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REVIEW : ADIPOSE TISSUE IS A REAL MEDICAL ENDOCRINE WEALTH-LEPTIN IS AN IMMUNE, PROTECTIVE, THERAPEUTIC HORMONE

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Review: adipose tissue is a real medical endocrine wealth- Leptin is immune, protective and therapeutic hormone.

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SUMMARY

Human adipose tissue is a highly active endocrine organ secreting more than 100 soluble products,called adipokines,and adipose tissue hormones adding to fatty acids and prostaglandins.

The most important polypeptide adipose tissue derived hormone is leptin. Previous studies reported many functions of leptin as a metabolic and energy storage hormone. Recently leptin represents a link between the endocrine and immune systems. That is affected by diseases, nutritional status, starvation and other factors, The current report reviewed the immune function of adipokines with special focus on leptin and its mode of action normally and in some diseases.

The current report highlighted and concluded the following medical aspects:

- Adipose tissue has a potent effective immune function because of the similarity of its cytokines secretions and cytokines existed between those of immune cells.
- Leptin has an immune stimulating and regulating effect with a direct action on immune cells to produce cytokines
- Leptin could be used as useful marker of disease activity and response to therapy.

-Leptin is a beneficent therapy to recover the immunity in some leptin-deficiency diseases and in preventing the induced thymus apoptosis, and adiponectin protect islet B-cells against apoptosis and in obesity, where no leptin production because of the mutation in the obese gene, where there is impaired cellular immunity and thymus.

-However, disturbed leptin and adipocytokines expression and secretion (elevated circulating levels as in obesity and low leptin level as in cancer and malnutrition) may be contribute to risk complications.

-The use of leptin and adipocytokines therapy to modify their levels in patients is promising tool

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for the treatment and prevention of complication risks. Recently, many results revealed that saturated and unsaturated fatty acids are more effective in modulating leptin levels, this may be a useful practical tools, if further studies were done considering immune parameters and factors affecting leptin level.

INTRODUCTION

Adipose tissue in human is a highly active endocrine organ . (Guerre - Millo, 2002 ;Prins, 2002; Kershaw and Flier, 2004, and Krysiak et al. 2005). It plays an active role in energy balance (Klaus, 2004) because it is not only a lipid storing and mobilizing tissue but also consists of functionally specialized tissues able to produce heat in brown adipose tissue and to produce or release a vast number of so called adipokines, adipocytokines or adipose tissue hormones. These tissues consist of polypeptides which are metabolically active molecules belonging to different functional categories like immunity (complement factors, haptoglobulin), endocrine function (leptin, sex steroids, various growth factors) metabolic function (fatty acids, adiponectin , resistin) and cardio-vascular function (angiotensinogen) fatty acids and prostaglandins. To date more than 100 products of adipose tissue are carried by the blood (systemic level) or remain attached to the endothelium of capillaries around the adipose cell (local) e.g. the lipoprotein lipase.

The most studied substance produced by adipose cell is the leptin, a protein , made of 164 amino acids (Junqueria and Carneiro, 2003), which is discovered in 1994 Zhang et al., (1994). Leptin molecule, participate in the regulation of the amount of adipose tissue in the body and in food ingestion. It acts mainly in the hypothalamus to decrease food intake and increase energy consumption (Mantovani et al. 2001, Siegmund et al. 2002 and Huanre, 2005).

It has an important role in hemopoiesis within the bone marrow environment, leptin regulation by these apheliotropic cytokines could contribut to controlling the proliferation and differentiation of hemopoietic precursors as well as the maturation of stromal cells (Laharrague, et al.,2000). In reproduction, leptin has equal potency as LHRH to release gonadotropin by nitric oxide.

GnRH-III specifically releases FSH in rats and cows (McCann et al. 2001), lactation (Holtenius et al ,2003), cardiovascular function and immunity (Krysiak et al. 2005) .The endocrine function of adipose tissue , especially that of leptin is linked to energy storage and this might provide insights into obesity and other diseases associated with energy imbalance (Ahima, 2005).

Leptin regulates immunity and inflamation (Siegmunt et al. 2004), Now it has a modest immune modulatory effect in hypoleptinemic human (Oralea et al. 2006).

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Leptin is an adipocyte derived hormone represents a functional link between the endocrine and immunosystem (Kaser et al. 2002), (Siegmund et al. 2002) and (Matarese et al. 2002).

This report aimed to review some of recent topics of adipokine and cytokines with special focus on leptin that may be of particular importance for immunity and to know whether there was a possibility usage of leptin as a benefit therapy to improve immunity. Alternatively, it has a protective role or as diseases markers?

Glossary:

Cytokines: Secreted proteins that function as mediators of immune and inflammatory reactions. In innate immune response, cytokines are produced by macrophages and natural killer (NK) cells and, in adaptive immune responses, mainly by T lymphocytes.

