

Diagnostic and Therapeutic Efficacy of Leptin in Type I Diabetes



Rohini Gomathinayagam¹ and Kumaravel Velayutham^{2*}

¹Scientist & Head, Department of Molecular Genetics, Alpha Hospital and Research Center, India

²Director & Endocrinologist, Alpha Hospital and Research Center, India

Submission: November 15, 2017; **Published:** November 21, 2017

***Corresponding author:** Kumaravel Velayutham, Director & Endocrinologist, Alpha Hospital and Research Center, 2B/2C, Gate Lock Road Mela Anuppannady, Madurai-9, Tamil Nadu, India, Tel: +91 9940582328; Email: drvkumaravel@gmail.com

Abstract

The single chain proteo-hormone leptin is recognized to play a vital role in the regulation of fat metabolism and storage. Circulating leptin concentration is considered to be reflective of body mass and is primarily tied up with the proportion of adipose tissue. Emerging evidences have indicated that leptin levels are modulated in diabetic conditions and leptin therapy significantly improves diabetic disease management. The present review focuses to discuss the variations in the leptin levels, the potentiality of Leptin therapy in type I diabetes.

Keywords: Leptin levels; Adipose tissue; Obesity; Type I diabetes

Introduction

Leptin is a single chain proteo-hormone product of the 'ob' gene and is recognized to play a vital role in the regulation of fat metabolism and storage. Predominantly made by the adipose cells, leptin primarily helps to regulate energy balance by acting on the central nervous system, in particular the hypothalamus to signal for satiety and stimulate energy expenditure. Circulating leptin concentrations is reflective of body mass and in the absence of fasting and irregular eating cycles, leptin levels are primarily tied up with the proportion of adipose tissue. Biologically, leptin synthesis is observed to be stimulated in over feeding conditions, by insulin, glucocorticoids and the inhibition in the synthesis of leptin is observed under fasting conditions. Further, synthesis of leptins in adipose tissues is observed to be under the neuro-endocrine control [1] and is modulated by non hormonal and hormonal variables, cAMP and β_3 -adrenoreceptor agonists [2]. Earlier reports demonstrated the role of leptin in the inhibition of insulin biosynthesis, its secretion from the pancreatic β -cells and opened up interesting avenues to examine the role of leptins in obesity and diabetes [3].

Hyper leptinemia, is commonly observed in conditions pertaining to rapid consumption of energy rich diets and age-related obesity leading to the decline in brain leptin concentrations [4]. Correlatively, obese individuals are reported to exhibit increased concentration of leptins. It is also

observed that short-term fasting in lean individuals induces a significant decline in the free-leptin concentrations and that lean individuals exhibit a greater proportion of bound leptins than obese individuals. Thus, several reports have brought forward a strong positive association between serum leptin concentrations, body mass index (BMI) and body fat content.

Detailed investigations on leptin bring to light that although leptin is expressed in different fat compartments, the basal leptin concentrations are proportional only to the total body fat and that age, basal glucose concentrations, ethnicity do not influence leptin concentrations. Basal concentrations of insulin and leptin are identified to correlate positively when factored with body fat only in insulin sensitive individuals. Other findings also bring forth that diabetic conditions do not influence leptin synthesis in lean, obese individuals. Such findings also re-iterate that despite the strong correlation between body fat and leptin concentrations, a greater heterogeneity in leptin concentrations is observed to prevail at a given body fat index [5]. On the other hand exciting research results also indicate that about 5% of the obese population is categorized as leptin deficient and could benefit from leptin therapy [6]. While several experimental findings demonstrate that leptin treatment improves blood sugar control in diabetic animal models, human subjects and that leptin as a therapeutic agent may significantly alleviate diabetic

disease pathogenesis and progression [7,8], a cumulative standpoint of the levels of leptin in type I diabetes and the potentiality of leptin in type I diabetic therapy remains to be compiled. Hence, the present review focuses in discussing the influence of leptin, circulating leptin levels, and leptin therapy in type I diabetes.

