseases such as diabetes, cardiovascular diseases and certain types of cancer. Nutritional status has an important effect on the immune system with both under and overnutrition known to alter to immunocompetence. While slight excess of several nutrients, especially in populations at risk of nutrient deficiencies, can stimulate the immune system, excessive intake of lipids and many micronutrients is known to have adverse consequences on various components of the immune system.

OBESITY
Obesity is defined as an excess storage of fat in the body to such an extent that it causes health problems leading to excess mortality. It is being measured by means of the Body Mass Index (BMI), taking into account the weight for a given height: BMI=Weight (kg)/height (m)² which highly correlates with total body fat and is very useful for epidemiological purposes. The World Health Organization (WHO) has established different cut-off points enabling the classification of obesity (Table 1).1

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Table 1. Classification of adult obesity. (1)

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk of comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>18.5–24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.0</td>
<td>Increased</td>
</tr>
<tr>
<td>Preobesity</td>
<td>25.0–29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity class I</td>
<td>30.00–34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obesity class II</td>
<td>35.00–39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Obesity class III</td>
<td>≥40.0</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence of Adult Obesity (June 2010) (4)

The fact that any increase in body mass is always connected to an increase in fat stores has been the base for the definition of obesity. Apart from that, lean (non-fat) body mass contributes to the total body mass and may show considerable heterogeneity for a given size of fat mass, while it is also correlated and etiologically linked to fat mass. (2)

Obesity is the outcome of the imbalance between energy intake and energy expenditure. In other words, excess body fat accumulates when more energy is consumed than it is spent. With the biological mechanisms of this imbalance being unclear, different factors are known to play an important role in body weight regulation. When both parents are obese children have more chances becoming obese (80%) compared to less than 10% when neither is obese. On the other hand studies in twins have shown interesting results such as twins being raised apart from each other and having large weight differences. (2)

Obesity is a common problem not only in developed countries, where considerable proportion of the population are overweight, but also in the developing nations. Childhood obesity has also been increasing in Western societies during the past three decades, representing as much as 30% of all adult obesity. (3),(4)

Due to its high worldwide prevalence, obesity is currently the most common metabolic disease in the world. The WHO estimates that more than one billion people are overweight and, of these, 300 million can be considered as obese, with a BMI above 30 kg/m² according its own BMI based classification of obesity. Actually, there is a great concern because the global figures of obesity are progressively increasing from an estimate of 200 million people affected in 1995 to the current 300 million, which is a 50% increase in only seven years. It is estimated that if no action is taken against this, these figures could double in 20 years. Moreover, this increase in obesity prevalence is a global trend, not only confined to affluent societies but also seen in emerging countries such as China. However, the prevalence of obesity varies widely among different continents and countries, ranging from almost one third of the whole population in USE and Greece to a prevalence below 10% in the Netherlands and Switzerland. Obviously, beyond the genetic background there are some other influences, namely cultural and life style, which could explain these differences.(4)

Figures 1-2 are an attempt to summarize the current numbers about the world wide prevalence of obesity particularly in some countries that periodically undertake population-based health surveys. Apart from the high obesity prevalence, the trends in obesity prevalence are also showing a progressive and non-stop rising tendency. This rising trend is clearly demonstrated by epidemiological studies comparing current and previous data. As a matter of fact, the prevalence of adult obesity in the U.S.A. (BMI≥30 kg/m²) has doubled from 1986 to 2000, from 10% of the adult population to a 20%. During the same period of time, severe obesity has quadrupled from 0.5 to 2% of the adult population with same scale growing trends being seen in many other countries of the world.(5)
The dramatic changes in children’s lifestyle have also led to an increasing prevalence of obesity in childhood in western societies. (Figure 2)(6)(7)
The increase in childhood obesity prevalence is a sad privilege not exclusive to fully developed countries. Countries like Mexico are also experiencing a rise in obesity prevalence in childhood. Mexican children 10 to 17 years of age have a current prevalence of obesity varying with age from 30.5% in boys, 31.5% in girls. These figures, even though being approximately one half of those seen in the U.S.A., are really concerning given its rising trend. (4)(5)
The complex regulation of energy balance and thus, body weight regulation seems to be adjusted by Leptin, a protein product of the obese (ob) gene, secreted exclusively by adipocytes. Despite all the evidence leptin’s physiological roles and mechanisms of action have not been extensively studied and still remain poorly understood. A loss of body fat would lead to a decrease in leptin, which induces a state of positive energy balance, with food intake exceeding energy expenditure. On the other side, adiposity increase leads to an increase in leptin and a state of negative energy balance, with energy expenditure exceeding food intake. Therefore, in absence or deficiency of leptin, food intake cannot be restrained and the patient become obese, suggesting resistance of leptin actions and thus, persistence of obesity. Human obesity has been associated with elevated serum leptin concentrations. (8)