Interferon (IFN-gamma): A cytokine produced by T-lymphocytes and natural killer cells whose principal function is to activate macrophages in both innate immune responses and adaptive cell mediated immune responses. (In the past, IFN was also called immune or type II interferon.)

Interleukin: Another name for a cytokine, originally used to describe a cytokine made by leukocytes, that acts on leukocytes. It is now generally used with a numerical suffix to designate a structurally defined cytokine regardless of source or target.

Interleukin-1 (IL-1): A cytokine produced mainly by activated mononuclear phagocytes whose principal function is to mediate host inflammatory responses in innate immunity. There are two forms of IL-1 that bind to the same receptors and have identical biologic effects, including induction of endothelial cell adhesion molecules, stimulation of chemokine production by endothelial cells and macrophages, stimulation of synthesis of acute-phase reactants by the liver, and fever.

Interleukin-2 (IL-2): A cytokine produced by antigen activated T cells that acts in an autocrine manner to stimulate T cell proliferation and also potentates apoptotic cell death of antigen-activated T cells. Thus, IL-2 is required for both the induction and regulation of T cell-mediated immune responses. IL-2 also stimulates proliferation and differentiation of natural killer cells and B cells.

Interleukin-3 (IL-3): A cytokine produced by CD4+ T cells that promotes the expansion of immature marrow progenitors of all blood cells. IL-3 is also known as multilineage colony-stimulating factor. (multi-CSF).

Interleukin-4 (IL-4). A cytokine produced mainly by the TH2 subset of CD4+ helper T cells whose functions include inducing differentiation of TH2 cells from naive CD4+ precursors, stimulation of IgE production by B cells, and suppression of interferon- gamma -dependent macrophage functions.

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Interleukn-5 (IL-5): A cytokine produced by CD4+ TH2 cells and activated mast cells, which stimulates the growth and differentiation of eosinophils and activates mature eosinophils.

Interleukin-6 (IL-6): A cytokine produced by many cell types including activated mononuclear phagocytes, endothelial cells, and fibroblasts, which functions in both innate and adaptive immunity. IL-6 stimulates the synthesis of acute phase proteins by hepatocytes and stimulates the growth of antibody-producing B-lymphocytes.

Interleukin-7 (IL-7): A cytokine secreted by bone marrow stromal cells that stimulates survival and expansion of immature precursors of B and T lymphocytes.

Interleukin-8 (IL-8): A cytokine secreted by keratinocyte, fibroblasts, monocytes IL-8 stimulates the neutrophil chemotaxic and activation.

Interleukin-9 (IL-9): A cytokine secreted by T cells IL-9 stimulating proliferation of T cells. Thymocytes, mast cells.

Interleukin-10(IL-10): A cytokine produced by activated macrophages and some helper T cells whose major function is to inhibit activated macrophages and therefore maintain homeostatic control of innate and cell mediated immune reactions.

Interleukin-12 (IL-12): Cytokine produced by mononuclear phagocytes and dendritic cells that serves as a mediator of the innate immune response to intracellular microbes and is a key inducer of cell-mediated immune responses to these microbes. IL-12 activates natural killer (NK) cells, promotes interferon- gamma production by NK cells and T cells, enhances cytolytic activity of NK cells and cytolytic T lymphocytes, and promotes the development of TH1 cells.

Interleukin-15 (IL-15): A cytokine produced by mononuclear phagocytes and other cells in response to viral infection whose principal function is to stimulate the proliferation of natural killer cells. Structurally, it is similar to interleukin-2.

Interleukin-18 (IL-18): A cytokine produced by macrophages in response to LPS and other microbial products, which functions together with IL-12 as an inducer of cell-mediated immunity. IL-18 synergizes with interleukin-12 stimulating the production of IFN- gamma by natural killer cells and T cells.

Major Histocompatibility complex (MHC-I) : proteins on surfaces of all body cells

Major Histocompatibility complex (MHC-II): proteins on surfaces of some immune cells.

CD4: Signaling and adhesion co-receptor in class MHCclass-II restricted antigen-induced T cell

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activation (binds to class II MHC molecules); thymocyte development; primary receptor for HIV retroviruses.

CD8 (alpha &beta): Signaling and adhesion co receptor in MHC class-I restricted antigen-induced T cell activation (binds to class I MHC molecules); thymocyte development

Th1 cells: A functional subset of helper T cells that secretes a particular set of cytokines, including interferon- gamma and whose principal function is to stimulate phagocyte-mediated defense against infections, especially with intracellular microbes.

Th2 cells: A functional subset of helper T cells that secretes a particular set of cytokines, including IL-4 and IL-5, and whose principal functions are to stimulate IgE activation of macrophages, and to counteract the effects of pro-inflammatory cytokines.

Tumor necrosis factor (TNF-alpha) : A cytokine produced mainly by activated mononuclear phagocytes that functions to stimulate the recruitment of neutrophils and monocytes to sites of infection and to activate these cells to eradicate microbes. TNF stimulates vascular endothelial cells to express adhesion molecules and induces macrophages and endothelial cells to secrete chemokines.

