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Endocrinological Assessment and Treatment of Weight Gain & Obesity.

Obesity has become a major health epidemic and has dramatically increased over the last decades. Studies show that now approximately one-third of the U.S. population is classified as obese and over two-thirds are significantly overweight. While the cause is multifactorial, studies are clear that almost all overweight individuals have metabolic and endocrinological dysfunction that is causing or contributing to their inability to lose weight. It is not simply a problem that individuals are taking in more calories than they are consuming, but rather it is a complex vicious-cycle of endocrinological and metabolic dysfunction. Contemporary medicine has failed to address these dysfunctions in overweight individuals and doctors and patients continue to believe that all cases are a matter of will-power and lifestyle. Thus, it is no surprise that obesity is reaching epidemic proportions.

Leptin

The hormone leptin has been found to be a major regulator of body weight and metabolism and dysfunctional leptin signaling results in one of many viscous-cycles that prevent individuals from losing weight. Leptin is secreted by fat cells and the levels increase with the accumulation of fat. The leptin should then feed-back to the hypothalamus as a signal that there are adequate energy (fat) stores, and this should signal the body to burn fat rather than continue to store excess energy.

Studies are finding, however, that the majority of overweight individuals that are having difficulty losing weight have varying degrees of leptin resistance. The leptin is unable to produce its normal effects of weight loss, with the severity correlating with the degree of obesity (1-5). This leptin resistance results in a leptin deficiency in the hypothalamus, which in sensed as starvation, so multiple mechanisms are activated to increase fat stores, as the body perceives a state of starvation (1-30). Baseline leptin levels and the degree of leptin resistance is shown to be a good predictor of a person's likelihood of achieving successful weight loss with dieting (68-70).

The metabolic effects of leptin resistance include a diminished TSH secretion, a suppressed T4 to T3 conversion, an increase in reverse T3, an increase in appetite, an increase in insulin resistance and an inhibition of lipolysis (fat breakdown) (1-29,31). These effects of leptin resistance on thyroid hormones contribute to the drop in TSH and T3 levels that occur with dieting and results in decreased tissue thyroid action and a depressed metabolic rate that inhibits weight loss and promotes weight gain (1,6,10,14,18-23,29,30-37). Unfortunately, standard thyroid function tests miss over 80% of this type of hypothyroidism, as the TSH, free T4 and free T3 levels are typically in the normal range (1,6,10,14,31,38-46). In primary hypothyroidism, diminished thyroid hormones stimulate the hypothalamus to increase TRH secretion, which in-turn stimulates the pituitary to secrete TSH. Thus, the TSH serves as the basis for the diagnosis of primary hypothyroidism, but with the suppression of TSH that occurs with leptin resistance, this feed-back is interrupted and a normal TSH level cannot be used to rule out a significant thyroid deficiency (1,6,10,14,31,38-46).

Starvation dieting can decrease resting metabolic rate by as much as 40% and food restriction at a level to maintain just a 10% reduction in body weight results in significantly decreased intracellular thyroid hormone levels and a diminished metabolic rate that does not return to normal even after a normal diet is resumed (10,18-23,29,30,32,33-37). When combined with the effect of leptin resistance, this accounts for the majority of regained weight in weight reduced subjects (17-22,25,26,31,35,36,47). Low intracellular leptin levels are inversely correlated with reverse T3 (rT3), which may currently be the best marker, along with the T3/rT3 ratio, for diminished T4 to T3 conversion and cellular hypothyroidism in chronic illness (18,48-59). Reverse T3 has been thought to be an inactive metabolite, but it has been shown to be a competitive inhibitor of T3 (blocks T3 activity), directly decreasing cellular energy production, and to directly suppresses T4 to T3 conversion (47,56-59). In fact it is shown to be a more potent inhibitor of T4 to T3 conversion than PTU (56), a medication used to decrease thyroid hormone levels in hyperthyroidism.

In addition, increased adipose tissue results in a maladaptive stimulation of inflammatory cytokines, including TNF-alpha, IL-6 and CRP, which further suppress TSH secretion and the conversion of T4 into T3, as well as increasing the conversion of T3 into rT3 (60-64).

