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Serum leptin level as a diagnostic and prognostic marker in infectious diseases and sepsis
A comprehensive literature review

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Abstract

Background: Infections and sepsis are common causes of morbidity and mortality, with an increasing incidence worldwide. Leptin is involved in the inflammatory process and may modulate the cytokine production, immune cell proliferation and endothelial function. There are conflicting results regarding alterations of leptin levels in infectious diseases and the outcome from sepsis.

The aim of the current article is to provide an overview of the medical literature on the correlations between variations of leptin levels and infectious diseases and sepsis.

Methods: We performed an extensive literature search in PubMed and Google Scholar databases, using keywords to identify articles related to leptin in infectious diseases and sepsis. Searches were referenced using medical subject headings that included "leptin," "adipokines," "sepsis," "infectious diseases," "leptin deficiency," "leptin resistance" or "hyperleptinemia." The language of publication, journal, or country were not included as limitation criteria.

Articles or abstracts containing adequate information, such as age, sex, anthropometric indices, clinical presentation, comorbidities, and management were included in the study, whereas articles with insufficient clinical and demographic data were excluded. We assessed the quality of the studies selected.

The final review of all databases was conducted on June 18, 2020.

Results: We find the results from the current review to be of great importance due to the possible therapeutic role of leptin analogs in states of leptin deficiency associated with infectious diseases or sepsis.

In hyperleptinemia, a therapeutic plan for obtaining leptin neutralization also needs further investigations. This could lead to the reduction of proinflammatory responses.

There is a need for further studies to demonstrate the specificity and sensitivity of leptin in the early diagnosis of sepsis and the need to measure serum leptin levels in routine evaluation of the critical patient.

Conclusion: The multiple effects of leptin are of growing interest, but further studies are needed to elucidate the role of leptin signalling in infectious diseases and sepsis. Because very few human studies are reported, we recommend the need for further research.

Better understanding of the pathophysiology of sepsis and the implication of circulating total leptin in this process could help physicians in managing this life-threatening condition.

Abbreviations: AgRP = agouti-related protein, CD = cluster of differentiation, ERK = extracellular-signal-regulated kinase, HIV = human immunodeficiency virus, IL = interleukin, INF = interferon, JAK = Janus kinase, mTOR = mammalian target of rapamycin, NK = natural killer, Ob-R = leptin receptor gene, POMC = pro-opiomelanocortin, PTP = protein tyrosine phosphatase, SIRS = systemic inflammatory response syndrome, SOCS-3 = suppressor of cytokine signaling-3, SOFA = Sequential [Sepsis-related] Organ Failure Assessment, STAT = signal transducer and activator of transcription, TNF-α = tumour necrosis factor-α.

Keywords: hyperleptinemia, infectious diseases, leptin deficiency, leptin resistance, sepsis

1. Introduction

Infections and sepsis are common causes of morbidity and mortality, with an increasing incidence worldwide. Sepsis is a life-threatening condition and an adequate management is decisive to overcome sepsis-associated mortality.[1,2]

Leptin is involved in the inflammatory process and may modulate the cytokine production, immune cell proliferation, and endothelial function. There are conflicting results regarding alterations of leptin levels and the outcome from sepsis.[3,4]

The aim of the current article was to provide an overview of the medical literature on the correlations between variations of leptin levels and infectious diseases and sepsis.

Leptin deficiency and leptin resistance are studied as pathogenic factors in bacterial, viral, and parasitic infections, with effect on cytokine production, increased susceptibility to infections and altered inflammatory response, and hyperleptinemia is considered an independent predictable factor in the development of sepsis and an unfavourable outcome.[3,5–8]

2. Methods

We performed an extensive literature search in PubMed and Google Scholar databases, using keywords to identify articles related to leptin in infectious diseases and sepsis. Searches were referenced using medical subject headings that included "leptin," "adipokines," "sepsis," "infectious diseases," "leptin deficiency," "leptin resistance," or "hyperleptinemia." The language of publication, journal or country were not included as limitation criteria.