Natural killer (NK) cells: A subset of bone marrow-derived lymphocytes, distinct from B and T cells, that function in innate immune responses to kill microbe-infected cells and to activate phagocytes by secreting interferon- gamma NK cells do not express clonally distributed antigen receptors like immunoglobulin of T cell receptors, and their activation is regulated by a combination of cel! surface stimulatory and inhibitory receptors, the latter recognizing self MHC molecules.
(Junqueria and Carneiro, 2003 and Abbas and Lichtman, 2004)

Sources of leptin: Leptin hormone secreted mainly by adipose tissues (Laharrague et al. 2000, Chatzantoni el at., 2004 and Unno el at., 2006). It is also produced by preadipocytes upon TNF-alpha or IL-1 beta stimulation. That preadipocytes could contribute more to total circulating leptin levels than has been previously considered especially in diseased conditions were these pro-inflammatory factors play a prominently role. (Simons et al. 2005).

There are non adipose tissue produce leptin has been reported such as human scalp hair follicles papilla cells and express the functional leptin receptor in vivo and vitro suggestion its autocrine function (Iguchi et al. 2001). The placenta and the stomach secrete it also (Fujita et al. 2002)

Leptin is a product of obese ob gene (Wieland et al. 2005).More recent result reported that the

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source of these secreted factors is not only mature fat cells but also poorly - identified cell present in the stromal - vascular fraction including macrophages (Hauner, 2005).

Leptin receptors:

Leptin receptor is expressed not only in the central nerve system but also in other cells and systems such as somatotrophs (Cai and Hyde, 1999), reproductive, hematopoietic tissues (Martin et al. 2000), macrophages (Raso et al. 2002) and hypothalamus. Leptin acts partly on the long isoform of its receptors on T-lymphocyte (Siegmund et al. 2004), mainly on T-helper lymphocyte.

In addition to leptin, there are other a adipokines, adipocytokines and hormones are produced by adipose tissue.

Adipose tissue produces and releases a variety of proinflammatory and anti-inflammatory factors (IL-1 receptor antagonist) including the adipokines leptin adiponectin, resistin (Milan et al. 2002) and visfatin (Little is known regarding the clinical relevance of visfatin). But recent research has revealed many functions of adipocytokines extending for beyond metabolism, such as immunity, cancer and bon formation (Koerner et al. 2005). As well as cytokines and chemokines such as TNF-alpha, IL-6 monocyte chemottractant protein 1, and others (Juge-Aubry et al. 2004, Kraus et al. 2005 and Matares et al. 2005). In addition to the above production there are more secretions from adipose tissue include acylation stimulation protein (ASP), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, complement components, adipsin, in addition to fatty acids and prostaglandins. Adipose tissue is also a major site for metabolism and production of sex steroids and glucocorticoides. (Gunerre-Millo, 2002, Kershaw and Flier, 2004 and Krysiak et al. 2005).

It should be notice that above adipose tissue secretions are similar with those of immune cell secretions (cytokines).

Immunity and leptin hormone: The immunoresponse to many infections have long been known to share features with autoimmune responses. These observation could be explained partly by taking into consideration the immune effects of the adipocyte derived hormone leptin, which has been shown recently to acts as a link between nutritional status and the immune response (Matarese et al. 2002).

Palacio et al. (2002) suggested an association between the increase in leptin and immunological recovery observed following refeeding of malnourished infants. In the absence of leptin, immunity is suboptimal (Lord et al. 2002). Leptin can also modulate immune and inflammatory response, the role of leptin in intestinal inflammation was focused in study of (Siegmund et al. 2002).The product of the obese gene, leptin, can

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directly influence T-cell function and explored the role of leptin in the development of spontaneous autoimmunity in the Nona obese diabetic mouse, an animal mellitus (type I diabetes), leptin can favour pro-inflammatory cell response and directly influence development of autoimmune disease mediated by Th-1 response (Matarese et al. 2002).

Mechanism of leptin action on immunity:

Is usually via T lymphocytes, macrophage and cytokines.

A)T-lymphocyte:

Leptin is a peptide hormone regulates immune response, its receptors found on hypothalamus and it acts partly on the long isoform of it receptor expressed on T-lymphocytes, promoting T helper1 and by influencing the production of cytokines. (Matarese et al. 2001, Siegmund et al. 2004 and Angelucci et al. 2005). 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 variety of inflammatory conditions, although their pathogenic role has not been completely clarified (Matarese et al. 2005). On other hand, (Sennello ja et al. 2005) reported that leptin increases susceptibility to hepatotoxicity by regulating cytokine production and T-cell activation. Adiponectin protects hepatocytes from TNF alpha-induced death.