For a given measure of obesity, leptin levels have been found to be higher in women, indicating gender-based differences. Quantitative changes in leptin concentration lead to biological responses that control body weight. Therefore, it is important to consider factors that regulate ob gene expression, such as eating patterns and hormones. (8)
The levels of leptin seem also to be associated with the size of adipocyte and its lipid content following a pulsative and diurnal pattern, with a 40% increase during the night. (8)

THE IMMUNE SYSTEM
We are frequently exposed in our environment to a number of microorganisms, including viruses, bacteria and fungi. Host defence requires different recognition systems and a wide variety of effector mechanisms to seek out and destroy the wide variety of pathogens in their various habitats within the body and its surface. The immune system (Image 1) defends the host against infection with two main mechanisms: innate and adaptive immune systems. Innate immunity serves as a first line of defence but lacks the ability to recognize certain pathogens and to provide the specific protective immunity that prevents reinfection. On the other hand the adaptive immune system apart from eliminating a pathogen, generates increased numbers of differentiated memory cells thus allowing a more rapid and effective response upon reinfection.

INNATE IMMUNITY
The innate or antigen-nonspecific immunity consists of physical barriers, the complement system, phagocytes, interferons and other humoral factors. Skin and mucous membranes, together with their glands and secretions: lysozyme (eyes, blood), fatty acids (skin), acid pH (stomach, urine) are physical barriers; they constitute the external defence and first mechanism against infectious organisms. The complement system is an important mediator of inflammation consisting of a group of about 20 proteins (in particular 9 complement components, some some of them along with subcomponents and inhibitors), being present in plasma. It is antibody-activated via the classical pathway or by certain microbial antigens via the alternate pathway. These two pathways merge at C3, which on activation is cleaved into C3a and C3b fragments with the latest and other active fragments of complement components being responsible for a
variety of functions. Macrophages, phagocytes, and neutrophils, take up microorganisms and destroy them inside phagolysosomes. (9)

Innate immunity is an essential prerequisite for the adaptive immune response, as the antigen-specific lymphocytes of the adaptive immune response are activated by costimulatory molecules that are induced on cells of the innate immune system during their interaction with microorganisms. (Image 2) Phagocytes recognize their target antigens through antibody binding to the Fc receptors on their surface or through complement binding to their C3 receptors.(8)(9).

Innate immunity is characterized by rapid action, low specificity and inherence while its response does not depend on prior contact with the infectious agent. Non-specific immune mechanisms serve as first defence line against many microorganisms and retard the establishment of overt infection (8),(9).

ADAPTIVE IMMUNITY

Prior exposure to invading microorganisms or antigenic determinants results to cellular memory inducing the so called adaptive immunity. This immune system is very effective in preventing the spread of the infection and eliminating the invading organisms. It consists of the humoral and cell-mediated immune responses. (Image 2)

