World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

An Update on the clinical usefulness of Leptin

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Received: 13-01-2015 / Revised: 22-01-2015 / Accepted: 26-01-2015

ABSTRACT

Leptin is a hormone secreted by fat cells present in adiposities and is said to play a host of useful functions in a variety of disorders like insulin resistance, dyslipidemia, hypodystrophy, lipoatrophy, hyperinsulinemia, glycemic control, obesity, weight loss and hepatic steatosis. The clinical and pharmacological usefulness of leptin has been extensively studied recently. This review article present an up-to-date research findings carried out during the last decade highlighting its usefulness in a variety of disease status such as diabetes, PCOS, Ovulatory menstruation, cancer, regulation of hepatic, kidney, cardiac, reproductive and immune functions.

Key Words: Leptin,Insulin Resistance, Obesity,T2DM,Lipoatrophy

INTRODUCTION

Leptin is the first of a group of adipocyte-secreted hormones to be used clinically to treat hypoleptinemic states.Leptin induces satiety and a dramatic loss of weight in children with congenital hypoleptinemia with extreme obesity.Leptin also ameliorates insulin resistance (IR), hyperglycemia ,hyperinsulinemia, dyslipidemia, and hepatic steatosis in leptin deficient patients.Further, leptin therapy restores gonadotropinsecretion as well as Luteinizing and thyroid stimulating hormones pulsatility (1).In hypoleptinemic patients, a dramatic improvement was observed in glucose metabolism, dyslipidemia and hepatic steatosis when leptin was administrated. Leptin is the first and the only adipocyte hormone to show effects in all of the above disorders (2). Leptin administration is the safe and effective therapy for patients with resistance diabetes, congenital lipodystrophy and hypertriglyceridemia (3).Leptin certainty represent an important hormone in many disorders associated with diabetes mellitus affecting organs of liver and cardiac muscle (4).

To have therapeutic potential, leptin needs to be modified and upregulated to allow it to enter the brain more easily. To achieve effective weight loss, it may also be necessary to overcome central leptin insensitivity by developing agents that act downstream of leptin action [5]. Following r-metHuLeptin therapy, serum LH response to LH releasing hormone did not show significant changes. In both genders, insulin-like growth factor increased significantly and there were no differences in growth hormone, thyroid, or adrenal hormone levels following r-metHuLeptin therapy. Glycemic parameters significantly improved after r-metHuLeptin therapy and hence such therapy plays an important role in insulin sensitivity. In females, it plays an additional role in normalizing menstrual function [6].R-metHuLeptin led to significant and sustained improvements in glycemia, dyslipidemia and hepatic steatosis. Leptin represents the first novel, effective and long-term treatment for severe forms of lipodystrophy [7]. Leptin treatment also prolonged the survival of syngeneic islets transplanted into Bio Breeding Diabetic Resistance (BBDR) rats. In diverse therapeutic settings, leptin treatment makes significant beneficial effects in modulating virally induced type 2 Diabetes Mellitus (T2DM). Further evaluation of leptin as a potential adjunct therapeutic agent for treatment of human type 1 diabetes to be explored [8].

Leptin deficiency is also evident in patients with diet- or exercise-induced hypothalamic amenorrhea and lipoatrophy. Replacement of leptin in physiologic doses restores ovulatory menstruation in women with hypothalamic amenorrhea and improves metabolic dysfunction in patients with

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lipoatrophy, including lipoatrophy associated with HIV or highly active antiretroviral therapy. The applications of leptin continues to grow and soon it may be used therapeutically [9]. Leptin appears to play a major role in organogenesis which may adversely affect the risk of developing a number of diseases in adulthood. Greater understanding of the role of leptin during development may therefore assist in the prevention and treatment of a number of disease states that occur in adulthood [10]. Leptin may play a crucial role in mediating malignant cell and tumor micro environment interactions. Leptin plays as an amplifier of estrogen signaling in tumor epithelial cells contributing to the promotion of carcinogenesis and acts as a crucial player in mediating tumor-stroma interaction and influencing epithelial to mesenchymal transition linked mechanisms that may sustain breast cancer growth and progression [11].