Although it is known that leptin stimulates T-cell immunity and also T-cell mediated immune response is critical in the outcome of chronic hepatitis B virus infection (Selimoglu and Ertekin, 2005). Leptin produced by adipocytes increases Th-1 dependent. Immunostimulation and autoimmune diseases (Bleau et al. 2005). But some findings show an inverse relationship between leptin secretion and the frequency of T cells relapsing-remitting multiple sclerosis (RRMS) and may have implications for the pathogenesis of and therapy for multiple sclerosis (MS). In leptin-deficient ob/ob mice, an animal model for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, insufficient norepinphrine increases hepatic natural killer T-cell proinflammatory cytokine polarization. (Li and Diehl, 2003)

B) Mononuclear phagocyte:

White adipose tissue is no longer considered an inert tissue mainly devoted to energy storage but is emerging as an active participant in regulating physiological and pathological processes including immunity and inflammation. Macrophages are components of adipose tissue and actively participate in its activities. Further more cross talk between lymphocytes and a dipocytes can lead to immune regulation. Possible molecular mechanisms of modulation by leptin of phagocytes activity, oxygen - dependent microbicidity, and nitric oxide generation by mononuclear phagocytes are analyzed, as well as the role of leptin in the

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formation of produced cytokine pattern.(Meier et al. 2003. Fantuzzi ." Fantuzzi et al. 2005 and Shirsher and Orlova, 2005)

C) Cytokines:

Many studies clarified the relationships between cytokines and leptin's effect on immunity.

Cytokines serum levels of inflammatory markers and other cytokines important in the T helper cell response.

Stepwise regression analysis showed that there were a significantly positive correlations between IL-1 beta and IL-6, IL-1 beta and nitric oxide, IL-4 and tumor-necrosis factor(TNF)-alpha, IL-4 and leptin. IL-8 and IL-2, and interferon (IFN)-gamma and IL-6, as well as significantly inversed correlations between IL-6 and IL-2, IL-8 and interferon-gamma, and leptin and TNF-alpha in siblings not in the children with diabetes. However, there were significantly positive correlations between IL-2 and IL-4, IL-2 and leptin, IL-4 and IL-6, and TNF - alpha and IL-6 in children with diabetes.

Alterations in circulating IL-8 and nitric oxide levels and cytokine network in children with diabetes may be associated with cardiovascular disease in their adulthood. (Lo et al. 2004).The effect of proinflammatory i.e. interleukin (IL-1 beta, IL-6, interferon (IFN)- gamma, and tumor necrosis factor (TNF-alpha) versus anti-inflammatory cytokines (i.e. IL-4), IL-10 and transforming growth factor (TGF)-beta l) on leptin and adiponectin secretion during in vitro human adipogenesis have studied by (Simons et al. 2005) who found that INF-gamma strongly reduced leptin production. Leptin level was an independent risk factor for INF resistance namely, a high level of serum leptin attenuated the effect of IFN on both male and female patients with low viremia. High serum leptin level is negative predictor of response to antiviral treatment in chronic hepatitis c with low viremia. (Eguchi et al. 2006).

Inhibition of leptin secretion that had been induced by the IFN-gamma-lipopolysaccharide LPS mixture. It is likely therefore that nitric oxide (NO) mediates down regulation of leptin caused by the IFN-gamma-LPS mixture in 3T3-L1 adipocytes, which suggests an important role for NO in adipocyte function (Unno et al. 2006).The beneficial effect of IFN-beta on some secondary progressive multiple sclerosis (SPMS) patient might be associated with the reduced levels of leptin and reduced IL-6 production by SPMC (Angelucci et al. 2005). Leptin replacement restored the reduced INF-gamma response observed in ob/ob mice (Wedland et al. 2005). That the CBA4P isolate reduces levels of leptin in SJL mice, leading to lower INF-gamma production. There fore the CBA4P isolate of L.acidohpilus is a promising new probiotic strain for the control of the inflammatory diseases (Bleau et al. 2005).

The role of leptin, adiponectin, the growth

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hormone axis, glucocorticoides, sterol response element binding protein 1c(SREP-1C), the tumor necrosis factor alpha axis (TFN-alpha), Interleukin-6 (1L-6), Interleukin-18 (1L-18), interferon-alpha (IFN-alpha) tissue plasminogen activator (TPA), and plasminogen activator inhibitor (PAI-1) in the pathophyiology of lipodystrophy (LD) were studied. Adiponectin levels are generally decreased in LD, whereas leptin levels are increased. While some cytokines show promise as markers for LD, it is difficult to tell whether their derangement is a cause of the effect of LD (Krause et al. 2005). Although the higher leptin value observed in children with ETR was not statistically significant, because of close interactions between leptin, cytokines and lymphocytes, it is thought that leptin should be investigated as a predictive factor of ETR in further studies (Selimoglu and Ertekinv, 2005).

D) Leptin acts by humoral immunity also, It can serve as neuroendocrine signal between body fat and immunity regulating humoural immune response (Demas and Sakaria., 2005).