Humoral immunity is mediated by specific antibodies that recognize the antigen and inactivate it with the help of the complement. Antibodies are secreted by B lymphocyte cells after their appropriate antigenic stimulation in which they differentiate and proliferate. These antibodies (immunoglobulins) are glycoproteins composed of two heavy and two light chains, with a variable and a constant region. Each molecule has two main fragments: the Fc (crystalline fragment) is formed from the two identical heavy chains, interacts with complement components and various cells of the immune system (phagocytes) and the Fab (antibody fragment) binds specifically to the antigen which stimulated the production of the antibody. There are five immunoglobulins based on the isotypes of the heavy chain used (IgG, IgA, IgM, IgD and IgE) and many subclasses. Each class has a particular biological activity and acts primarily at different sites in the body. Cellular immunity is mediated by thymus dependent T lymphocytes. When these T cells are exposed to antigens, usually by accessory cells (macrophages), metabolic changes occur at cell surface and inside the cell. Cells are stimulated to divide and clones of cells that carry receptors to the sensitizing antigen are formed. Upon re-exposure to the same antigen, T lymphocytes bearing the appropriate antigen receptor, release soluble lymphokines that with the help of other cells can destroy the antigen. There are two major types of T cells: CD41 helper cells and CD81 cells; they recognize antigens associated with major histocompatibility class molecules (MHC), MHC I and MHCII, respectively. Although humoral and cellular immune responses act in concert, each acts primarily against different types of microorganism. B lymphocytes recognize extracellular antigens, for instance Staphylococcus, whereas T lymphocytes recognize intracellular antigens expressed on the surface of body cells.(8),(9).

EFFECTS OF NUTRIENTS ON IMMUNE SYSTEM

Nutrition is an important determinant of immune response with enough evidence suggesting that nutrient deficiencies alter immunocompetence increasing in that way the risk and severity of infection. While malnutrition depresses the immune system at the same time infection deteriorates nutritional status. In that way malnutrition and infection are invariably linked together and aggravate one another (10). Impaired cell-mediated immune response has been observed in nutritional imbalances, both under- and overnutrition. Excessive intake of nutrients and
vitamins is also considered a type of “malnutrition” so, overnutrition and obesity are also known to reduce immunity. (10),(11)

**IMMUNE SYSTEM IN OBESITY**

In both animal and human obesity a high incidence of infection has been demonstrated with various epidemiological, clinical and experimental studies indicating that immune function is altered in obesity(11).

**LEPTIN AND IMMUNE SYSTEM**

The hormone leptin, known to regulate energy balance, is involved in a range of physiological processes with recent findings suggesting a new role for leptin on the immune response. Leptin has been proved to activate several components of signalling pathways from several cytokines with studies in ob/ob mice reporting lower E. coli killing capacity than in normal mice. Supposing that leptin had immunoregulatory activity, leptin deficiency would promote many associated complications of obesity by altering cytokine levels such TNF-a and others. This hypothesis has been recently investigated by evaluation, in genetically obese rodents, of macrophage phagocytic function and cytokine production before and after LPS stimulation in presence and absence of recombinant leptin. The impaired phagocytosis and altered cytokine production observed, indicates that leptin regulates macrophage function. In a recent study, Human leptin stimulates proliferation of monocytes and activates its function in vitro, by inducing TNF-a and IL-6 production. A mechanism for leptin immune responses based on release of IL-1 and prostaglandins has also been proposed. Leptin actions on food intake and body temperature seem to be mediated by IL-1. Adipsin is secreted abundantly in adipose tissue. This protein has complement factor D activity and catalyzes the first activation step in the alternative pathway of complement. Adipsin recombines with two other essential components of alternative pathway, factor D and C3. Previous studies have shown decreased adiponectin levels in serum and adipose tissue in obese mice, and impaired complement factor D activity in obesity. (8),(11).

**LEPTIN AND T-LYMPHOCYTES (T cells)**

T cells are a subset of lymphocytes responsible for some cell-mediated immune responses. T cells are generally defined by their development in the thymus and their heterodimeric receptors, which associate with proteins of the CD3 complex. Naive T-cells have not yet encountered their antigens which activate, divide and differentiate them into short-lived armed effector T cells and longer-lived memory T cells. Although all T cells carry cell surface proteins, unlike effector T cells, memory T cells require re-stimulation by antigen before they can act on target cells. Differentiation of naive T-cells into memory T-cells is associated with an alteration of cell-surface molecules.

