Research Article

The Role of Leptin and Insulin like Growth factor-1 in patients with Thyroid dysfunction

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Abstract

Aims: To evaluate the relationship between serum Leptin, Growth factor-1 (IGF-1) levels and untreated thyroid dysfunction patients.
Patients and Methods: A study was made on 50 untreated goiterous patients (female and males) with range between (25-55) years; and25 controls subjects (females and males) with range between (14-55) years. Serum T3, T4 &TSH were by Radio immune assay (RIA) method. Serum Leptin and Insulin like growth factor-1 (IGF-1) was measured by ELISA method.
Results: The mean Serum Leptin level was significantly lowest in hyperthyroidism than control subjects. While Insulin growth factor level was significantly highest in hyperthyroidism than control subjects (3.82 vs. 2.49)
Conclusions: the objective of the study was to provide new data on the relationship between serum Leptin, Insulin like Growth Factor-1 levels and thyroid dysfunction.

Keywords: Leptin Hormone, Insulin like growth factor-1 Hormone (IGF-1), Thyroid Hormone, Hyperthyroidism

INTRODUCTION

Leptin is Greek leptose meaning thin; it's a neuromodular protein of 167 amino acid, 16KDa. The Ob (Lep.) Gene (obese Leptin) located on chromosome 7 in human. It's one of most important adipose derived hormone having a four-helix bundle with one very short strand segment and two relating long interconnected loops. This is consistent with classification as Cytokine four-helix bundle.[1, 2]

Leptin acting on its receptor in hypothalamus and several peripheral tissues exerts diverse biological effects by playing a key role in regulating energy intake and energy expenditure including appetite and metabolism and mainly secreted from adipose tissue small amounts also secreted by cells of epithelium, stomach and placenta.[3-5] Leptin also acts directly on the cells of the liver and skeletal muscles where it stimulates the oxidation of fatty acids in the mitochondria. This reduces the storage of fat in those tissues (but not in adipose fat tissue).[6]

Due to sex differences in body fat distribution and testosterone level, females have higher Leptin level than males when matched by age, weigh, and body fat.[1, 7]

Several factors regulate the synthesis and secretion of Leptin from adipose tissue including nutrient, hormones and the sympathetic nervous (SNS).[7] Insulin, steroid hormones and noradrenalin are important regulator of Leptin production and secretion.[8, 9]

The changes in Leptin expression in response to fasting and feeding are mediated by insulin. Fasting can inhibit Leptin expression, while after feeding Leptin synthesis is increased.[10]

Individuals with mutations in the gene or in the Leptin receptor gene characterized by sever early onset obesity with marked hyperphagia, hypogonadotrophic,

hypogonadisim, sympathetic nervous system under activity, defects in immune functions, this syndrome is called Leptin deficiency syndrome.[7]

Leptin is taken up into the central nervous system (CNS) by a saturable transport mechanism and binds to the long form of the Leptin receptor (Ob Rb), which is principally located in the arcuate nucleus of the hypothalamus.[8]

Within the arcuate nucleus Leptin is able to directly inhibit the expression of orexigenic neuropeptide like the neuropeptide Y and Agouti-related peptide (AGRP) peptides that increase food intake and decrease energy expenditure.[28] In contrast, expression of anorectic peptides that decrease food intake, such as cocaine and amphetamine regulated transcript (POMC) are increased [7], the Leptin effect is most probably mediated by the melanocortin pathway, as alpha melanocyto-stimulating hormone (MSH), which is secondary to Leptin falls during fasting.[11]

Insulin like growth factor-1 (IGF-1) is known as somatomedin C or mechano growth factor is a protein that in humans is encoded by the (IGF-1) gene.[12, 13] (IGF-1) has also been referred to "sulfation factor" and effects were termed "nonsuppressible insulin-like activity" (NSILA).[14]

Insulin like growth factor-1 (IGF-1) plays an important role in the childhood growth and continues to have anabolic effects in adults. A synthetic analog of (IGF-1), measurement is used for the treatment of growth failure.[15]

