LEPTIN CENTERED THERAPY FOR DIABETES: GREAT HOPE FOR IMMINENT

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ABSTRACT
Diabetes is a metabolic syndrome characterized by the chronic elevation of blood sugar levels resulting from faults in insulin secretion, insulin resistance, or both. Leptin is a hormone known to have positive effects on hunger and energy expenditure and glucose breakdown. Leptin has beneficial effects on the glucose-insulin metabolism, by decreasing hyperglycemia, enhancing insulinemia and insulin resistance. Leptin is a protein of high molecular mass (16 kDa). Leptin is translated as a 167 amino acid protein with an amino-terminal secretory signal order of 21 amino acids. Leptin and insulin are important for weight regulation by controlling appetite levels and can be important for preventing diabetes by controlling blood sugar levels. Hypothalamic insulin and leptin signaling play a crucial role in the regulation of glucose homeostasis and in the development of insulin resistance. Leptin microinjections into the nucleus of the solitary tract (NST) have been shown to elicit sympathoexcitatory responses and potentiate the cardiovascular responses to activation of the chemo reflex.

Keywords: diabetes, leptin, insulin, appetite, weight regulation.

INTRODUCTION
The occurrence and prevalence of diabetes is increasing worldwide. More than 250 million people have diabetes universal and this figure is expected to exceed 400 million by 2030.1
This is a major health concern given that diabetes is related with increased risk of cardiovascular disease and both macro vascular and micro vascular diseases with blindness, neuropathy, nephropathy, myopathy etc. Diabetes is a metabolic disease characterized by the chronic elevation of blood sugar levels resulting from defects in insulin secretion, insulin resistance, or both. Thus, insulin secretion is diminished in these individuals and is insufficient to compensate for the insulin resistance in peripheral tissues.²

Leptin is a hormone known to have positive effects on hunger and energy expenditure and glucose metabolism. Leptin was found in current studies to normalize hyperglycemia, hyperinsulinemia and raise insulin sensitivity. Leptin plasma concentrations increase in the body relative to body fat mass to maintain body fat stores. It is found to be deficiency of leptin responsible for obesity, insulin resistance, hyperinsulinemia, impaired glucose and diabetes. Leptin given to rodents with reduced leptin levels ended up having developments in diabetes and obesity. Leptin is a hormone made by fat tissue that acts on the brain to regulate food intake and body weight.

In the genetically knock out animal, it was observed that enhanced both type 1 and 2 diabetes along with obesity. More studies need to be completed looking into the clinical use of leptin but leptin gene therapy looks like a hopeful treatment option for diabetes and obesity. Glucose homeostasis is closely regulated not only by insulin, but also by leptin. Both hormones act centrally, regulating food intake and adiposity in humans. Leptin has several effects on the glucose-insulin homeostasis, some of which are independent of body weight and adiposity. Those effects of leptin are determined centrally in the hypothalamus and peripherally in the pancreas, muscles and liver. Leptin has beneficial effects on the glucose-insulin metabolism, by decreasing glycaemia, insulinemia and insulin resistance. Leptin controls food intake and energy expenditure and has also several actions in the endocrine and immune systems, including fertility, bone formation, tissue remodeling and inflammation.³

In endocrine system, leptin regulates the circadian rhythms of the gonadotropic, thyrotrophic and adrenal axes. It also plays important role in the regulation of glucose homeostasis and insulin sensitivity, independent of actions on nutrition intake, energy expenditure and body weight.⁴

**Molecular aspects of leptin**

Leptin is a protein of high molecular mass (16 kDa). Leptin is the most abundant hormone
produced by adipocytes. It has structural homology with the cytokines of the long-chain helical family that contains interleukin (IL)-6, IL-11, IL-12, and oncostatin M, and so is portion of the adipokines family. Its heights are correlated with fat mass and the increase in human or rodent fat masses due to genetic operation or environmental induction causes an increase in leptin levels. Several metabolic and hormonal factors affect the synthesis and secretion of leptin in the body, such as cytokines, cortisol, catecholamines, fatty acids, glucose and insulin.