Influence of leptin in obesity and type I diabetes

Assessing the diagnostic efficacy of circulating leptin concentrations and the possibility of leptin therapy in the treatment of diabetes is an actively researched avenue. Initial studies pertaining to the serum leptin levels in type I diabetes children and adolescents clearly revealed that serum leptin levels significantly correlated with age and BMI. Other results also include findings that demonstrate that females had higher serum leptin concentrations than males and insulin-treated young adult patients had higher levels of leptin when compared to healthy non diabetic reference population [1]. A recent study that assessed serum leptin, adiponectin levels; lipid profile; bioelectric impedance in 75 children with Type I diabetes revealed that serum leptin levels in children were similar to their controls and correlated positively to body fat mass [9]. Several other studies including ours (unpublished data) demonstrate that mean leptin levels in prepubertal, lean and obese female, male children vary and correlate with Body Mass Index (BMI) [10]. Musil et al. [11] recently examined the influence of leptin, adiponectin in obese patients with Type I diabetes after 7 days

of fasting or 21 days of low calorie diet and reported that fasting significantly reduced the hyper leptinemia in Type 1 diabetes patients [11]. Other interesting studies have also brought forward that type 1 diabetes subjects with homozygotic variants in leptin gene (-2548 G/A) and leptin gene receptor (668 G/A) exhibit significant variations in leptin influenced fetal weight, growth in the first trimester [12]. Studies also demonstrate that leptin receptors may be differentially regulated in metabolic disorders including type I diabetes or obesity and primarily influence leptin sensitivity/leptin resistance [13].

Related studies also bring to light that blood, cerebrospinal leptin concentrations have not been reported to influence consumption or satiety [14] and leptin resistance has been associated with impaired leptin transport across the blood brain barrier, impaired leptin initiated signal transduction in the hypothalamus [15]. *In vivo* studies utilizing single shot leptin injections using adenoviral vectors in insulinopenic, hyperglycemic mice clearly demonstrated the role of central leptin therapy in the alleviation of hyperglycemia and the control of STZ induced type I Diabetes [16]. In par with these results conjunctive studies also bring to light that leptin injected in the ventromedial hypothalamic axis was sufficient to establish normoglycemia in rats with streptozotocin-induced uncontrolled diabetes [17]. The results obtained from such preclinical investigations have strongly suggested that central leptin therapy could serve as an alternative/adjunctive to insulin therapy in progressive type I diabetes patients.

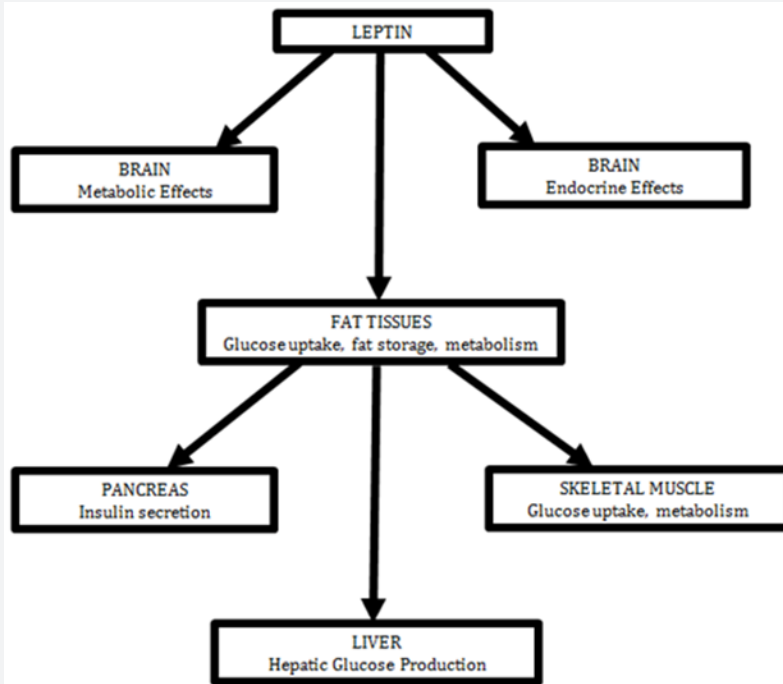


Figure 1: Regulatory role of leptin in hypothalamus and peripheral organs.