There are 2 main classes of effector T cells: T helper cells, activating other immune cells, such as macrophages and B cells; and T cytotoxic cells, preventing the spread of viruses and other pathogens by killing infected host cells. T helper cells express the CD4+ cell marker, whereas cytotoxic T cells express CD8+. CD4+ T helper cells are divided into TH1 and TH2 cells, with TH1 cells sometimes called inflammatory T cells due to the activation of macrophages and secretion of predominantly proinflammatory cytokines such as IL-2 and IFN-γ. On the other hand TH2 cells secrete cytokines with predominantly regulatory functions, including IL-4 and IL-10. They also participate in humoral immunity by activating B cells which then produce antibodies.(8)
Up to date there is enough evidence that leptin regulates the activation of the CD4+ TH1 response. In Leptin-deficient (ob/ob) mice and humans infectious morbidity and mortality is increased, with the outcome being reversed after the administration of leptin. Administration of recombinant Leptin in children with congenital leptin deficiency resulted in the reversal of depressed circulating CD4+ T cells as well as the reversal of T-cell hyporesponsiveness. It is also reported that leptin administration reversed suppression of production of the TH1 cytokine IFN-γ, and increased the depressed CD4+/CD8+ ratio to normal levels.(8),(14),(18)

LEPTIN AND B-LYMPHOCYTES
Antibodies (the secreted form of B cells) are glycoproteins that contribute to host immunity in 3 primary ways, which include binding to and neutralizing pathogens, opsonizing (coating) pathogens, which enhances phagocytosis by effector cells, and by activating the complement system. (5)

Only 1 published animal study has examined the relationship between leptin and B cells suggesting that leptin deficiency–induced impairment in T-cell responses likely contributes to the decrease in immunoglobulin production in leptin-deficient ob/ob and leptin-resistant db/db mice.(15)(17)

LEPTIN AND NK CELLS
NK cells are large lymphocytes that develop in the bone marrow and circulate in the blood. As an important part of the innate immune system, NK cells lack antigen-specific receptors but contain cytotoxic granules and provide important host defense against certain tumor cells as well as viruses and other intracellular pathogens. Natural killer cells also play a role in antibody-dependent cell-mediated cytotoxicity. Recognition of specific antibodies coating target cells by the Fc receptor on NK cells triggers a cytotoxic attack on the antibody-coated cell by the NK cell. Although the clinical relevance of in vitro NK-cell studies is not well defined, multiple studies found NK cytotoxicity to be inversely associated with risk and severity of infection. Natural killer cytotoxicity appears to be affected by fluctuations in body weight. Shade found that among 114 healthy overweight and obese postmenopausal women, those who reported ever losing more than 10 pounds had lower measured NK cytotoxicity than those who did not (P = .01).(20)

The association between leptin and NK-cell cytotoxicity in humans remains unclear. So far animal models and in vitro studies using human cells provide preliminary evidence for leptin’s role in stimulation of NK-cell proliferation and cytotoxicity. Leptin-deficient ob/ob mice had a significant reduction in NK-cell numbers compared with lean mice. A study of adult leptin receptor–defective (db/db) mice demonstrated significant reductions of both NK cell numbers and NK cytotoxic capacity compared with wild-type mice. Psychological factors such as mood states are also known to influence immune function. In this respect, a slight degree of depression, common in obesity and during dieting, may negatively affect immunity.(21)

CONCLUSION
Obesity and nutrition are associated with the immune responses. Amongst other, nutritional, endocrine and metabolic factors seem to be involved in the result of impaired immunity. The excessive intake of nutrients in overnutrition alters several functions of the immune defence mechanisms increasing thus susceptibility to infections and other chronic diseases. Since immunity depends on nutritional status, a better understanding of the immunological aspects and mechanisms altered in obesity could be of clinical significance. Adipocyte hormone leptin, which is known to regulate appetite and energy expenditure, is involved in a variety of regulatory mechanisms including the immune system. Further research in this interesting area would be of help in predicting obesity-prone populations and so, development of prevention strategies and new pharmacological therapies.

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