Articles or abstracts containing adequate information, such as age, sex, anthropometric indices, clinical presentation, comorbidities, and management were included in the study, whereas articles with insufficient clinical and demographic data were excluded. We assessed the quality of the studies selected.

The final review of all databases was conducted on June 18, 2020.

3. Results

This review aims to evaluate the role of serum leptin in the early diagnosis of sepsis and as a predictive factor of its evolution. There were significant findings that we observed while conducting this literature review.

The nutritional status is essential for an adequate immune response in infections.[1] Obese patients have increased leptin levels because of hyperleptinemia or leptin resistance and in malnutrition patients present leptin deficiency. Aberrant leptin levels may induce an altered inflammatory response and increased susceptibility to bacterial, viral, and parasitic infections. Hyperleptinemia is considered a predictable factor in the development of sepsis and of an unfavourable outcome.[1,8–12]

There are studies that emphasize the importance of monitoring serum leptin levels in critically ill patients to distinguish between sepsis and non-infectious systemic inflammatory response syndrome (SIRS).[9,13] One of them showed a correlation between leptin, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) in sepsis. The authors found out that a serum leptin threshold of 38 μg/L can differentiate sepsis from noninfectious SIRS, with a sensitivity of 91.2% and a specificity of 85%.[9]

There is an increase in leptin levels in patients with sepsis and a decrease in leptin levels in patients with an unfavourable outcome. Higher leptin levels in patients who survived from acute sepsis were reported in literature. A study reveals that leptin levels above 10 ng/mL were significantly associated with in-hospital mortality.[3] Low leptin and high IL-6 levels indicated an unfavourable prognosis in patients with sepsis, probably because of the absence of the leptin's protective effect.[10]

Experimental studies reveal that leptin-deficient and leptin receptor-deficient mice present thymic atrophy and a defective immune response.[1] Reduced leptin levels in individuals with malnutrition were also associated with altered immune functions and thymic atrophy. These conditions can be reversed by exogenous leptin administration according to the results published in different studies.[1,14–17]

We find the results from the current review to be of great importance due to the possible therapeutic role of leptin analogs in infectious diseases and sepsis.

In hyperleptinemia, a therapeutic plan for obtaining leptin neutralization also needs further investigations. This could lead to the reduction of proinflammatory responses in patients with obesity.

Because few human studies have been reported in literature, there is a need for further studies to demonstrate the specificity and sensitivity of leptin in the early diagnosis of sepsis and the need to measure serum leptin levels in routine evaluation of the critical patient.

4. Discussion

4.1. Leptin

Leptin, a hormone mainly generated by adipocytes, mediates the relationship between food intake and energy expenditure, has a role in body mass control, metabolism and endocrine functions, in the immune response and homeostasis, in the development and functioning of the lung tissue, in reproduction and in the onset of puberty.[18–20] There are other cells that secrete leptin under certain conditions, such as those in the pituitary gland and hypothalamus,[21] placenta,[22] mammary epithelium,[23] lung epithelium, bronchial tissue, type II pneumocytes and lipofibroblasts, stomach,[24] colon, skeletal muscle,[25,26] and bone.[18]

Leptin is a polypeptide and it belongs structurally to the cytokine family. It is encoded by the Ob gene, located on the long arm of chromosome 7, at the position 31.3 (7q31.3), has about 20 Kb length and its receptors have an almost ubiquitary distribution, thus causing multiple biological effects.[8,27,28]

Leptin has a role in both innate and adaptive immunity, it acts as a proinflammatory cytokine and its concentration is influenced by the body mass index, hormones and gender, women having higher concentrations of total circulating leptin compared to men.[1,29,30]

Leptin synthesis is regulated by food intake and correlates with insulin levels. It is increased by glucocorticoids and ovarian sex steroids, and inhibited by testosterone.[31–33] Proinflammatory cytokines acutely increase leptin expression, but chronic stimulation with proinflammatory cytokines suppress leptin production.[34–37]