**Figure 1: Inter relation between leptin, glucagon and insulin**

There are at least four different isoforms of the leptin receptor in humans: O0 b-Ra, Ob-Rb and Ob-Rc (membrane-anchored) and Ob-Re (soluble); these are all products of alternatively spliced forms of the Ob-R gene. The membrane-anchored isoforms have matching extracellular, ligand-binding and transmembrane domains, with different lengths of the intracellular domain. The transduction of leptin's signals is mediated by known pathways, namely Janus kinase-signal transducer and activator of transcription (JAK-STAT), extracellular signal-regulated kinase (ERK)-1/2, phosphatidylinositol-3-kinase (PI3K) and AMP-activated protein kinase (AMPK). The AMPK pathway is particularly involved in preventing insulin resistance, in part by inhibiting pathways that antagonize insulin signaling.

**Biosynthetic aspect of Leptin**

Transcription of the leptin gene in mice yields mRNA of 3.5 kb that is expressed principally in adipose tissues but recent studies have recognized that some other tissues also express leptin, including placenta, ovaries, skeletal muscle and stomach.\textsuperscript{5,7}
In humans, leptin is encoded by a gene located in human chromosome 7q31.3 and is comparable to that in rodents. Leptin is translated as a 167 amino acid protein with an amino-terminal secretory signal sequence of 21 amino acids. The signal sequence is functional, and results in the translocation of leptin into microsomes with the subsequent elimination of the signal peptide. Thus, leptin circulates in the blood as protein of 146 amino acid residues.

Leptin and insulin are two homeostatic hormones crucial for human health, each connected to diseases like diabetes, obesity and cancer. Both leptin and insulin are important for weight regulation by controlling hunger levels and can be important for avoiding diabetes by controlling blood sugar levels. When these hormones are maintained at healthy levels, the body is said to be sensitive to their effects and can use their assistances more effectively. Although drugs have been developed to indulge malfunctions in these two hormones, most doctors agree that a strategy that includes healthy eating, exercise and stress reduction is ideal for disease prevention.

In the fields of biology, endocrinology and nutrition there is the study of two important hormones named leptin and insulin. Leptin rises after a meal and suppresses the hunger hormone, telling the body that it does not require any more intake of energy or food. Insulin also increases after a meal and takes in that energy, which is merely broken down sugar molecules, into the cells of the body to use as a prime energy source. When both hormones are raised excessively, the body can become less sensitive to their effects and the risk of developing illnesses like diabetes and obesity increases. When levels of leptin remain elevated for long periods of time, cells within the body become less sensitive to its effects. This can effectively turn off the hunger-suppressing hormone and lead to increased hunger which can cause an increased consumption of food.

After consuming an excess of food, insulin can spike to high levels in an attempt to take in the energy derived from food, mainly in the forms of simple sugars, into the cells. These cells can become insensitive to the effects of insulin over time, leading to failure to take in glucose. This is called diabetes and usually results when both leptin and insulin stay elevated for long periods of time and lose their ability to properly signal healthy cells. There is some research suggesting that high elevations of both leptin and insulin can lead to cancer, but more research is needed to find a direct correlation.
Leptin and the adipoinsular axis

The adipose tissue plays an important role in overall energy homeostasis. Glucose and lipid metabolism is regulated by complex interactions that occur within the adipoinsular axis. Insulin acutely stimulates lipogenesis while decreasing lipolysis, whereas leptin exerts opposite effects.

Abnormal accumulation of triglycerides in non-adipose tissues, caused by the upregulation of lipogenesis, leads to a deleterious state known as lipotoxicity. Lipotoxicity is characterized as the accumulation of triglycerides in the surrounding hepatocytes and is thought to be a major contributor to islet cell transplantation failure in diabetics. Lipotoxicity also contributes to the increase in insulin resistance. Given that leptin is thought to oppose insulin action by decreasing hepatocyte lipogenesis, leptin administration may result in decreased lipotoxicity, existence useful for the treatment of lipodystrophy syndromes. However, when used for treating obesity-associated non-alcoholic fatty liver disease, leptin might instead promote insulin resistance, fibrosis and hepatocellular carcinoma.

