Role of Leptin in Diabetes: Analytical Essay

Abstract:

Diabetes is a disease in which your blood glucose, or blood sugar, levels are too high. Glucose comes from the foods you eat. Insulin is a hormone that helps the glucose get into your cells to give them energy. With type 1 diabetes, your body does not make insulin. With type 2 diabetes, the more common type, your body does not make or use insulin well. Without enough insulin, the glucose stays in your blood.

Leptin is a peptide hormone released from adipose tissue and encoded by the obese (ob) gene. It is often called the" satiety" hormone. While leptin's role is classically described in the regulation of appetite, neuroendocrine function, and energy homeostasis, it seems to influence several other physiological processes. These include metabolism, endocrine regulation, and immune function with possible other functions still awaiting characterization. Leptin abnormalities have associations with a variety of metabolic syndromes, particularly obesity. The study of leptin physiology has contributed to our understanding of energy homeostasis, and it seems likely that it will play a pivotal role in developing an effective treatment and a solution to the growing obesity epidemic. The total body fat mass index (BMI), metabolic hormones, and gender are the factors that have the greatest effect on circulating plasma leptin concentrations. Women have higher levels of circulating leptin compared to men.

This review aims to shed some light on the relationship between leptin and diabetes in general.

Introduction:

Leptin:

Leptin is produced by the white adipose tissue of the body that is known to act on the hypothalamus. The hypothalamus in turn is responsible for controlling when and how much food the body consumes. The greater the amount of leptin present in the blood the lesser the brain feels that it should consume food and burn more calories. The converse is also true as lower levels of leptin have been found to increase appetite. The leptin hormone system follows a negative feedback inhibition loop. Leptin signalling is done via the JAK/STAT pathway and is well described.

Diabetes:

Diabetes mellitus is a great public health concern throughout the world because of its increasing incidence and prevalence. In this background Leptin, the adipocyte hormone, plays an important role in the control of glucose metabolism, promotes weight loss, regulation of appetite and can reverse diabetes by improving glucose tolerance. The mainstay in the treatment of diabetes is the action of insulin as a key metabolic regulator that is vital to glucose and lipid homeostasis and affects many aspects of growth and development. Current life-saving interventions include daily insulin administration, as insulin therapy reduces hyperglycaemia. However, even with insulin therapy, there are many complications that include debilitating

conditions, such as heart disease, neuropathy, and hypertension. But when looking at leptin, leptin's role in obesity and preventing insulin resistance can go a long way as far as leptin replacement therapy is concerned.

Recently, the therapeutic effects of central leptin gene therapy have been reported in insulin-deficient diabetes in obesity animal models such as ob/ob mice.

Leptin Signalling Pathway:

Leptin is primarily secreted from the adipocyte cells of the body and it acts on the hypothalamus area of the brain. Leptin is secreted in the blood and needs to cross the blood-brain barrier before it can have an effect. Leptin receptors have been found in the choroid plexus and are suspected to act as transport from the circulation system into the central nervous system. These leptin receptors are also present in the arcuate and the dorsomedial nuclei of the hypothalamus. After leptin binds to the receptors it regulates the actions of neuropeptides in the hypothalamus. Hypothalamic neuropeptides like neuropeptide Y and the agouti related peptide have been found to make the body increase its food uptake. Other neuropeptides like he cocaine and amphetamine-regulated transcript (CART) and alpha melanocyte-stimulating hormone (AMSH) have an anorexic effect. Leptin has found to increase the number of neuropeptides with anorexic effects. It has also been found that Postglandin E2 (PGE2) and arachidonic acid stimulate the secretion of leptin, however, higher cyclic AMP levels is known to inhibit the leptin release. It has also been hypothesized that leptin may use the COX-2 pathway.

Leptin structure:

The native leptin molecule is extremely prone to accumulating together in regular physiological conditions which made it hard to study the structure as it showed poor solubility. Site-directed mutagenesis was done to aid the crystallization ability of the molecule. A leptin analogue (Leptin-E100) with a single amino acid substitution of Glu for Trp at position 100. This leptin analogue showed much greater solubility and was crystallized using the hanging-drop vapor-diffusion method and the structure was studied.