Can alterations in leptin levels be used as a marker for some diseases activity and response to therapy?

Gordeladze et al. (2001) there is pharmacological interference showed with transcriptional control of osteoblasts, a possible role for leptin and fatty acids in maintaining bone strength and body lean mass. (Widjaja et al. 2001) reported that bound leptin levels are elevated in patients with hepatitis C and decrease during antiviral therapy, suggesting either a direct interferon-dependent effect on the leptin system or an alteration of other leptin secretagogues (Sigmund et al.2002). Leptin-deficiency, not obesity is responsible for protection from Con-A-induced hepatitis in mice. During the first year of IFN beta-1 a treatment, leptin significantly decreased since 2 months after starting therapy in 11 patients who had no relapses. a significant decrease in IL12/IL10 ratio was observed in this group of patients only after 1 year of treatment. An increase of leptin was observed before the first clinical exacerbation in 13 relapsing patients.

Leptin may play a pathogenic role in MS and can be a useful marker of disease activity and response to therapy (Batocchi et al. 2003).Some cytokines also show promise as markers for lipodystrophy (LD) (Krause et al. 2005).

Can leptin be used as therapy, or modulates immunity?

The presence of the leptin receptor in human circulating CD4 (+) and CD8 (+) T-lymphocytes and a functional role of leptin as a modulator (enhancer) of lymphocyte stimulation with a shift toward Th1 cytokine - production profile. Leptin is capable of modulating the immune response, RNA expression for the leptin receptor was detected in

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human peripheral blood monocyte.This functions may have relevance in the pathophysiology of immunological alteration and when considering leptin therapy and my partly explain the relationship among leptin, proinflammatory cytokines, insulin resistance and obesity (Martin et al. 2000 and Zarkesh-Esfahani.et al. 2001). However, production of interleukin (IL)-2 by splenic lymphocytes from obese mice was suppressed, whereas interferon (IFN) gamma and IL-4 production were increased. Exogenous leptin regulated the cytokine production by cultured splenocytes from control and obese mice, respectively up regulation of IFN-gamma and down regulation of IL-2 in control mice, and down regulation of IL-4 in obese mice. These result suggest that changes in cytokine production by splenic lymphocytes in obesity are indicative of altered complications immune functions that might contribute to related , although the effect of difference in nutrient intake (macro and micro) may also have contributed to changes.(Mito et al. 2000).

It is known that metallothionein (MT) synthesis occur in the liver in various stressful situations such as immobilization and fasting. However, the mechanism of MT synthesis in stressful situations is not fully understood. Kondoh et al. 2002) who examined the involvement of leptin, the obese gene product, MT synthesis induced by fasting stress. There is an adaptation to starvation. On the other hand, subcutaneous leptin infusion in fasted mice via an osmotic pump resulted in increases in hepatic MT levels compared to the levels in vehicle-treated mice after 24 hr of fasting. These results suggest that MT synthesis in fasting stress is not correlated with decrease in plasma leptin levels but that leptin it self is a potent inducer of MT in a fasting situation.

Does a dipocytes hormones (leptin and an adiponectin play protective roles or/therapy against infections and cells apoptosis?

Nutritional deprivation suppresses immune function. Impaired cell-mediated immunity and reduced levels of leptin are both features of low body weight in humans. Indeed malnutrition predisposes to death from infections diseases. It is reported additionally that leptin has a specific effect on T-lymphocyte responses. Differentially regulating the proliferation of naive and memory T cells. As well as increased TH 1 and suppressed TH2 cytokine production. Administration of leptin to mice reversed the immunosuppressive effects of a cute starvation. These findings suggest a new role for leptin in linking nutritional status to conjugate cellular immune function, and provide a molecular mechanism to account for the immune dysfunction were observed in starvation (Lord et al.1998).

The fast was markedly reduced serum leptin and insulin like growth factor-1 concentrations and

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the non-significant differences occurred in serum cortisol or prolactin before and after fasting as well as decreases in CD4+ lymphocyte activation during fasting correlated with decreases in body weight. These results suggested that the clinical and laboratory improvements in fasting RA (rheumatoid arthritis) patients may be attributed to decreased CD4+ T-cell activation and an increase in the number and / or function of IL-4- producing Th2 cells. The mentioned factors were associated with loss of body weigh during acute starvation appeared to have an inhibitory effect on CD4+ lymphocyte activation (Fraser et al.1999). Additionally, leptin in is induced by lipopolysaccharide (LPS) and cytokines (Faggioni et al. 1999) who investigated the role of leptin in LPS-induced toxicity using, leptin deficient (ob/ob) and leptin receptor-deficient (db/db) in mice. Moreover, treatment with leptin reversed the increased sensitivity to LPS-induced lethality found in ob/ob mice. These results suggested that leptin participates in the host response to inflammation by modulating the host immune and cytokine responses after LPS.

Leptin deficiency enhances sensitivity to endotoxin - induced lethality.