Thyroid hormones have important roles in normal growth and skeletal muscle development. (IGF-1) is one of the most important growth factors and is needed for the proliferation and development of thyroid cells. It stimulates fibroblasts, follicular and endothelial cells in the thyroid gland. It has been shown that thyroid hormones play an important role in regulation of (IGF-1) and (IGFBP-3). The right amount of thyroid hormones must be secreted at all times to maintain normal levels of metabolic activity in the body, in order to achieve this specific feedback mechanism which operate through the hypothalamus and anterior pituitary gland to control the rate of thyroid secretion by a specific mechanism.[16, 17]

Abnormal thyroid function is associated with changes in body weight and energy expenditure, but it remains to be established whether thyroid hormones independently affect plasma Leptin levels in humans. Several studies with diverse methodologies have addressed the field of Leptin in the hypothyroid state. On the other hand, thyroid hormones exert a negative influence on serum Leptin levels in rats,[18, 19] these thyroid hormones tell the cells in our bodies how fast to use the energy and create proteins. The thyroid gland also makes calcitonine hormone that helps to regulate calcium levels in the blood by inhibiting the breakdown (reabsorption) of bone and increasing calcium excretion from the kidneys.[20]

Thyroid diseases are primarily conditions that affect the amount of thyroid hormones being produced. Some crate too few, leading to hypothyroidism and a slowing of body functions.[21] If a thyroid disordered creates excessive amount of thyroid hormones. The result is hyperthyroidism and the lead to the acceleration of body functions.[22]

PATIENTS AND METHODS

A study was made on 50 untreated goiterous patients (female and males) with range between (25-55) years; and 25 controls subjects (females and males) with range between (14-55) years.

Serum T3, T4 & TSH were by Radio immune assay (RIA) method. Serum Leptin and Insulin like growth factor-1 (IGF-1) was measured by ELISA method.

RESULTS

Hormonal data of serum Leptin and serum Insulin like Growth Factor-1 (IGF-1) (Mean value and SD) for untreated thyroid patients and control were shown in table (1). In which high significant decrease of serum Leptin was found in hyperthyroidism patients P value (<0.0001) and high significant increase of serum Insulin like growth factor-1 (IGF-1) was found in hyperthyroidism patients P value (<0.0001) and high in comparison with normal control group figure (1) & (2). The mean serum Leptin in hyperthyroidism group is significantly decreased than that of thyroid function test T4, p value (<0.00001), while the mean value of Insulin like growth factor-1 (IGF-1) significantly increase than that of thyroid function value (<0.00001), while the mean value of Insulin like growth factor-1in comparison with their mean values, (IGF-1) not significantly increase than that of thyroid function test for both of T4 and TSH hormones, P value (<0.00001) in figure (4) & (5). While the mean serum Leptin in hyperthyroidism group is significantly increase than that of thyroid function test (<0.00001), and also for the mean value of Insulin like growth factor-1 (IGF-1) significantly increase than that of thyroid function T3 (figure 3). In the control group, serum Leptin and serum Insulin like growth factor-1 (IGF-1) levels showed a positive correlation with serum

T4 and TSH hormones but for untreated hyperthyroidism patients serum Leptin and serum Insulin like growth factor -1 (IGF-1) levels are correlated negatively with T3 figure (1).

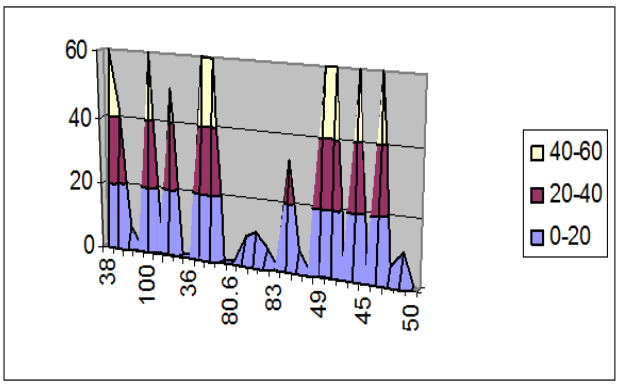

Figure 1. Thyroid hormones Serum T3, T4 & TSH with serum Leptin and serum IGF-1 levels for untreated hyperthyroidism patients in (ng/100ml)**.**