Leptin and insulin play important metabolic roles. A majority of the studies suggest that leptin decreases insulin synthesis and secretion by pancreatic β cells and increases insulin hepatic extraction. As a result, insulin delivery is compact by leptin. This so-called adipoinsular axis is part of a leptin-mediated inhibitory feedback on insulin secretion in order to decrease adipogenesis. Leptin also decreases hepatic glucose production, increases insulin sensitivity and decreases glucagon levels. Insulin, in turn, also plays a role in stimulating leptin production and secretion in the adipose tissue.

Hypothalamic insulin and leptin signaling play a vital role in the regulation of glucose homeostasis and in the expansion of insulin resistance. Insulin controls hepatic glucose production, skeletal muscle glycogen synthesis, brown adipose tissue thermo genesis and white adipose tissue lipolysis. Central leptin, in turn, regulates hepatic gluconeogenesis and insulin sensitivity, skeletal-muscle lipid oxidation and glucose uptake/utilization, brown adipose tissue glucose uptake and white adipose tissue lipolysis and insulin secretion. These effects seem to be mediated by the autonomic directive of skeletal muscle, liver, pancreas and adipose tissues. In the hypothalamus, the leptin signaling PI3K pathway plays an important role in decreasing peripheral insulin resistance, as central leptin improved tolerance to glucose, increased PGC1 α expression and regulated AKT, AMPK, ACC and JAK2 phosphorylation in the soleus muscle of rats fed with regular chow. In untreated
diabetic mice, hypoleptinemia caused by decreased fat mass leads to severe insulin resistance, which is reversed by leptin replacement, giving support to the usefulness of leptin in the treatment of diabetes.  

Figure 2: Leptin normalization of blood glucose levels in Diabetes mellitus.

Leptin management straight into the brain normalizes diabetic hyperglycemia in Diabetes mellitus by both potently suppressing hepatic glucose production, as well as increasing glucose uptake despite persistent severe insulin deficiency, an effect associated with normalization of elevated plasma glucagon levels.  

It has been shown that direct action of insulin and leptin on the Pro-Opio-Melano- Cortin (POMC) neurons is required to maintain normal glucose homeostasis. In Ob-R deficient mice; restoring leptin receptor expression only at POMC neurons normalizes blood glucose and ameliorates hepatic insulin resistance, hyperglucagonemia, and dyslipidemia, independent of changes in body weight. The effects of leptin can be clarified by its actions in increasing hypothalamic insulin understanding. However, it has also been established that leptin ameliorates hyperglycemia by suppressing hepatic glucose production and by increasing tissue glucose uptake, independent of insulin.
Another potential mechanism by which leptin ameliorates glucose levels is the increase in IGF binding protein 2 (IGFBP2) levels, which reduces blood glucose in wild-type and diabetic mice and potently suppresses hepatic glucose production, as well as genes involved in hepatic gluconeogenesis and fatty acid synthesis.26

More recently, the bone has been implicated in the control of energy homeostasis. Osteocalcin is a marker of bone formation that is synthesized and secreted by the osteoblasts. Osteocalcin increases insulin expression and insulin sensitivity in animals and mice that lack osteocalcin are glucose intolerant.27 It has been shown that the inhibition of insulin secretion exerted by leptin is partly mediated by leptin's effect on inhibiting the metabolic activity of osteocalcin: leptin stimulates the sympathetic tone, which in turn stimulates the expression of Esp, a gene that inhibits osteocalcin.28 In human, osteocalcin has been associated negatively with insulin resistance and leptin has been correlated negatively with osteocalcin levels both in cross-sectional and longitudinal analyses.29

Therefore, obesity may lead to insulin resistance done a leptin-mediated suppression of osteocalcin. The stimulatory role of osteocalcin on pancreatic insulin secretion has been questioned by studies showing that raised osteocalcin is associated with suppressed blood insulin.