Malnutrition compromises immune function, reducing resistance to infection. (Faggioni et al. 2000) examine whether the decrease in leptin induced by starvation increases susceptibility to lipopolysaccharide (LPS) and tumor necrosis factor (TNF) induced lethality. Fasting increased sensitivity to the lethal effect of TNF^2 itself, which was also reversed by leptin treatment. Thus, leptin seems to be protective by both inhibiting TNF^2 induction by LPS and reducing TNF^2 toxicity.

Thymus atrophy is a prominent feature of malnutrition. Forty-eight hours starvation of normal mice reduced the total thymocyte count to 13% of that observed in freely fed controls, predominantly because of a diminution in the cortical CD4(+) CD8(+) thymocyte subpopulation. Prevention of the fasting-induced fall in the level of the adipocyte-derived hormone leptin by administering exogenous recombinant leptin protected mice from these starvation-induced thymus changes. The ob/ob mouse, which is unable to produce functional leptin because of a mutation in the obese gene, has impaired cellular immunity together with a marked reduction in the size and cellularity of thymus. They found that ob/ob mice had high level of thymocyte apoptosis resulting in a ratio of CD4(+) CD8 (+) CORTICAL TO CD4 (-) CD8(-) (precursor) thymocyte was 4-fold lower than observed in wild-type mice. Peripheral administration of recombinant leptin to ob/ob mice reduced thymocyte apoptosis and substantially increased both thymus cellularity and the CD4(+) CD8(+)/ CD4(-) CD8(-) ratio. In contrast, a comparable weight loss in pair-fed treated ob/ob mice had no impact on thymocyte number in vitro, leptin protected thymocytes from dexamathasone-induced apoptosis. These data indicate that reduced circulating leptin concentration are pivotal in the path-

ogenesis of starvation-induced lymphoid reduction. (Haward et al.1999).

Continuous injection of leptin prevents the reduction in lymphocyte numbers normally observed in fasted and steroid-injected mice. Consistent with leptin-induced protection, it is observed up-regulation of the bcl-xl gene as a result of signal transduction via leptin receptors on lymphocytes it suggest that leptin might contribute to the recovery of immune suppression in malnourished mice by inhibiting lymphocyte apoptosis. (Fujita et al. 2002). Leptin is a peripheral immune enhancing reagent that directly activates splenic lymphocytes in mice. Peripheral leptin replacement completely restored this response in fasted animals.

These results suggest that peripheral leptin has a dominant role in maintaining T-cell-mediated immune responses in rats, and central leptin is unable to compensate for the immunosuppressant associated with peripheral hypoleptinemia. Furthermore, preservation of normal cell-mediated with peripheral hypoleptinemia immune responses does not require fat tissue as along as serum leptin levels are maintained. (Zhang et al. 2002).

In cultured pancreatic islets, Shimabukuro et al. (1997) demonstrated direct extra neural effects of leptin to deplete fat content. Leptin lowered triglyceride (TG) content by preventing TG formation from free fatty acids (FFA) and by increasing (FFA) oxidation. In vivo hyperleptinemia, induced in normal rats by a deno-virus gene transfer, depleted TG content in liver, skeletal muscle, and pancreas without increasing plasma FFA or ketones suggesting intracellular oxidation.

By maintaining insulin sensitivity and preventing islet lipotoxicity, this activity of leptin may prevent an in cultured pancreatic islets adipogenic diabetes.

The thiazolidinedione, anti-diabetic, drugs increase endogenous a adiponectin production in rodents and humans, supporting the Idea that the development of new drugs targeting adipokine might represent a promising therapeutic approach to protect obese patients from insulin resistance and atherosclerosis. (Guerre - Millo, 2004).

Pancreatic beta - cell apoptosis is common feature of type I and type 2 diabetes and leptin exerts an anti-apoptotic function in these cells. The beta-cell line INS-1 was used to test the hypothesis that the adipocyte hormone adiponectin (gAcrp30) might mediate an anti-apoptotic effect comparable to leptin. Novel beta cell protective function of gAcrp30 might serve to counteract autoimmune and lipotoxicity induced beta-cell destruction. (Rakatzi et al .2004)

Furthermore, Leptin replacement restored the reduced IFN-gamma response observed in ob/ob mice. Leptin plays a role in the early immune

response to pulmonary tuberculosis (Wieland et al.2005). But Montez etal,(2005) suggest that high-dosage of leptin treatment can induce a state of acquired leptin resistan

ce.