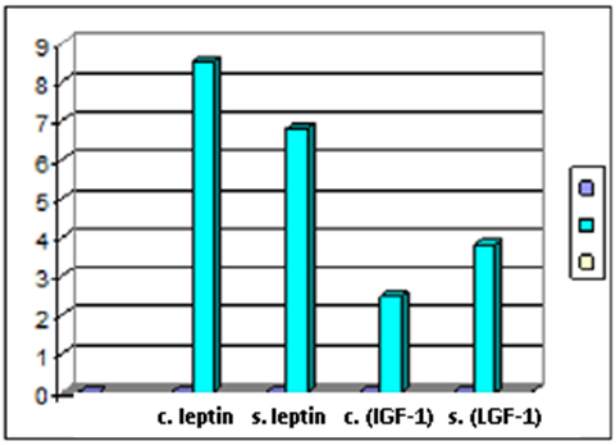

Figure 2. The serum Leptin and serum IGF-1 levels in (ng/100ml) compared with their controls for untreated hyperthyroidism patients. (c. control, s. serum).

Table 1. The levels of serum Leptin, serum Insulin Growth Factor-1and their normal controls for untreated patient with thyroid dysfunction groups.

	Hyperthyroidism	**Control**	
No.	50	25	
Age	25-55	14-55	
Average of age	40	32	
Type of disease	1-nodular goiter 2-multinodular goiter 3-toxic goitre		
Mean serum leptin level (ng/100ml)	6.79 3.0-10.48		
Mean-serum (IGF-1) level (ng/100ml)	3.83 1.18-6.47	2.49 1.99-2.99	
p-value	T3	T4	TSH
For S. Leptin	**0.000096433**	**1.336E- 9**	**0.0198027**
For S.IGF-1	**4.955E- 5**	**1.1198E- 9**	**0.0152394**
For serum Leptin with (IGF-1) P value = 5.5687E- 5			

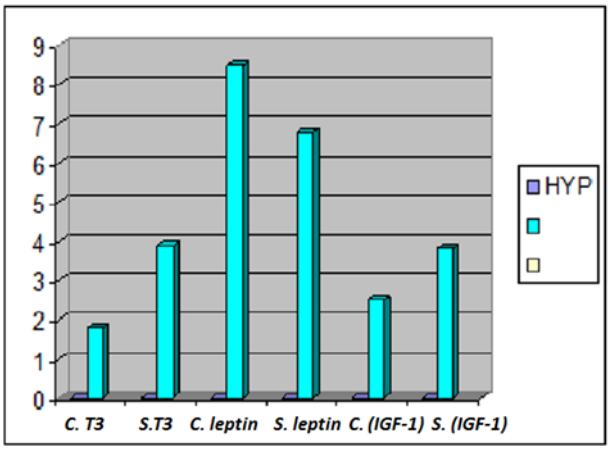

Figure 3. The serum Leptin and serum IGF-1 levels compared with serum T3 levels for untreated hyperthyroidism patients. (c. control, s. serum).

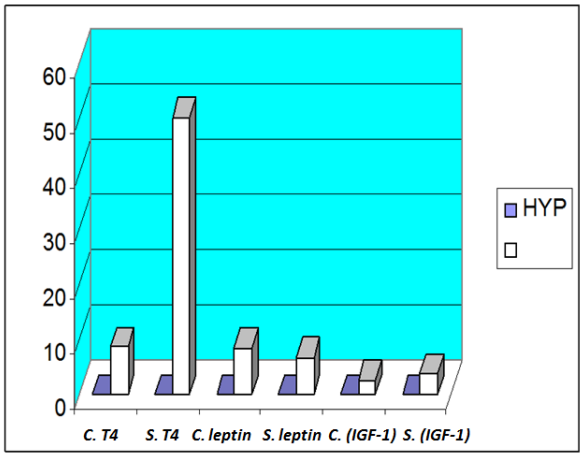

Figure 4. The serum Leptin and serum IGF-1 levels compared with serum T4 levels for untreated hyperthyroidism patients in (ng/100ml). *(c. control, s. serum).*