Leptin hormone acts via a specific receptor in the brain to regulate energy balance and body weight, although this protein can also elicit a myriad of actions in peripheral tissues. Obese individuals, rather than be leptin deficient, have in most cases, high levels of circulating leptin. The failure of these high levels to control body weight suggests the presence of a resistance process to the hormone that could be partly responsible of disturbances on body weight regulation [12]. The clinical utility in leptin deficient individuals and its potential to improve metabolic bone disease need further studies. Future randomized studies are needed to fully assess the potential and risk-benefit of leptin's use in metabolic bone disease, particularly in leptin deficient individuals [13]. Elevated circulating leptin levels in obesity appears to contribute to the low-grade inflammatory background which makes obese individuals more susceptible to increased risk of developing cardiovascular diseases(CVD), diabetes, or degenerative disease including autoimmunity and cancer. An overview of recent advances on the role of leptin in the pathogenesis of several autoimmune disorders that may be of particular relevance in the modulation of the autoimmune attack through metabolic-based therapeutic approaches have been extensively presented [14].

It is widely accepted that leptin can directly link nutritional status and pro-inflammatory T helper1 immune responses, and that a decrease of plasma leptin level during food deprivation can lead to an impaired immune function. Several studies have implicated leptin in the pathogenesis of chronic inflammation. Reduced levels of leptin such as those found in malnourished individuals have been linked to increased risk of infection and reduced cell-mediated immune responses. The functional influences of leptin in the pathophysiology of inflammation, and the effects of leptin in the modulation of such responses has already been documented [15]. There was a significant association of leptin with pathogenetic risk of Coronary Heart Disease (CHD) and stroke, and raised leptin levels could significantly increase the pathogenetic risk of CHD [16]. Lean women with Poly Cystic Ovarian Syndrome (PCOS) had higher serum leptin levels than those without PCOS, which was not the case for overweight/obese women. Adipose tissue might play an important role in the metabolic complications in women with PCOS. Impact of obesity biomarkers in women with PCOS, overweight/obese and lean women should be considered separately [17].

Leptin and adiponectin have opposite effects on subclinical inflammation and IR. Leptin upregulates proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 which are associated with IR and T2DM. In contrast, adiponectin has anti-inflammatory properties and down regulates the expression and release of a number of proinflammatory immune mediators. Therefore, it appears that interactions between angiotensin II and leptin/adiponectin imbalance may be important mediators of the elevated risk of developing T2DM and CVD associated with abdominal obesity [18]. Treatment of obese people with leptin was given less attention and the focus of obesity research shifted towards the prevention and reversal of the state of leptin resistance. Many of these new promising approaches aim to restore or sensitize the impaired function of the leptin receptor by pharmacological means [19].Leptin has key roles in the regulation of energy balance, body weight, metabolism and endocrine function. Leptin levels are undetectable or very low in patients with lipodystrophy, hypothalamic amenorrhea and congenital leptin deficiency (CLD) due to mutations in the leptin gene. For these patients, leptin replacement therapy with metreleptin (a recombinant leptin analog) has improved or normalized most of their phenotypes, including normalization of endocrine axes, decrease in IR and improvement of lipid profile and hepatic steatosis. A better understanding of the physiological roles of leptin may lead to the development of leptin-based therapies for other prevalent disorders such as obesity-associated nonalcoholic fatty liver disease (NAFLD), depression and dementia [20].

Some of the major markers are IL-2, IL -6 andTNF-α in the pathogenesis of DM and its complications. It is established that patients with T2DM lasting from 5 to 10 years represent the

highest leptin and cytokines levels, and during this period cardiovascular complications of T2DM are formed. Also it is found that leptin level was significantly lower in patients with normal body weight, while the levels of IL-6 and TNF-α are the highest in these patients. Obviously, the increased level of these cytokines helps to maintain a normal body weight in these patients. Despite the fact that T2DM is considered a non-autoimmune disease, it is known that for a long glucose toxicity and lipotoxicity metabolic immunosuppression occurs, which causes changes in T-cell immunity and consequently to autoimmunity [21].