Leptin deficiency and leptin resistance induce alterations in cytokine production and increase the susceptibility towards infectious diseases.[8] There are studies that associate the effects of an increased body mass index, which induces leptin resistance, as well as the effects of malnutrition, which induces leptin

deficiency, with the likelihood of developing bacterial and viral lung infections, and also parasitic infections.[1,38]

4.2. The mechanism of action of leptin

Leptin circulates freely in the blood stream and its actions take place using membrane bound leptin receptors. Leptin receptor gene (Ob-R) includes short isoforms (Ob-Ra, Rc, Rd, and Rf), 1 long isoform (Ob-Rb), and 1 soluble isoform (Ob-Re).[28,39] Leptin acts via a transmembrane receptor, which is structural related with the class I cytokine receptor superfamily. Class I cytokine receptor superfamily is characterized by extracellular domains.[8,39,40]

The primary signalling route is Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway.[41–43] JAK2 activation induces phosphorylation of tyrosine-based motifs, which act as binding sites for signalling molecules as STAT-1, STAT-3, STAT-5, and STAT6. Other alternative pathways can be induced by leptin, including the phosphoinositide 3-kinases/ phosphodiesterase 3B/cyclic adenosine monophosphate pathway, adenosine monophosphate-activated protein kinase, mammalian target of rapamycin (mTOR), and the mitogen-activated protein kinases cascade.[8,20,42,44] Leptin signalling is inhibited by the increased expression of SOCS-3, which affects JAK/STAT pathway by binding to the Ob-Rb and induces dephosphorylation of JAK2.[28,45] There is also data in literature according to which changes in SOCS-3 expression are related to leptin resistance found in obesity. A negative feedback regulator of Ob-R signalling is protein tyrosine phosphatases 1B (PTP1B), which determines dephosphorylation of JAK2.[8,20,28,44,46–49]

The central function of leptin is metabolic homeostasis, by providing information about the total body fat mass to the hypothalamus. The hypothalamus responds by regulating glucocorticoids and insulin, food intake, and energy balance.[1] Leptin acts via specific receptors in the hypothalamus to control food intake and to permit energy expenditure and appropriate glucose homeostasis.[50,51] Leptin activates a neural circuit which includes anorexigenic and orexigenic neuropeptides to regulate appetite.[51] Orexigenic peptides include neuropeptide Y, melanin-concentrating hormone, agouti-related protein (AgRP), galanin, orexin, and galanin-like peptide. Anorexigenic peptides include pro-opiomelanocortin (POMC), cocaine-regulated transcript and amphetamine-regulated transcript, neurotensin, corticotropin-releasing hormone, and brain-derived neurotrophic factor.[52] Long-term leptin administration in leptin-deficient mice has been shown to increase the number of synapses on neurons that produce POMC and to reduce the number of synapses on neurons that produce Neuropeptide Y.[51,53] Leptin activates POMC neurons, which secrete α-melanocyte-stimulating hormone. α-melanocyte-stimulating hormone activates the melanocortin-4 receptor to induce satiety and increase energy use. Leptin also inhibits AgRP neurons, promoting feeding and reducing energy expenditure. These facts suggest that POMC and AgRP neurons are essential for leptin action and for energy homeostasis.[50]

Leptin also interacts with the mesolimbic dopamine system, which is involved in the interest for feeding, and with the nucleus of the solitary tract, which controls satiety.[51]

Leptin regulates glucose metabolism in the liver through leptin receptors and indirectly through the hypothalamic receptors. Leptin increases glycogen synthesis and storage, suppresses gluconeogenesis, and prevents glucose oxidation by reducing the metabolism of glucose in peripheral tissues.[54]

High leptin levels increase the energy use proportional to body fat and decreases food intake. "Leptin may increase energy expenditure by triggering the uncoupling protein action."[54]

Fasting and prolonged caloric restriction have been shown to result in a decrease in plasma leptin concentration and this induces a neuroendocrine response, reducing the energy use and promoting an orexigenic signal. It also reduces hepatic insulin sensitivity and increases hepatic glucose production.[50,51] Low leptin levels also induce a decrease in sexsteroids levels, a decrease in thyroid hormone levels that will reduce the metabolic rate, a decrease in insulin-like growth factor-1 levels that will slow growth-related processes, and an increase in growth hormone levels that will mobilize energy stores. These results were obtained in both mice and human studies.[51,55–57]