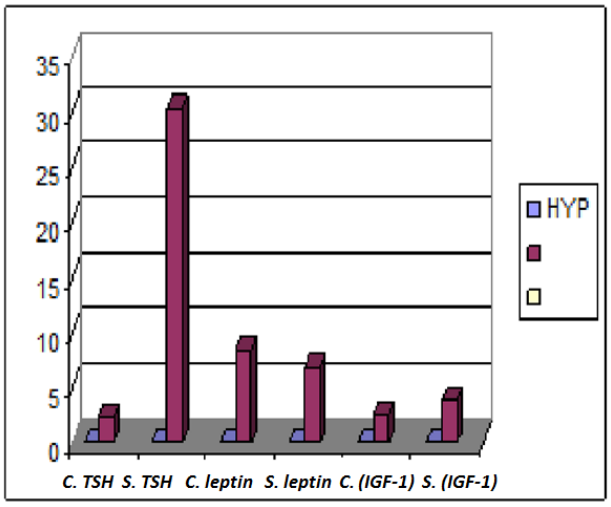

Figure 5. The serum Leptin and serum IGF-1 levels compared with serum TSH levels for untreated hyperthyroidism patients. *(c. control, s. serum).*

DISCUSSION

Leptin is a pliotropic hormones that has helped to redefine adipose tissue as an endocrine organ.[7] The findings of untreated hyperthyroidism patients indicate the resistance of a defect Leptin action. This resistance may fall to cross the blood brain barrier, the hypothalamic receptors may be down regulated or downstream singling may be inhibited.[23] We fined correlation between serum levels of serum Leptin in hyperthyroidism group, serum Insulin like growth factor -1 (IGF-1) and T3 fig.3. The low serum levels of T4, associated with chronic starvation were thought to be the result of impaired peripheral conversion of T4 to T3. However decreased levels of T3 were still apparent even after a partial weight gain and the concentration of T4 was been lower.

The significant decrease in the mean value of serum Leptin and the significant increase in the mean value of Insulin like growth factor-1 (IGF-1) in hyperthyroidism group; this agree with[24-26] The diminished serum level of TSH in Anorexia Nervosa (AN), however, appeared to return to the level of controls .On the basis of these results, we assume that low serum thyroid hormones in AN reflect dysfunction of the HPT axis in an AN patients. It is known that in man serum serotonin levels correlate positively T3 levels. It is possible that the low serum levels of thyroid hormones in AN subjects result in low serum serotonin and its product, melatonin. While IGF01 reflects the energy intake of the previous few weeks, the serum Leptin concentration reflects the status of the adipose stores, a fact that has useful clinical implication.[27]

REFERENCES

1. Brennan AM, Mantzoros CS. Drug insight: the role of Leptin in human physiology & pathophysiology-emerging clinical applications. ***Nat Clin Pact Endocrinol Metab*** 2006;2:318-27.
2. Green ED, Maffei M, Braden VV, Proenca R, DeSilva U, Zhang Y, et al. The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome7. **Genome Res** 1995;5:5-12.
3. Yang J, Zhao XQ, Guo SC, Li HG, Qi DL, Wang DP, et al. Leptin cDNA cloning and its mRNA expression in plateau pikas (Ocotona curzoniae) from different altitudes on Qinghai-Tibet Plateau. ***Biochem Biophys Res Commun*** 2006;345:1405-13.
4. Friedman JM. The function of leptin in nutrition, weight and physiology. ***Nutr Rev*** 2002;60:S1-14.
5. Alonso-Vale MI, Andreotti S, Peres SB, Anhê GF, das Neves Borges-Silva C, Neto JC, et al. Melatonin enhances leptin expression by rat adipocytoes in the presence of Insulin. ***Am J Physiol Endocrinol Metab*** 2005;288:E805-12.
6. Chan JL, Mantzoros CS. Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhea and anorexia nervosa. ***Lancet*** 2005;366:74-85.
7. Wilding JP. Leptin and the control of obesity. ***Curr Opin Pharmacol*** 2001;1:656-61.
8. Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. ***Peptides*** 1996;17:305-11.