A moderate weight reduction in obese participants over a short period significantly improved IR. Such weight reduction concomitantly decreased serum leptin, increased ghrelin and elevated some erythrocyte unsaturates. Only leptin correlated independently with IR improvement using multivariable logistic regression analysis, which indicates that leptin may play a role in the modulation of IR following weight loss [22].C reactive protein (CRP) is an inflammatory marker believed to be of value in the early prediction of T2DM. Recent studies have shown a positive significant correlation between leptin and CRP levels in healthy controls and patients with newly diagnosed DM and after metformin therapy, while there was no significant correlation between leptin and CRP in patients with long-standing therapy [23].Coadministration of leptin with islet transplantation robustly improved control of glucose and lipid metabolism without increasing circulating insulin levels. Low-dose leptin administration can reduce the number of transplanted islets required to achieve metabolic control in streptozotocin induced diabetic mice [24].There is a pressing need for new effective therapeutic strategies for addressing the epidemic of T2DM. Leptin has been shown to reduce hyperglycemia in rodent models of T1DM and has recently been shown to normalize fasting plasma glucose concentrations in a rodent model of polygenic obesity and T2DM suggesting that leptin may be an effective therapeutic option for both type 1 and type 2 DM patients [25].

Leptin exerts antidiabetic actions that are independent of its regulation of body weight and food intake. In particular, leptin can correct both form of DM in animal models. In addition, long-term leptin replacement therapy improves glycemic control, insulin sensitivity and plasma triglycerides in patients with severe IR due to lipodystrophy [26].Various studies have proposed that excessive or deficient physiological effects mediated by leptin make an important contribution, yet many paradoxical observations often preclude a clear definition of the role of leptin [27]. Relationships between fasting morning leptin levels and cognitive ability and estimated cognitive change when tested, significantly estimated overall cognitive decline and poor performance in mental flexibility and other functions amongst men. High morning leptin levels in elderly men with T2DM are associated with estimated age-related cognitive change [28].

Elevated resistin and TNF-α levels and low levels of adiponectin secretion may have implications for the risk of development of T2DM and CVD [29]. Leptin regulates energy homeostasis reproductive, neuroendocrine, immune and metabolic functions. The long-term efficacy and safety of leptin treatment in hypothalamic amenorrhea and acquired lipoatrophy are currently under investigation. Whether combination therapy with leptin and potential leptin sensitizers will prove effective in the treatment of garden-variety obesity(GVO) and whether leptin may have a role in weight loss maintenance is being greatly anticipated [30].States of energy excess such as GVO are associated with hyperleptinemia that reflects either leptin tolerance or leptin resistance. For those conditions, development of leptin sensitizers is currently a focus of pharmaceutical research [31].

Leptin is the best characterized adipokine involved in energy metabolism and inflammatory status, being associated with the development of a number of diseases, including atherosclerosis, DM, certain cancers and immune-mediated processes. Recently leptin was found to exert neurotrophic effects and neuroprotective activity slowing down neuronal damage after acute brain injuries as well as during long-term neurodegenerative processes. Moreover there are evidences that leptin influences receptor signalling as well as the synthesis and releasing of several neurotransmitters [32]. Studies shows that circulating leptin diminishes together with body mass index after successful weight loss following lifestyle modifications or bariatric surgery. Studies providing evidence for the effect of other medications on leptin levels inNAFLD populations are limited and of low power. Data from small studies claim that recombinant leptin administration had a possibly beneficial effect on steatosis, but not fibrosis in NAFLD patients with hypoleptinemia. Although the aforementioned dual leptin action has not yet been validated in humans, leptin administration in NAFLD patients with normoleptinemia or hyperleptinemia is discouraged. Further well-controlled studies in cautiously selected populations are needed to elucidate whether leptin has any prognostic and therapeutic role in NAFLD patients [33].