Due to the structural similarities with members from cytokine family, leptin acts as a cytokine, having a key role in immunity, hematopoiesis and angiogenesis. Because it is derived from adipose tissue, it is also called "adipokine," together with adiponectin, apelin, chemerin, and others.[28]

Leptin functions as a hormone and as a regulator of immunity, acting as a proinflammatory cytokine-like IL-1, IL-6, IL-8 and TNF-α. In this way, leptin deficiency increases the susceptibility to infections.[1,38,58] Leptin has a proinflammatory immune response in lungs, stimulating neutrophil and macrophage chemotaxis and increasing oxidative stress, phagocytosis, and cytokine production.[8,20,44,59–62] Leptin induces T-lymphocytes proliferation, has antiapoptotic effects on them and increases T helper cell differentiation.[8,20,44,63–65] Leptin regulates both innate and acquired immunity, increases the immune response by mediating the production of proinflammatory cytokines and by activating Th cells, leading to the activation of monocytes and macrophages and preventing the apoptosis of various immune cells.[1] In innate immunity, leptin amplifies the function of neutrophils, by releasing oxygen free radicals, and the cluster of differentiation molecule 11B (CD11b) expression, leading to the migration of immune cells at the site of inflammation. It also activates monocytes and dendritic cells, thus increasing the secretion of proinflammatory cytokines such as TNF-α, IL-6 and IL-12, leading to the activation of natural killer (NK) cells.[1,66,67] In adaptive immunity, leptin reduces the rate of apoptosis of thymic T-cells by inhibiting FAS-directed apoptosis pathway, but also by up-regulating the expression of B-cell lymphoma-extra large and T-box transcription factor, inducing the maturation of thymic T-cells.[1,68–70]

"Leptin deficiency, a reduced leptin signalling and an increased expression of SOCS-3, all reported in obesity, hypertriglyceridemia, insulin resistance and malnutrition, represent risk factors in host immunity." "Viral infections cause elevated SOCS-3 expression, which inhibits leptin signalling." It results in immunosuppression by T-regulatory cells and the host defence system fails to manage the aggression of pathogens, inducing infections and diminished vaccine-specific antibody response.[28]

Alti and colleagues presented the intervention of leptin in infections and they proposed leptin as an adjuvant tool in the development of new vaccines. Administration of exogenous leptin was used with promising results as vaccine against *Rhodococcus equi* and *Helicobacter pylori* in mice. Leptin signaling in gut cells offered protection against *Clostridium difficile* (*C difficile*) and *Entamoeba histolytica* infections.[28]

4.3. Plasma leptin levels in inflammation and respiratory infections

There are studies on mice that demonstrated that leptin has a role in the respiratory function. Tachypnea, hypoventilation, and respiratory depression are more frequent in cases of obesity and seem to be attenuated by long-term leptin administration.[71,72] These findings suggest that leptin may be a modulator of central respiration.

Malnutrition, which is associated with reduced leptin levels, and obesity, which is associated with leptin resistance, increase the susceptibility to bacterial or viral respiratory infection, such as the H1N1 flu epidemic.[1,38,73–78]

Diez and colleagues studied the implications of leptin levels in community acquired pneumonia. They suggest that leptin does not act as an inflammatory reactant but as a nutritional marker in community acquired pneumonia.[79]

Parmentier and colleagues showed in their study that serum leptin levels were not associated with ventilator-associated pneumonia, but they emphasize the need for further studies to confirm their results and to define the inflammatory role of leptin as a biomarker in intensive care unit patients.[80]

4.4. Leptin in bacterial infections

Some studies showed that in leptin-deficient mice, there are alterations in macrophage- and neutrophil-mediated phagocytosis of bacteria.[8,81–84] Macrophages also showed impaired leukotriene synthesis in vitro and alterations in leukotriene synthesis has been found in patients predisposed to pulmonary infections. All these pathological changes were demonstrated to be restored by the administration of leptin in leptin-deficient mice.[8,82,85–87] Signalling routes STAT3 and ERK play an essential role in host defence against bacterial pneumonia.[82,86,87]