Leptin plays a significant part in the pathophysiology of insulin resistance related to obesity. Leptin replacement reverses insulin resistance and diabetes in mice homozygous for mutations of the ob gene, in aP2-nSREBP-1c mice with moderate fat deficiency and in severely lipoatrophic A-ZIP/F-1 mice.30-32 In non-obese diabetic (NOD) mice, leptin therapy alone or combined with low-dose insulin reverses the catabolic state through suppression of hyperglucagonemia, mimics the anabolic actions of insulin and normalizes hemoglobin A1c. In contrast with insulin, leptin drops lipogenic and cholesterol genic transcription factors and reduces plasma and tissue lipids.33,34 Therefore, leptin and insulin may become a potential combination therapy for type 1 diabetes, but there are concerns regarding hypoglycemia. In human, leptin levels are connected with adiposity. Moreover, leptin is positively correlated with insulin resistance, independently of body weight or adiposity, both in normoglycaemic and in diabetic patients.

In leptin-deficient humans, leptin therapy has been shown extraordinary effects by increasing insulin sensitivity on the long term, by decreasing insulinemia and ultimately by reversing diabetes in patients. In lipodystrophic patients, leptin therapy also has positive metabolic
effects. However, no clinically evident benefits have been observed in patients with type 2 diabetes.

The development of leptin-based therapies for treating diabetes and disorders that present insulin resistance, further human studies need to elucidate the effects of leptin on the glucose-insulin homeostasis, both in the leptin-sensitive and in the leptin-resistant milieus.

**Mechanism of action**

Leptin interacts with six types of receptors (Ob-Ra–Ob-Rf, or LepRa-LepRf), that in turn are encoded by a solo gene, LEPR. Ob-Rb is the only receptor isoform that can signal intracellular via the Jak-Stat and MAPK signal transduction pathways and is present in hypothalamic nuclei.\(^{35}\)

Whether leptin can cross the blood–brain barrier to access receptor neurons is unknown, because the blood–brain barrier is attenuated in the area of the median eminence, close to where the NPY neurons of the arcuate nucleus are located. Leptin is generally thought to enter the brain at the choroid plexus, where the intense expression of a form of leptin receptor molecule could act as a transport mechanism.\(^{36}\)

Once leptin has bound to the Ob-Rb receptor, it activates the stat3, which is phosphorylated and travels to the nucleus to presumably effect variations in gene expression. One of the main effects on gene expression is the down-regulation of the expression of endocannabinoids, responsible for increasing appetite. Other intracellular pathways are stimulated by leptin, but less is known about how they function in this system. In response to leptin, receptor neurons have been shown to remodel themselves, changing the number and types of synapses that fire onto them.

Leptin action is recognized to be more decentralized than previously assumed. In addition to its endocrine action at a distance from adipose tissue to brain, leptin also acts as a paracrine mediator. Freshly, leptin microinjections into the nucleus of the solitary tract (NTS) have been shown to elicit sympatoexcitatory responses and potentiate the cardiovascular responses to activation of the chemoreflex.\(^{37}\)

**CONCLUSION**

In the current scenario, various newer treatment option available for diabetes and its complication. Present available drugs are work by either increasing insulin secretion or it
sensitivity on various tissue. The leptin has advantage of suppressing appetite which is helpful in curbing polyphagia in patients. In this leptin based therapy for diabetes treatment is latest concept. Leptin play important role in appetite suppressant by affecting hypothalamus. Obesity and Diabetes creating stress in the hypothalamus especially area concerning to appetite center. Leptin inhibit glucagon synthesis in pancreas and control hyperglycemia. Recently it has been found that higher levels of adipose tissue hormone leptin in the blood reduces blood vessels' ability to dilate, impair blood clotting both of which increase the risk of heart attack and stroke incidence. The role of leptin in various tissue indicate advance targeted delivery must be utilized so it will prove helpful in controlling diabetes without creating side effects of cardiovascular.

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