Leptin therapy in type I diabetes patients

As leptin critically participates and regulates glucose uptake, fat storage, metabolism in fat tissues; glucose uptake and metabolism in skeletal muscles; glucose production in liver and insulin secretion in the pancreas (Figure 1), poorly controlled type I diabetes results in decreased uptake of glucose by peripheral tissues and skeletal muscle [18], increased insulin resistance and decreased insulin mediated biological functions [19]. Other findings that add importance to such concerns is the findings that leptin levels are altered in off springs' born to mothers with Type I diabetes [20]. Put together, these concerns indicate a progressive increase in the incidence of type I diabetes underscoring the importance to procure effective treatment strategies that would prevent disease incidence and progression. Current therapies for type I require daily administration or continuous infusion of insulin, and combination therapies that comprise of insulin and anti diabetic. Owing to the fact that such therapeutic regimens require a constant monitoring for glycemic control, patients' invariably report emotional, economic burden. Hence, alternative therapies with better therapeutic outcomes are acutely needed and in such a scenario, leptin therapy is continuing to be evaluated for its therapeutic possibility/efficacy. As a beginning, current diagnostics in obese and non-obese type I diabetic patients may include the assessment of adipokines and cytokines status [19,21]. Such an understanding of the serum adiposity-induced biomarkers also enables physicians to understand the cardiovascular risk of children/patients with new onset type I diabetes [22].

Recent evidences in the leptin therapeutic scenario have strongly favored the effect of metreleptin (recombinant methionyl human leptin) therapy in hyperglycemia, dyslipidemia, and insulin sensitivity in lipodystrophic syndrome patients [23]. Metreleptin has also been reported to improve insulin secretion and hence is considered as a prospective candidate in the treatment of obese, lean type I diabetes patients. As mentioned earlier these results promise that leptin therapy could serve as an eminent tool in type I diabetes control.

Conclusion

While exciting discoveries have brought forward that leptin serves as a therapeutic tool that could act on the central nervous system to treat obesity and type I diabetes mellitus, detailed investigations are critical to validate these findings and elucidate the entire physiological consequences. It is of equal importance to take into consideration that heterogeneity in the levels of leptin poses a great challenge in optimizing leptin based therapeutic outputs. Nevertheless, patient based therapeutic regimens with leptin analogs are expected to bring in drastically improved management of type I diabetes.

References

1. Kiess W, Anil M, Blum WF, Englaro P, Juul A, et al. (1998) Serum leptin levels in children and adolescents with insulin-dependent diabetes mellitus in relation to metabolic control and body mass index. *Eur J Endocrinol* 138(5): 501-509.