Factors affected leptin and cytokines levels:

The following factors should be concerned when leptin and other adipocytokines were recommended as therapy or as immune modulators.

a- Sex:

Circulating leptin levels show a marked sexual dimorphism, being higher in females than in males , the findings indicated that leptin administration to susceptible females resulted in more severe disease , and that reduced leptin levels in male SJL mice may contribute to the gender-related differences in the induction phase of EAE (experimental autoimmune encephalomyelitis) (Matarese et al. 2001). Gonadal steroids affect serum leptin concentration in adult male and female rats (Mohamed et al. 2004).

b- Fat diet:

For induction of obesity, C57BL/6J mice were fed high-fat diet for 13 weeks , In mice fed the high-fat diet, body weight , fat pad, weight, and tumor necrosis factor (TNF) alpha production by adipocytes were significantly increased relative to mice fed the normal diet. Lipopolysaccharide (LPS) stimulated proliferation of cultured splenocytes from diet-induced obese mice was also increased (Mito et al. 2002).

Also saturated and unsaturated fatty acids affects leptin levels (A1-Suhaimi., 2006 and A1- Suwaigh. 2006).

c- Diseases:

Serum leptin levels are elevated in some pathologic disorders. Disturbances in adipokine production may have potential repercussions in the pathophysiology of obesity, insulin resistance and dyslipdemia and other disease.(Huner, 2005 and Krysiak et al.2005)

1- Obesity:

Mito et al. (2000) observed decreased T-cell function in obese human subjects and genetically obese animals. But, no decrease in NK, T-cell was observed in con A-injected ob/ob mice, it concluded that leptin - deficiency not obesity, is responsible for protection from con A-induced hepatitis. (Siegmund et al. 2002).

Li et al. (2005) noted that NK T cells are selectively reduced in the fatty livers and obese.When other wise normal mice are fed with high fat or sucrose diet, they become obese, develop fatty livers, and acquire hepatic innate immune system abnormalities, including increased NK T cells apoptosis.The latter reduces liver NK T cell population and promotes excessive hepatic production

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of Th-1 cytokines that promote hepatic inflammation. These diet-induced alterations in the hepatic innate immune system may contribute to obesity-related liver disease:

Obesity is associated with the increased expression of several chemokine gene in adipose tissue. Leptin selectively induces the expression and secretion of interferon-gamma-inducible protein (IP-10) in a human monocytic cell, potentially contributing to the vascular complications associated with hyperleptinemic obesity in humans; in contrast, no significant effect on other inflammatory protein was observed, such as metalloproteinase and other chemokines. (Meier et al.2003) and (Simons et al. 2005).

Immune response can be deeply affected by obesity, playing leptin on important role. Properties of leptin, alteration of leptin levels in different situations and its changes with different medical and surgical therapies for obesity were described in article of Munoz, (2004).

The defects in innate immune function observed in genetically obese animals were not mimicked by dietary obesity and may more likely reflect the gross abnormality in leptin function of these models (Bedoui. 2005). However, (Iorio et al. 2006) reported that leptin did not correlate with hepatic statuses, aminotransferases and serum lipids. Children with obesity-related liver disease showed significantly higher peripheral NK and B. cells and IgA levels.

Question? There is now growing evidence that many secretory factors play an important role in the pathophyiology of the metabolic and cardiovascular complication of obesity. The question arising from these observations is how the secretory pattern of adipose tissue can be modified by dietary and pharmacological measures to reduce the health risks of obesity. (Hauner, 2005).

The answer may be:

More recently, plasma leptin levels were affected by administrated orally fats, saturated fats increase leptin level scientifically but monounsaturated fatty acids (Palestine olive oil) and polyunsaturated fatty acids (fish oil) decreased leptin levels, whereas administration of equal volume of saturated and unsaturated fats modified leptin level to reach its normal levels as in normal human (Kratz et al. 2002) and birds (A1-Suhaimi 2006 and A1- Suwaigh, 2006).This answer may be useful, but need more studies in human.

Many reports explained the association of haplotype A1-A4 with obesity and increased leptin levels. (Puga et al, 2005)

2- Cancer:

On other hand serum levels of leptin in cancer patients were significantly lower than those of

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healthy individuals at all times (7 a. m. noon, 3p.m.) no significant differences were found in circadian rythm between patients and controls . serum levels of IL-1 alpha, IL-6 , and TNF alpha were significantly higher in cancer patients than in healthy individuals , an inverse correlation between serum levels of leptin and IL-6 was found in cancer patient (Mantovani etal.2000, Mantovani et al. 2001, Aleman etal. 2002 and Siegmund et al. 2002).

Cancer anorexia and cachexia are not due to a dysregulation of leptin production. Circulating leptin concentration is not elevated in weight-losing. cancer patients and are inversely related to the intensity of the inflammatory response. In advanced lung cancer patients serum leptin concentrations only depend on the total amount of fat. (Aleman et al.2002).

Despite increased serum leptin levels, animals with MCF-7 IL-1 alpha cell- derived tumors were not anorexic suggesting only peripheral action of tumor-derived leptin, which principally targets lipid metabolism. These suggest that cancer cell-derived cytokines, such as IL-1 alpha,(is an autocrine and paracrine inducer of prometastatic genes in vitro systems) induce cachexia by affecting leptin-dependent metabolism path ways.