Leptin circulates in proportion to body fat mass, thus serving as a satiety signal and informing central metabolic control centers as to the status of peripheral energy stores. It participates in numerous other functions both peripherally and centrally, as indicated by the wide distribution of leptin and the different isoforms of its receptor in different tissues including the heart. This hormone has distinct effects on the reproductive, cardiovascular, and immune systems; however, its role in the heart could mediate wide physiological effects observed in obese individuals. Oxidative stress is associated with obesity and may be considered to be a unifying mechanism in the development of obesity-related comorbidities. It has been reported that obesity may induce systemic oxidative stress; in turn, oxidative stress is associated with an irregular production of adipokines [34]. Weight-loss induced hypoleptimia raises insulin sensitivity and promotes its parasympathetic anabolic actions while obesity-induced hyperleptinemia supresses insulin lipogenic action and inhibition by leptin of bone mineral accrual suggesting that leptin may contribute to the maintenance of stability of skeletal, lean-body, as well as adipose tissue masses [35].The stringent binding affinity of leptin and its receptor Ob-R, as well as the highly upregulated expression of both leptin and Ob-R in cancer cells compared to normal cells, makes leptin an ideal drug target for the prevention and treatment of Hepatocellular carcinoma, especially in obese patients [36].

Functional crosstalk between leptin, IL-1 and Notch signaling (NILCO) found in breast cancer cells could represent the integration of developmental, proinflammatory and pro-angiogenic signals critical for leptin-induced breast cancer cell proliferation/migration, tumor angiogenesis and breast cancer stem cells (BCSCs) [37]. Significant correlations between obesity and incidence of various cancers have been reported. Obesity, considered a mild inflammatory process, is characterized by a high level of secretion of several cytokines from adipose tissue. These molecules have disparate effects, which could be relevant to cancer development. Among the inflammatory molecules, leptin, mainly produced by adipose tissue and over expressed with its receptor (Ob-R) in cancer cells is the most studied adipokine [38].

In obese people, proinflammatory cytokines/ chemokines including TNF-α,IL-1, IL-6, insulin, insulin-like growth factors, adipokines, plasminogen activator inhibitor-1, adiponectin and leptin are found to play crucial roles in the initiation and development of cancer. The cytokines induced by leptin in adipose tissue or tumor cells have been extensively studied. Leptin-induced signaling pathways are critical for biological functions such as adiposity, energy balance, endocrine function, immune reaction and angiogenesis as well as oncogenesis. Leptin is an activator of cell proliferation and anti-apoptosis in several cell types and an inducer of cancer stem cells; its critical roles in tumor genesis are based on its oncogenic, mitogenic, proinflammatory and pro-angiogenic actions [39]. The role of leptin in regulating immune response has been assessed in vitro as well as in clinical studies and it has been shown that conditions of reduced leptin production are associated with increased infection susceptibility. Conversely, immune-mediated disorders such as autoimmune diseases are associated with increased secretion of leptin and production of proinflammatory pathogenic cytokines suggesting that leptin is a mediator of the inflammatory response [40]. Obesity leads to the dysfunction of adipocytes and correlated with the imbalance of adipokines levels. In obese and diabetic conditions, leptin deficiency inhibited insulin pathways. Functional balance of both adipocytes and immune cells is important to exert their effects on endocrine metabolic disorders; furthermore, adipose tissue should be renamed not only as a functional part of the endocrine system but also as a new part of the immune system [41]. Besides physiological roles, leptin may influence pathological conditions like obesity-associated atherosclerosis, oxidative stress and cancers [42]. The steroid hormones are linked to the regulation of leptin and the leptin receptor and probably interact with other pregnancy-specific, serum-borne factors to regulate leptin dynamics during pregnancy. In addition to its effects on normal conceptus development, leptin is linked to mechanisms affecting a diverse array of pregnancy-specific pathologies that include preeclampsia, gestational diabetes and intrauterine growth restriction. Association with these anomalies and with mechanisms pointing to a fetal origin for a range of conditions affecting the individual's health in adult life, such as obesity, DM and CVD reiterates the need for continued research dedicated to elucidating leptin's roles and regulation throughout gestation [43].