Mice infected with *Klebsiella pneumoniae* (*K pneumoniae*) showed high leptin levels. It remains to be studied if this is because of the increased synthesis of leptin in the lungs or because of the leakage of leptin from the circulation, both present in pulmonary inflammation.[8,20,44,82,86,87] Leptin deficient mice showed a low survival rate after *K pneumoniae* infection, *Streptococcus pneumoniae* (*S pneumoniae*) and *Mycobacterium abscessus* (*M abscessus*). This demonstrates that leptin has a significant role in the immune response against bacterial aggressions.[8,82,83,86–88]

4.5. Leptin in viral infections

There is some data reported in literature on the effects of hyperleptinemia, which leads to leptin resistance, on the immune response to viral infections. An inadequate immune response, with alterations in NK-cell cytotoxicity and delayed proinflammatory cytokine response were found in diet-induced obese mice, which also presented a higher mortality rate upon viral infections.[8,20,44,89,90] Because of the peripheral leptin resistance which leads to impairment in the IL-15 function, diet-induced obesity can affect the T-cell populations in the lung tissue.[8,20,44,91,92]

In diet-induced obesity and leptin deficiency in experimental models with influenza infection there are alterations in mononuclear cells and dendritic cells functions, with consequences on the immune system.[8,44,91–94]

Morgan and Azzoni reported that impaired leptin signalling is caused by an altered defence response in host for influenza AH1N1 and human immunodeficiency virus (HIV) infections, due to the alterations of the immunologic, metabolic, and endocrine processes.[28,95,96]

The findings of Zhang et al showed that leptin has no implication in viral replication, but high levels of serum leptin are associated with severe lung injury by AH1N1 in diet-induced obesity in mice.[27] Low leptin levels in patients with obesity suppress the function of memory T-cell, Interferon (IFN)-α, IFN-β, and IFN-γ and could increase the susceptibility to influenza virus infections.[1]

Patients with HIV infection have an exaggerated expression of leptin receptors and exogenous leptin administration in these patients may reduce their metabolic complications. Oxidative status of monocytes, which leads to an altered immune response in HIV infection, may be diminished by leptin analogs.[1]

4.6. Leptin resistance and hyperleptinemia

Only a few studies reported the effects of high leptin levels and leptin resistance secondary to obesity on the immune response to viral infections and have shown an increase in the mortality rate.[1,3,8,9,20,44,96]

The prevalence of obesity is increasing and obesity is frequent in patients with sepsis.[97,98] The adipose tissue, through the production of cytokines and adipokines, with vasoactive effect, is considered a modulator of inflammation and immunity.[82,83] Adipokines modulate cytokine production, immune cell proliferation, and endothelial function, having a key role in the inflammatory process.[65,99]

In a study published by Jacobsson and colleagues, which was the first prospective study to determine total serum levels of leptin and adiponectin in patients with sepsis, high levels of circulating leptin at baseline were reported to be predictors of sepsis and leptin predicted sepsis-related in-hospital death rate. High levels of circulating leptin were correlated with a first sepsis event and there was a stronger association between high levels of leptin at baseline and more severe forms of sepsis.[1] Jacobsson and colleagues found out that leptin levels above 10 ng/mL were significantly associated with in-hospital mortality.[3]

Baseline leptin levels reflect the nutritional status and correlate to the amount of fat mass.[99–101] High levels of leptin have a proinflammatory effect, inducing the activation of the innate immune system and the release of proinflammatory cytokines. The systemic inflammation and vasoplegia in sepsis lead to hypotension and septic shock. Hyperleptinemia in obese patients induces alterations in endothelial functions and determines an unfavourable evolution or septic shock.[3,102–104] Experimentally, diet-induced obesity in mice leads to a chronic increase in leptin and leptin resistance, inducing a modified immune response, including low cytotoxicity of NK cells and delayed expression of proinflammatory cytokines.[1,8,20,44]