Cancer anorexia-cachexia syndrome results from a multifactorial process involving many mediators, including hormones (e.g. leptin), neuropeptides (e.g, neuropeptide y, melanocortin,melanin-concentrating hormone and orexin) and cytokines (e.g. interleukin 1, interleukin 6, tumor necrosis factor alpha and interferon gamma). It is likely that close interrelation among these mediators exists in the hypothalamus, decreasing food intake and leading to cachexia. In the pathogenesis of cancer anorexia, cytokines play a pivotal role influencing the imbalance of orexigenic and anorexgenic circuits that regulate the homeostatic loop of body-weight regulation, leading to cachexia. Interfering pharmacologically with cytokine expression or neural transduction of cytokine signals can be an effective therapeutic strategy in anorectic patients before they develop cancer anorexia-cachexia syndrome. (Ramos et al, 2004)

3- Diabetis :

Leptin accelerated autoimmune destruction of insulin-producing beta cells and significantly increased interferon-gamma production in peripheral T-cells. These findings indicated that leptin could favor proinflammatory cell responses and directly influence development of autoimmune disease mediated by Th.1 responses. (Matarese etal. 2002). In addition, leptin has been implicated in the pathogenesis of multiple sclerosis (MS) leading to speculation about a beneficial effect of fasting to autoimmune patients and that do not warrant a beneficial effect of fasting to MS patient. (Chatzantoni etal. 2004).

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d- Body weight:

The circulating levels of the ob gene product leptin were also significantly correlated with body weight and is not acutely regulated by insulin (Hotta etal. 1996). The modest obesity in hGHRH transgenic mice is associated with increase in leptin synthesis and secretion as well as insulin secretion. (Cai and Hyda.1999).

e- Nutritional status and fasting:

Fasting increases leptin receptor mRNA expression in lean but not obese (ob/ob) mouse Lin and-Huang. 1997), and reduced serum leptin mRNA levels in adipose 48 and 72 h fast in rats.

leptin act as a link between nutritional status and the immune response (Chen et al. 1999, kondoh et al. 2002, Matarese et al. 2002, Zhang et al. 2002 and kappeler et al. 2004. The action of the adipocyte-derived hormone was studied by Moor et al. (2002). They found that leptin has cytokine like function and may mediate the effects of starvation on immunity. Mice with congenital leptin deficiency (ob/ob) have small hypocellularthymuses and impaired cellular immunity. In humans, leptin influences the differentiation of naive and memory cells in vitro, and genetic leptin deficiency has been associated with an ill-defined susceptibility to infection. To describe the in vivo relation of leptin and immune function in children. Fasting plasma leptin concentrations, immune function (T and B cell mediated vaccine responses and delayed type hypersensitivity), and mucosal function (dual sugar permeability test and salivary sIgA concentrations. The data confirm that leptin acts as a peripheral signal of energy restriction, but do not support on association between fasting plasma leptin levels and immune function in children of this age.

f-Other factors:

The ob gene mRNA expression in rats brown adipose tissue (BAT) and epididymal white adipose tissue (WAT) was measured on Northern blots hybridized with a rat ob gene probe. The level of ob gene mRNA in BAT was about 40% of that in WAT. Fasting (36 h) or semi-starvation (10 days) decreased the ob gene mRNA level in both tissues by 62-68% and cold exposure at 6 degrees C (24h) decreased it in BAT -84 but not in WAT. Acute administration of the beta 3-adrenergic agonist Ro 16-8714 decreased ob gene mRNA level in BAT -15% and WAT -28% of lean zucker rats and only in BAT -74% of obese falfa rats. This study demonstrated that, in the rat, the ob gene is not only expressed in WAT but also in BAT, and suggests that in these tow tissue, the modulation of the ob gene expression might be more closely associated with known alteration in cell lipid content than with changes in sympathetic activity. (Moinat et al. 1995).

Effects of seasonality and fasting on the plasma leptin and thyroxin levels of the raccoon dog (Nyctereutes procyonoides) and the blue fox (Alopex lagopus) were studied by (Nieminen et

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al. 2001).

Tauchmanova et al. (2004) reported that increased serum leptin has been described after various organ transplants, the physiological correlation with BMI was lost in the allogeneic setting, indicating a strong influence of factors other than the nutritional status on circulating leptin. No relationship was found between serum leptin levels and time from transplant, age, cortisol, C - reactive protein, and T-lymphocyte CD4 to CD8 ratio. Among the cytokines secreted by type-1/typ-2 T-helper lymphocytes, only serum interferon-gamma significantly correlated with serum leptin levels. Anti-leptin blocking antibodies partially inhibited T-cell activation in mixed lymphocyte reaction, suggesting a link between leptin and T-lymphocyte activation in the allo-SCT setting. These findings suggest that increased serum leptin concentration may contribute to T-cell activation during development of chronic graft- versus-host disease (cGVHD)

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