9. Rayner DV, Trayhum P. Regulation of Leptin production: sympethatic nervous system interaction. ***J Mol Med*** 2001;79:8-20.
10. Boden G, Chen X, Mozzoli M, Rayan I. Effect of fasting on serum leptin in normal human subjects. ***J Clin Endocrinol Metab*** 1996;81:3419-23.
11. Fekete C, Légrádi G, Mihály E, Huang QH, Tatro JB, Rand WM, et al. Alpha melanocyte stimulating hormone is contained in nerve terminals innervating thyrotropin releasing hormone-synthesizing neurons in the hypothalamic paraventricular nucleus and prevents fasting-induced suppression of prothryrotropin-releasing hormone gene expression. ***J Neurosci*** 2000;20:1550-8.
12. Kursunluoglu R, Turgut S, Akin F, Bastemir M, Kaptanoglu B, Genc O, et at. Insulin-like growth factor-I gene and insulin-like growth factor binding protein-3 polymorphism in patients with thyroid dysfunction. ***Arch Med Res*** 2009;40:42-7.
13. Höppener JW, de Pagter-Holthuizen P, Geurts van Kessel AH, Jansen M, Kittur SD, Antonarakis SE, et al. The human gene encoding insulin-like growth factor-1 is located on chromosome 12. ***Hum Genet*** 1985;69:157-60.
14. Jansen M ,van schaik FM, Ricker AT, Bullock B, Woods DE, Gabbay KH, et al. Sequence of cDNA encoding human insulin-like growth factor-1precursor. ***Nature*** 1983;306:609-11.
15. Salmon WD, Daughaday WH. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. 1956. ***J Lab Clin Med*** 1990;116:408-19.
16. Keating GM. Mecasermin. ***BioDrugs*** 2008;22:177-88.
17. Motomura K, Brent GA. Mechanisms of thyroid hormone action. Implications for the clinical manifestation of thyrotoxicosis. ***Endocrinol Metab Clin North Am*** 1998;27:1-23.
18. Minh Liu. Leptin; A piece of the obesity pie. The science creative Quarterly 2004; issue three.
19. Zhou A, Wei Z, Read RJ, Carrell RW. Structural mechanism for the carriage & released of thyroxin in the blood. ***Proc Natl Acad Sci USA*** 2006;103:13321-6.
20. Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United State National Health And Nutrition Examination Survey 2001-2002. ***Thyroid*** 2005;15:692-9.
21. Joffe RT, Brimacombe M, Levitt AJ, Stagnaro-Green A. Treatment of clinical hypothyroidism with thyroxin and triiodothyronine: a literature review & metaanalysis. ***Psychosomatics*** 2007;48:379-84.
22. Arvan P, Di Jeso B. Thyroglobulin structure, function, &biosynthesis. In: Braverman LE, Utiger RD. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. 9th ed. Lippincott Williams & Wilkins; 2005.
23. Lins MC, de Moura EG, Lisboa PC, Bonomo IT, Passos MC. Effects of maternal leptin treatment during lactation on the body weight and leptin resistance of adult offspring. ***Regul Pept*** 2005;127:197-202.
24. Pinkney JH, Goodrick SJ, Katz J, Johnson AB, Lightman SL, Coppack SW, et al. Leptin and the pituitary –thyroid axis: a comparative study in lean obese, hypothyroid, and hyperthyroid subjects. ***Clin Endocrinol (Oxf)*** 1998;49;583-8.
25. Vaclavi R, Zini M, Penio R, Casnueva FF, Dieguez C. Influence of thyroid status on serum immunoreactive leptin levels. ***J Clin endocrinol metab*** 1997;82:1632-4.
26. Iglesias P, Bayón C, Méndez J, Gancedo PG, Grande C, Diez JJ. Serum insulin-like growth factor type 1, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 concentrations in patients with thyroid dysfunction. ***Thyroid*** 2001;11:1043-8.
27. Nedvídková J, Papezová H, Haluzík M, Schreiber V. Interaction between 5 serum Leptin levels and hypothalamo-hypophyseal-thyroid axis in patients with Anorexia Nervosa. ***Endocr Res*** 2000;26:219-30.
28. Wang Q, Bing C, Al-Barazanji K, Mossakowaska DE, Wang XM, McBay DL, et al. Interactions between leptin and hypothalamic neuropeptide Y neurons in the control of food intake and energy homeostasis in the rat. ***Diabetes*** 1997;46:335-41.