CONCLUSION

Leptin, a hormone secreted by adipose tissue has been implicated in a variety of disease states particularly in T2DM. Research carried out during the last decade on the clinical usefulness of leptin has linked its role is a variety of organ functions. Leptin shows a host of functions related to dramatic loss of weight, insulin resistance,

hyperglycemia, dyslipidemia, hepatic steatosis, menstrual regulation, cancer prevention, metabolic bone diseases, poly cystic ovarian syndrome, chronic liver disease, infections to name a few. This review articles brings in a nutshell the research findings on leptin during the last decade. The contents of this paper will through some awareness on research scholars and pharmaceutical companies to further explore more clinical usefulness of leptin and to formulate a safe saving drug design for leptin treatment.

REFERENCES

1. Gorden P etal. The clinical uses of leptin.CurrOpinPharmacol. 2003 Dec;3(6):655-9.
2. Gorden P etal. The clinical efficacy of the adipocyte-derived hormone leptin in metabolic dysfunction. Arch PhysiolBiochem. 2006 Apr;112(2):114-8.
3. JazetIM etal. Therapy resistant diabetes mellitus and lipodystrophy, leptin therapy leads to improvement. Ned TijdschrGeneeskd. 2013;157(4):A5482.
4. Petersen KF etal. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest. 2002 May;109(10):1345-50.
5. Proietto J etal. The therapeutic potential of leptin.Expert OpinInvestig Drugs. 2003 Mar;12(3):373-8.
6. Musso C etal. The long-term effect of recombinant methionyl human leptin therapy on hyperandrogenism and menstrual function in female and pituitary function in male and female hypoleptinemiclipodystrophic patients. Metabolism. 2005 Feb;54(2):255-63.
7. Javor ED etal. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. Diabetes. 2005 Jul;54(7):1994-2002.
8. Kruger AJ etal. Leptin treatment confers clinical benefit at multiple stages of virally induced type 1 diabetes in BB rats. Autoimmunity. 2011 Mar;44(2):137-48.
9. Kelesidis T etal. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010 Jan 19;152(2):93-100.
10. BriffaJF etal. Leptin in pregnancy and development: a contributor to adulthood disease? Am J PhysiolEndocrinolMetab. 2014 Dec 16:ajpendo.00312.2014.
11. Ando S etal. The Multifaceted Mechanism of Leptin Signaling within Tumor Microenvironment in Driving Breast Cancer Growth and Progression. Front Oncol. 2014 Nov 26;4:340.
12. Sainz N etal.Leptin resistance and diet-induced obesity, central and peripheral actions of leptin.Metabolism. 2015 Jan;64(1):35-46.
13. Upadhyay J etal. The role of leptin in regulating bone metabolism.Metabolism. 2015 Jan;64(1):105-113.
14. Procaccini C etal. Leptin in autoimmune diseases. Metabolism. 2015 Jan;64(1):92-104.
15. Iikuni N etal. Leptin and Inflammation. CurrImmunol Rev. 2008 May 1;4(2):70-79.
16. Zeng R etal. Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis. Arq Bras EndocrinolMetabol. 2014 Nov;58(8):817-23.
17. Chen CI etal. Adiponectin and leptin in overweight/obese and lean women with polycystic ovary syndrome. GynecolEndocrinol. 2014 Nov 25:1-5.
18. Lopez-Jaramillo P etal. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes.HormMolBiolClinInvestig. 2014 Apr;18(1):37-45.