4.7. Leptin deficiency

Reduced serum leptin levels can induce malnutrition and a state of immunodeficiency.[1] Leptin deficiency in both mouse and human studies induces an altered immune response. The alterations in the immune responses are produced mainly by a decrease in total lymphocytes and CD4+ helper T cells number, and also by thymic cells apoptosis, resulting an increased susceptibility to infections.[1]

In leptin receptor-deficient mice, studies showed that STAT3, STAT5, and ERK pathways play a key role in host defence

against bacterial infections and in leukocyte function.[1,8,16,20,44,105]

Experimentally, mice with leptin deficiency or leptin receptor deficiency have been shown to have thymus atrophy and poor immune response. Similarly, in patients with malnutrition, in whom leptin deficiency is present, the same changes occur and these are reversible to the administration of exogenous leptin, emphasizing the possible therapeutic role of leptin analogues in the control of infectious diseases.[1,8]

Studies reported that leptin deficiency is correlated with nutritional deprivation or malnutrition, which affects the innate and acquired immunity of the host, by decreasing the number of T lymphocytes, CD4 + and CD8 +, thus increasing the incidence of infections and the mortality rate. The leptin deficiency present in malnutrition is correlated, through the deficient production of cytokines, with bacterial, viral and parasitic infections, such as pneumonia, flu, tuberculosis, sepsis, colitis, leishmaniasis, trypanosomiasis, amoebiasis, and malaria.[1,8,27,37,106–109]

Leukotrienes have been shown to increase macrophage-mediated phagocytosis and poor leukotriene synthesis has been found in some patients who have been shown to be susceptible to lung infections. Studies showed that leptin-deficient mice have poor survival rate after administration of K pneumoniae, S pneumoniae, and M abscessus, which does not appear to be due to impaired inflammatory cell recruitment but rather as a result of defective phagocytosis. Moreover, macrophages in leptin deficient mice showed decreased in vitro leukotriene synthesis. Mice infected intratracheally with K pneumoniae have elevated serum leptin levels. The macrophages- and neutrophils-mediated phagocytic response and the leukotrienes production can be restored by administration of leptin to leptin-deficient mice.[8,20,44]

Recent observational and interventional studies in humans showed that leptin replacement therapy could improve the management in leptin deficiency syndromes. "R-metHuLeptin replacement therapy could prove to be a new potentially useful medication for states of absolute or relative leptin deficiency to restore neuroendocrine, metabolic or immune function in low-leptin states such as (congenital or acquired) lipodystrophy or exercise-induced hypothalamic amenorrhea." To prove the efficacy of leptin analogs more long-term interventional studies are needed.[110] Leptin replacement therapy in pediatric patients with congenital leptin-deficiency restored the Th1/Th2 cytokine balance and induced proliferation of lymphocytes, neutrophils and monocytes, with no effect on body weight.[17,28]

4.8. Serum leptin levels in critically ill patients

Leptin is recognized for its role in the neuroendocrine response to stress, but also for its role in human defence mechanisms. In sepsis, the neuroendocrine and metabolic responses take place in an acute first phase, by activating the hypothalamic-pituitary-adrenocortical axis, with hypersecretion of growth hormone in the presence of low concentrations of insulin-like growth factor-1 and thyroid hormones, as well as low gonadal activity. Insulin resistance and a decreased glucose use appear, beneficial in reducing the energy consumption of the macroorganism. Systemic inflammation, insulin resistance and hyperglycemia are common features of critical illness.[111–114] In cases where this stage lasts more than 8 to 10 days, there is an inhibition of hypothalamic-pituitary function with the development of cachexia, even under conditions of a normal diet of the patient. The role of leptin has not been much investigated in sepsis, but the administration of endotoxin to healthy volunteers increases its concentration at much higher levels compared to control groups.[112–114]