The leptin molecule has the approximate dimensions of 20x25x45 A. It has four antiparallel a?helices, two crossover links between these helices and one short loop arranged in a left twisted helical bundle. The structure of leptin is found to contain several hydrophobic sites, some of which are involved in receptor binding. The surface hydrophobicity is found to be the reason that the molecule tends to aggregate and not dissolve easily.

Leptin application in animal model:

With the administration of leptin in rodents, it leads to the reduced intake of food and it increases energy expenditure. When involving transgenic animal models, such as leptin-deficient (ob/ob) mice, it exhibits the development of marked obesity, insulin resistance and impaired glucose homeostasis. Fasting rodents with reduced leptin levels and ob/ob mice exhibit a decreased level of hypothalamic POMC mRNA, which is normalized by exogenous leptin administration that subsequently improves obesity and diabetes.

Recent studies done on obese and non-obese humans demonstrated a strong positive

correlation of serum leptin concentrations with the percentage of body fat. Leptin is an important component in the long-term regulation of body weight. Leptin's effects on body weight are mediated through effects on hypothalamic centres that control feeding behaviour and hunger. It was also found out that adipocytes increase in size due to accumulation of triglycerides, which synthesis more and more leptin.

Leptin is dependent on its binding receptor, which are known as leptin receptor (LEPR). There are three types. They belong to a group of 130 family of a cytokine receptor. LEPR has different isoforms such as LEPRa, LEPRb, LEPRd and LEPRc. From all these isoforms, LEPRb is the longest and important signaling. Any defect in leptin signalling can cause obesity severe obesity. First missense mutations which were present in the leptin receptor (LEPR) were reported. These mutations disrupt LEPR signalling. Mutations associated to human obesity were involved in structural as well as functional relationships within the LEPR.

Leptin is a neurotransmitter that signals to the brain when a person stops to eat for maintaining his/her Body Mass Index. The neurotransmitter signals to the brain mainly in the hypothalamus. It has been observed that lab mice have a polymorphism in the leptin gene. Mutations in this gene prevent to manufacture the functional leptin protein. Due to less leptin expression, mice become morbidly obese.

Leptin therapy reversed endocrine as well as metabolic alterations associated with leptin deficiency. Leptin deficiency was related with less numbers of T cells, CD4 and defective T cell proliferation. These reductions were reversed by leptin therapy. Leptin replacement therapy at physiological concentrations after removal of high-dosage leptin not worked properly weight regain and hyperphagia was due to deficiency of leptin. Leptin replacement therapy will be very useful for the patients of congenital leptin deficiency. Leptin has also been used for the treatment of other forms of energy loss e.g. anorexia nervosa. It was found that immune function changed during leptin replacement. Congenital leptin deficiency was evaluated in a 5-year-old boy. Boy was evaluated before two weeks and after six weeks of leptin therapy. After that treatment, humoral and cellular immunity was detected by measuring levels of immunoglobulins and by the analysis of lymphocyte in response to mitogens, respectively

Other functions of Leptin:

Leptin has been found to have a vast number of roles in the human body apart from its primary role as an anti-obesity hormone and plays an integral role in signalling mechanisms influencing various biological functions. It has been found to play active roles in haematopoiesis, lymphoid organ homeostasis, angiogenesis, blood pressure, bone mass and T lymphocyte function. It functions throughout the body with the help of its specific cellular receptor. The leptin receptor is found primarily in the central nervous system and the peripheral tissues. It is structurally similar to class I cytokine receptors. Leptin has been found to help in thymic homeostasis and in regulation of immune function.

Relationship between leptin and obesity:

In 1996, Robert V Constantine, Madhur K Sinha et al. conducted a study where they measured serum concentrations of leptin in 136 normal-weight subjects and 139 obese. They found that that in obese subjects the mean serum concentration is almost 3 times the mean serum leptin

concentration found in normal-weight persons. In general, they concluded that leptin has strong correlation with body weight i.e. an obese person's body becomes resistant to leptin hence the leptin concentration in their body increases. The actual mechanism of leptin resistance is still unknown.