2. French S, Castiglione K (2002) Recent advances in the physiology of eating. *Proc Nutr Soc* 61(4): 489-496.
3. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P, et al. (1995) Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269(5223): 546-549.
4. Kalra SP (2011) Pivotal role of leptin-hypothalamus signaling in the etiology of diabetes uncovered by gene therapy: a new therapeutic intervention?. *Gene Ther* 18(4): 319-325.
5. Gale SM, Castracane VD, Mantzoros CS (2004) Energy homeostasis, obesity and eating disorders: recent advances in endocrinology. *J Nutr* 134(2): 295-298.
6. Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem* 50(9): 1511-1525.
7. Ahima RS, Kelly J, Elmquist JK, Flier JS (1999) Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. *Endocrinology* 140(11): 4923-4931.
8. Huml M, Kobr J, Siala K, Varvarovska J, Pomahacova R, et al. (2011) Gut peptide hormones and pediatric type 1 diabetes mellitus. *Physiol Res* 60(4): 647-658.
9. Majewska KA, Majewski D, Skowronska B, Stankiewicz W, Fichna P, et al. (2016) Serum leptin and adiponectin levels in children with type 1 diabetes mellitus - Relation to body fat mass and disease course. *Adv Med Sci* 61(1): 117-122.
10. Kamoda T, Saitoh H, Nakahara S, Izumi I, Hirano T, et al. (1998) Serum leptin and insulin concentrations in prepubertal lean, obese and insulin-dependent diabetes mellitus children. *Clin Endocrinol (Oxf)* 49(3): 385-389.
11. Musil F, Blaha V, Ticha A, Hyspler R, Haluzik M, et al. (2015) Effects of body weight reduction on plasma leptin and adiponectin/leptin ratio in obese patients with type 1 diabetes mellitus. *Physiol Res* 64(2): 221-228.
12. Iciek R, Wender OE, Zawiejska A, Seremak MA, Drews K, et al. (2010) The influence of metabolic parameters on fetal development weight in women with type 1 diabetes and homozygotic variant in -2548 G/A of leptin gene and its 668 A/G receptor polymorphism. *Ginekol Pol* 81: 571-577.
13. Schaab M, Kausch H, Klammt J, Nowicki M, Anderegg U, et al. (2012) Novel regulatory mechanisms for generation of the soluble leptin receptor: implications for leptin action. *PLoS One* 7(4): e34787.
14. Pan W, Tu H, Kastin AJ (2006) Differential BBB interactions of three ingestive peptides: obestatin, ghrelin, and adiponectin. *Peptides* 27(4): 911-916.
15. Burguera B, Couce ME, Curran GL, Jensen MD, Lloyd RV, et al. (2000) Obesity is associated with a decreased leptin transport across the blood-brain barrier in rats. *Diabetes* 49(7): 1219-1223.
16. Kalra SP (2009) Central leptin gene therapy ameliorates diabetes type 1 and 2 through two independent hypothalamic relays; a benefit beyond weight and appetite regulation. *Peptides* 30(10): 1957-1963.
17. Meek TH, Matsen ME, Dorfman MD, Guyenet SJ, Damian V, et al. (2013) Leptin action in the ventromedial hypothalamic nucleus is sufficient, but not necessary, to normalize diabetic hyperglycemia. *Endocrinology* 154(9): 3067-3076.
18. Fourlanos S, Harrison LC, Colman PG (2008) The accelerator hypothesis and increasing incidence of type 1 diabetes. *Curr Opin*

Endocrinol Diabetes Obes 15(4): 321-325.

19. Guclu M, Gul O, Cander S, Unal O, Ozkaya G, et al. (2015) Effect of rosiglitazone and insulin combination therapy on inflammation parameters and adipocytokine levels in patients with type 1 DM. *J Diabetes Res* 2015: 807891.
20. Lohse Z, Bytoft B, Knorr S, Clausen TD, Jensen DM, et al. (2017) Abnormal levels of adipokines in adolescent offspring of women with type 1 diabetes - Results from the EPICOM study. *Metabolism* 72: 47-56.
21. Timar R, Timar B, Degeratu D, Serafinceanu C, Oancea C, et al. (2014) Metabolic syndrome, adiponectin and proinflammatory status in patients with type 1 diabetes mellitus. *J Int Med Res* 42(5): 1131-1138.
22. Redondo MJ, Rodriguez LM, Haymond MW, Hampe CS, Smith EO, et al. (2014) Serum adiposity-induced biomarkers in obese and lean children with recently diagnosed autoimmune type 1 diabetes. *Pediatr Diabetes* 15(8): 543-549.
23. Vatier C, Fetita S, Boudou P, Tchankou C, Deville L, et al. (2016) One-year metreleptin improves insulin secretion in patients with diabetes linked to genetic lipodystrophic syndromes. *Diabetes Obes Metab* 18(7): 693-697.



This work is licensed under Creative Commons Attribution 4.0 License
DOI: [10.19080/CRDOJ.2017.04.555650](https://doi.org/10.19080/CRDOJ.2017.04.555650)

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
(Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
<https://juniperpublishers.com/online-submission.php>