Sepsis is defined, according to 2016 terminology, by life-threatening organic dysfunction caused by a defective response of the host to infection. "Sequential [Sepsis-related] Organ Failure Assessment" (SOFA) score is a marker for organ dysfunction and disease severity. Organic dysfunction is assessed based on an increasing SOFA score by 2 points or more, associated with in-hospital mortality greater than 10%.[3,115] The occurrence of circulatory, cellular, and metabolic abnormalities, which increase the risk of in-hospital mortality by over 40%, defines septic shock. Hypotension is associated with persistent sepsis, despite adequate volume rebalancing, which requires positive inotropic support.[115–117]

Monitoring circulating total leptin levels has been proven to have an important role in distinguishing sepsis from SIRS with an etiology other than infection. Yousef and colleagues found out that a serum leptin cut-off level of 38 µg/L has a key role in differentiation between sepsis and noninfectious SIRS, with a sensitivity of 91.2% and specificity of 85%.[9]

In a study conducted by Bornstein and colleagues, it was revealed that there is a loss of diurnal rhythm in cortisol and leptin secretion in patients who survived acute sepsis. In the control group serum leptin and cortisol levels had circadian rhythms with increased nocturnal total serum leptin levels and low nocturnal cortisol levels. "Mean leptin levels were three-fold higher in patients who survived the septic episode than in non-survivors."[10] Similar results were published, suggesting that hyperleptinemia may be a host defense mechanism during sepsis.[11]

Tzanela and colleagues showed that leptin levels are higher at the onset of sepsis and they correlate with insulin levels and insulin resistance. Low leptin levels were found in prolonged sepsis, but findings revealed that this was not related to survival.[12]

Severe hypotension, tachycardia, and immune response increase are observed in sepsis. Sepsis is responsible for multiple organ dysfunction and high mortality rate. Leptin administration has a protective role against the effects of sepsis and endotoxemia. It is has been suggested that leptin elevates blood pressure.[21,58,118] "Vallejos and colleagues reported that leptin administration reduced hypotension and tachycardia on experimental models." Their study also reported that leptin administration decreased the oxidative stress and reduced proinflammatory cytokines levels, such as TNF-α, IL-1β, and IL-6. They demonstrated that administration of exogenous leptin decreased the death risk in sepsis at early and late stages. It is taken into consideration the potential preventive therapy with exogenous recombinant leptin against sepsis in critically ill patients.[118]

There is some data published that shows that alteration of the STAT3 signalling pathway increases susceptibility to C difficile infectious colitis and bacterial peritonitis, and leptin administration has been shown to restore the protective response of the intestinal mucosa in C difficile infection in both mice and humans.[1,109]

Takahashi and colleagues report that leptin deficiency is fatal in mice suffering from sepsis due to multiple organ failure.[119] Systemic leptin replacement modulated the immune response against sepsis and increased survival in leptin-deficient mice. Tschöp and colleagues reported higher leptin levels in patients recovered from sepsis compared to that of nonsurvivors. These results also suggest the potential therapeutic benefits of leptin in infectious disease.[28,120]

5. Conclusions

Over the past decade, the role of total serum leptin in infectious diseases and sepsis has been explored in experimental models on mice and in few human studies.

This review shows results from different studies. A significant progress has been made in understanding the role of leptin in the immune response and in inflammatory and infectious diseases. Emerging data from animal models and humans indicates that leptin could control the systemic immune defense response and further suggests the possible therapeutic potential of exogenous leptin administration in infectious diseases and sepsis. Monitoring serum leptin levels in critically ill patients could be of great value for early diagnosis and prognosis of sepsis. The early diagnosis of sepsis, the identification of its origin and an adequate therapeutic management are crucial to overcome sepsis-associated mortality.

The multiple effects of leptin are of growing interest, but further studies are needed to elucidate the role of leptin signalling in infectious diseases and sepsis. This could contribute to new therapeutic approaches and a more favourable outcome in this pathology. Because most of the studies regarding this subject are based on animal models and very few human studies are reported, we recommend the need for further research.

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Correction

When originally published, the authors names were incorrect and written as Birlutiu Victoria and Boicean Loredana Camelia. They have been corrected to Victoria Birlutiu and Loredana Camelia Boicean.

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