In 1997, a study done by Collier GR et al, in ob/ob mice (Psammomys obesus), which lack circulating leptin, report that ob/ob mice show dramatic reductions in food intake and body weight after leptin treatment. In addition, studies in both humans with obesity and animal models of obesity have demonstrated hyperleptinemia they studied both humans and animal models of obesity, both have demonstrated hyperleptinemia. They concluded that the development of hyperleptinemia is associated with the development of obesity and subsequent metabolic abnormalities.

Relationship between obesity and diabetes:

Large epidemiologic studies reveal the parallel escalation of the obesity and diabetes epidemics. Both these metabolic disorders are characterized by defects of insulin action; the term 'diabesity' express their close relationship to each other. Up to date, several theories linking different pathogenic mechanisms that make obese individuals resistant to insulin and their pancreatic ?-cells to fail to lead eventually to frank diabetes have been suggested. A unifying hypothesis, however, still remains elusive.

In a study conducted in 1983 it was found that there was a high correlation between clinical diabetes and body fat distribution, especially in women. In a paper published by Dr Richard N Bergman, reported the relationship between body fat and diabetes. They found that in obesity, where there is high visceral fat content, leads to insulin resistance, which would eventually lead to type 2 diabetes. They hypothized that this visceral body fat is metabolized resulting in formation of free fatty acids (FFA). This FFA was believed to upregulate the liver's gluconeogenic enzymes leading to insulin resistance. It was also hypothized that the adipocytes themselves found in that area (visceral body fat) could be insulin resistant, thus leading to type 2 diabetes. Another theory suggests the sympathetic nervous system (SNS) favours lipolysis leading to an increased concentration of FFA which then causes type 2 diabetes.

Relationship between leptin and diabetes:

There are contradicting views as to a direct relationship between leptin and diabetes. In a study published in 2007 by S Soderberg et al., it was reported that subjects with diabetes had a higher mean serum leptin concentration as compared to non-diabetic subjects. They concluded that higher leptin levels were associated with the development of diabetes in the future, but they found that this association was independent of other factors in men but not in women.

In 2001 Velasquez MT et al., reported using a mouse model that circulating leptin appeared to be one of the best biological markers of obesity and that hyperleptinemia is closely associated with several metabolic risk factors related to insulin resistance in the diabesity syndrome.

In 2011 Pavani Bandaru et al., reported that higher plasma leptin levels were not independently associated with diabetes mellitus after adjustment for BMI, they reported that this was evident in both women as well as in men.

In a research paper published by Ghilberto Paz-Filo etal. in 2012, they reported that Leptin and insulin share common effects in the control of food intake and energy metabolism. In the blood glucose homeostasis, both play important roles. Leptin and insulin directly regulate each other. They reported that leptin inhibits insulin while insulin stimulates leptin synthesis and secretion. They also found that leptin increases insulin sensitivity, not only by decreasing adiposity and lipotoxicity, but also insulin-independent action, both centrally and peripherally and also decreases hepatic production of glucose, contributing to its glucose-lowering effects. They stated that in leptin-deficient humans, leptin therapy showed remarkable effects, increasing insulin sensitivity on the long term, by decreasing insulinemia, and ultimately by reversing type 2 diabetes in one previously diabetic patient.

Thus, further research needs to be done but it is clear that leptin levels are more pronounced in obese people and obese people have a higher risk for diabetes, so leptin must have an indirect effect on diabetes. Further research and studies are required. Leptin based therapies for treating diabetes and insulin resistance may be possible in the future, but further studies are required elucidate the effects of leptin on glucose-insulin homeostasis, both in the leptin-sensitive and in the leptin-resistant milieus