19. Roujeau C etal. New pharmacological perspectives for the leptin receptor in the treatment of obesity. Front Endocrinol (Lausanne). 2014 Oct 13;5:167.
20. Paz-Filho G etal. Leptin treatment: Facts and expectations. Metabolism. 2015 Jan;64(1):146-156.
21. Mankovsky BM etal. The blood leptin and the activity of the system inflammatory response in patients with diabetes mellitus type 2 with different body weight and disease duration. FiziolZh. 2014;60(4):56-60.
22. Wang TN etal. Relationships between changes in leptin and insulin resistance levels in obese individuals following weight loss. Kaohsiung J Med Sci. 2013 Aug;29(8):436-43.
23. Morteza A etal. lost correlation 0329. between leptin and CRP in type 2 diabetes. Eur Cytokine Netw. 2013 Mar;24(1):53-9.
24. The Denroche HC etal. Leptin administration enhances islet transplant performance in diabetic mice. Diabetes. 2013 Aug;62(8):2738-46.
25. Cummings BP. Leptin therapy in type 2 diabetes. Diabetes ObesMetab. 2013 Jul;15(7):607-12.
26. Coppari R, Bjoraek C. Leptin revisited: its mechanism of action and potential for treating diabetes. Nat Rev Drug Discov. 2012 Sep;11(9):692-708.
27. Abel ED, Sweeney G. Modulation of the cardiovascular system by leptin. Biochimie. 2012 Oct;94(10):2097-103.
28. Labad Jetal. Serum leptin and cognitive function in people with type 2 diabetes.Neurobiol Aging. 2012 Dec;33(12):2938-2941.e2.
29. Van Gaal LF etal. Health risks of lipodystrophy and abdominal fat accumulation: therapeutic possibilities with leptin and human growth hormone. Growth Horm IGF Res. 2003 Aug;13Suppl A:S4-9.
30. Dardeno TA etal. Leptin in human physiology and therapeutics. Front Neuroendocrinol. 2010 Jul;31(3):377-93.
31. Bluher S, Mantzoros CS. Leptin in humans: lessons from translational research. Am J ClinNutr. 2009 Mar;89(3):991S-997S.
32. Teryaeva NB. Leptin as a neuroprotector and functional stability factor in the central neural system.Ross FiziolZhIm I M Sechenova. 2013 Oct;99(10):1138-48.
33. Polyzos SA etal. Leptin in nonalcoholic fatty liver disease: A narrative review. Metabolism. 2015 Jan;64(1):60-78.
34. Martinez-Martinez E etal. Leptin, a mediator of cardiac damage associated with obesity. HormMolBiolClinInvestig. 2014 Apr;18(1):3-14.
35. Borer KT. Counterregulation of insulin by leptin as key component of autonomic regulation of body weight. World J Diabetes. 2014 Oct 15;5(5):606-29.
36. Jiang N etal. Leptin signaling molecular actions and drug target in hepatocellular carcinoma. Drug Des DevelTher. 2014 Nov 14;8:2295-302.
37. Newman G etal. Leptin-cytokine crosstalk in breast cancer.Mol Cell Endocrinol. 2014 Jan 25;382(1):570-82.
38. Guo S etal. Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. BiochimBiophysActa. 2012 Apr;1825(2):207-22.
39. Jiang N etal. Leptin signaling molecular actions and drug target in hepatocellular carcinomaDrug .Des DevelTher. 2014 Nov 14;8:2295-302.
40. Fernandez-Riejo P etal. Role of leptin in the activation of immune cells. Mediators Inflamm. 2010;568343.
41. A Suhaimi EA etal. Leptin, resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. Eur J Med Res. 2013 May 1;18:12.
42. Anubhuti, Arora S. Leptin and its metabolic interactions: an update. Diabetes ObesMetab. 2008 Nov;10(11):973-93.
43. Henson MC, Castracane VD. Leptin in pregnancy: an update. BiolReprod. 2006 Feb;74(2):218-29.