References

1. Leptin therapy, insulin sensitivity, and glucose homeostasis, Gilberto Paz-Filho, Claudio Mastronardi, Ma-Li Wong, and Julio Licinio, Indian J Endocrinol Metab. 2012 Dec; 16(Suppl 3): S549–S555.
2. Association Between Plasma Leptin Levels and Diabetes Mellitus, Pavani Bandaru, M.D., M.P.H. and Anoop Shankar, M.D., Ph. D Metab Syndr Relat Disord. 2011 Feb; 9(1): 19–23.
3. Serum Immunoreactive-Leptin Concentrations in Normal-Weight and Obese Humans, Robert V. Considine, Ph.D., Madhur K. Sinha, Ph.D., Mark L. Heiman, Ph.D., Adidas Kriauciunas, Ph.D., Thomas W. Stephens, Ph.D., Mark R. Nyce, M.S., Joanna P. Ohannesian, B.S.N., Cheryl C. Marco, R.D., Linda J. McKee, M.H.S., Thomas L. Bauer, M.D., and José F. Caro, M.D
4. Leptin and the development of obesity and diabetes in Psammomys obesus. Collier GR1, Walder K, Lewandowski P, Sanigorski A, Zimmet P., Obes Res. 1997 Sep;5(5):455-8.
5. Leptin and its relation to obesity and insulin in the SHR/N-corpulent rat, a model of type II diabetes mellitus, Velasque MT1, Bhathena SJ, Hansen CT., Int J Exp Diabetes Res. 2001;2(3):217-23.
6. Leptin predicts the development of diabetes in Mauritian men, but not women: a population-based study S Söderberg, P Zimmet, J Tuomilehto, P Chitson, H Gareeboo, K G M M Alberti & J E Shaw, International Journal of Obesity volume31, pages1126–1133 (2007)
7. Diabetes mellitus hoy, The two-edged sword, Richard N Bergman Keck Professor of Medicine. The University of Southern California.
8. Obesity and diabetes Konstantinos Lois and Sudhesh Kumar Warwickshire Institute of Diabetes, Endocrinology & Metabolism (WISDEM). University Hospital Coventry & Warwickshire. Warwick Medical School Coventry. UK.
9. Clinical study: Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women Miyao Matsubara, Shoji Maruoka1

and Shinji Katayose1 Division of Endocrinology and Metabolism, Otaru City General Hospital, Otaru and 1 Otsuka Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, et al. (1997) Congenital leptin deficiency is associated with severe early onset obesity in humans. Nature 387: 903–907.
10. Assay Institute, Sapporo, Japan, European Journal of Endocrinology (2002) 147 173–180 ISSN 0804-4643
11. Leptin as an important link between obesity and cardiovascular risk factors in men with acute myocardial infarction, Nergis Ekmen, Aysen Helvaci, Meral Gunaldi, Hadi Sasani and Sembol Turkmen Yildirmakd. Indian Heart J. 2016 Mar-Apr; 68(2): 132–137.art J. 2016 Mar-Apr; 68(2): 132–137.
12. Relationship of obesity to diabetes: Influence of obesity level and body fat distribution, Arthur J. Hartz, David C. Rupley Jr. Ronald D. Kalkhoff, Alfred A. Rimm, Preventive Medicine Volume 12, Issue 2, March 1983, Pages 351-357.
13. M J McNeely, E J Boyko, D S Weigle, J B Shofer, S D Chessler, D L Leonetti and W Y Fujimoto, Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans, Diabetes Care 1999 Jan; 22(1);65-70.
14. Paul Welsh, Heather M. Murray, Brendan M. Buckley, Anton J.M. de Craen, Ian Ford, J. Wouter Jukema, Peter W. Macfarlane, Chris J. Packard, David J. Stott, Rudi G.J. Westendorp, James Shepherd, and Naveed Sattar, Leptin predicts Diabetes but not Cardiovascular disease, Diabetes Care, 2009 Feb, 32(2):308-310.
15. S. Goya Wannamethee, Gordon D.O. Lowe, Ann Rumley, Lynne Cherry, Peter H. Whincup and Naveed Sattar, Diabetes Care, 2007 May, 30(5):1200-1205.
16. Van Heek, M., Compton, D. S., France, C. F., Tedesco, R. P., Fawzi, A. B., Graziano, M. P., … Davis, H. R. (1997). Diet-induced obese mice develop peripheral, but not central, resistance to leptin. Journal of Clinical Investigation, 99(3), 385–390.
17. Segal, K.R., M. Landt, and S. Klein. 1996. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes. 45: 988–991.
18. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404: 661-671.
19. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, et al. (1997) Congenital leptin deficiency is associated with severe early onset obesity in humans. Nature 387: 903–907.
20. Lavie C. J., Milani R. V., Ventura H. O. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. Journal of the American College of Cardiology. 2007;53(21):1925–1932.
21. De Luis DA, Perez Castrillon JL, Duenas A (2009) Leptin and Obesity. Minerva Medical 100: 229-236.
22. Miczke A, Pupek-Musialik D (2000) Leptin and Obesity. Pol Merkur Lekarski 8: 109-112.
23. Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 8:228–236
24. Fortuno A., Rodriguez A., Gomez-Ambrosi J., Fruhbeck G., Diez J. Adipose tissue as an endocrine organ: role of leptin and adiponectin in pathogenesis of cardiovascular diseases. Journal of Physiology and Biochemistry. 2003;59(1):51–60.
25. Stofkova A. Resistin and visfatin: regulators of insulin sensitivity, inflammation and immunity. Endocrine Regulations. 2010;44(1):25–36.
26. Akiyama, T., Tachibana, I., Shirohara, H., Watanabe, N., and Otsuki, M. (1996). High-fat hypercaloric diet induces obesity, glucose intolerance and hyperlipidemia in normal adult male Wistar rat. Diabetes Res. Clin. Pract. 31, 27–35.
27. Ahima, R. S., Prabhakaran, D., and Flier, J. S. (1998). Postnatal leptin surge and

regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. J. Clin. Invest. 101, 1020–1027.
28. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: The role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010; 152:93–100.
29. Berglund ED, Vianna CR, Donato J, Jr, Kim MH, Chuang JC, Lee CE, et al. Direct leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. J Clin Invest. 2012; 122:1000–9.
30. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science. 1995; 269:543–6.
31. Maffei M, Halaas J, Ravussin E, Pratley R, Lee G, Zhang Y, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med. 1995; 1:1155–61.
32. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. N Engl J Med. 1990; 322:1483–7.
33. Fried SK, Ricci MR, Russell CD, Laferrère B. Regulation of leptin production in humans. J Nutr. 2000; 130:3127S–31S.
34. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell. 1995; 83:1263–71
35. Fantuzzi G, Faggioni R. Leptin in the regulation of immunity, inflammation, and haematopoiesis. J Leukoc Biol. 2000; 68:437–46
36. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998; 395:763–70.
37. Uotani S, Bjørbaek C, Tornøe J, Flier J. Functional properties of leptin receptor isoforms: Internalization and degradation of leptin and ligand-induced receptor downregulation. Diabetes. 1999; 48:279–86.
38. Di Yorio MP, Bilbao MG, Pustovrh MC, Prestifilippo JP, Faletti AG. Leptin modulates the expression of its receptors in the hypothalamic-pituitary-ovarian axis in a differential way. J Endocrinol. 2008; 198:355–66.
39. Blüher S, Mantzoros CS. Leptin in humans: lessons from translational research. Am J Clin Nutr. 2009; 89:991S–997S.
40. International Diabetes Federation (2013) IDF diabetes atlas, 6th edn. International Diabetes Federation, Brussels
41. Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 8:228–236
42. Banting FG, Best CH (1990) Pancreatic extracts. 1922. J Lab Clin Med 115:254–272
43. The DCCT Research Group (1988) Weight gain associated with intensive therapy in the diabetes control and complications trial. Diabetes Care 11:567–573.
44. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N England J Med 329:977–986.
45. The Diabetes Control and Complications Trial Research Group (1997) Hypoglycaemia in the diabetes control and complications trial. Diabetes 46:271–286.
46. Morton GJ, Schwartz MW (2011) Leptin and the central nervous system control of glucose metabolism. Physiol Rev 91:389–411.
47. Dubuc PU (1976) The development of obesity, hyperinsulinemia, and hyperglycaemia in ob/ob mice. Metabolism 25:1567–157.
48. Wyse BM, Dulin WE (1970) The influence of age and dietary conditions on diabetes in the db mouse. Diabetologia 6:268–273.

49. Pelleymounter MA, Cullen MJ, Baker MB et al (1995) Effects of the obese gene product on body weight regulation in ob/ob mice. Science 269:540–543.
50. Schwartz MW, Baskin DG, Bukowski TR et al (1996) Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes 45:531–535.