Diagnosis:

If individuals are having difficulty losing weight, we recommend obtaining a metabolic panel that consists of a leptin level, TSH, free T4, free T3, reverse T3, TPO antibody, antithyroglobulin antibody, glucose, insulin, HgA1c, IGF-1, testosterone, CRP, TNF-alpha (highly sensitive), IL-6 (highly sensitive), CRP, homocystine, SHBG and lipids. In addition, the relaxation phase of the ankle or brachioradialis muscle can be measured. This has been shown to correlate with the degree of hypothyroidism and to be a better indicator of tissue levels of thyroid than standard thyroid function tests (50,65,66).

While a complete review of the interpretation of these labs is beyond the scope of this article, as it not as simple as looking at what is normal or abnormal and ratios typically need to be evaluated. In general, however, a leptin level greater than 10 is associated with leptin resistance. Thus, if the leptin level is above 10, the TSH is unreliable (artificially decreased) and a normal TSH cannot be used to rule-out significant cellular hypothyroidism. Likewise, if the inflammatory markers CRP, TNF-alpha or IL-6 are relatively (high normal) or overtly elevated,

(over)

which is often the case with numerous conditions including insulin resistance, diabetes, obesity, lupus, rheumatoid arthritis, stress, sleep apnea, depression, chronic fatigue syndrome, fibromyalgia, heart disease and insomnia, the TSH is not a reliable indicator of tissue levels of active thyroid hormone. The T3/rT3 ratio is typically the best marker for tissue hypothyroidism in these conditions, as again, the TSH is not reliable if leptin resistance or inflammation is present. Insulin levels along with the HgA1c, glucose and lipids are used to evaluate insulin resistance, another reason for problems with weight gain. A muscle reflex relaxation phase of greater than 110 msec also demonstrates low tissue levels of thyroid.

Treatment:

There are new medications, Byetta and Symlin, that decrease leptin resistance. These can be very beneficial treatments and can produce dramatic weight loss if given in conjunction with other metabolic treatments. While these medications are approved for type II diabetes and are showing significant weight loss in this patient population, they are showing promise in the non-diabetic population as well. The amount of weight loss varies according to the study design, but a significant percent of patients are having dramatic weight loss, despite little or no change in diet. Again, this demonstrates that many overweight patients have a metabolic problem rather than a problem of will-power. While these medications, by themselves, typically result in modest weight loss, combining these medications with metabolic treatments and a healthy lifestyle can allow for significant sustained weight loss.

A thorough analysis and work up will find that many overweight patients have, in addition to leptin resistance, dysfunction of the hypothalamus-pituitary-thyroid axis as well as dysfunction of the peripheral (cellular) thyroid metabolism and utilization. Correction of these dysfunctions can result in dramatic long term successful weight loss. If high reverse T3 is found, T4 preparations such as Synthroid or Levoxyl are shown to be ineffective in restoring tissue thyroid levels (67). T4/T3 preparations such as Armour thyroid are better but timed released T3 preparations are the most effective at restoring tissue T3 levels and often effective when Armour thyroid, Synthroid and Levoxyl fail to restore normal tissue levels of thyroid.

References

1. Dagogo_Jack S. Human Leptin Regualtion and Promis in Pharmacotheroapy. Current Drug Targets 2001;2:181-195.

2. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR. Ohannesian JP, Marco CC, Mckee LJ, Bauer TC, Caro JF. Serum immunoreactive-leptin. concentrations in normal-weight and obese humans New England Journal Medicine 1996;334: 292-295.

3. Dagogo-Jack S, Tanellis C, Paramore D, Brother SJ, Land TM. Plasma Leptin and Insulin Relationships in Obese and Nonobese Human, Diabetes 1996;45:695-698.

4. Maffei M et al. Leptin levels in human and rodent: measurement of plasma leptin and ob NAN in obese and weight-reduced subjects. Nature Medicine 1995;1;1155-1161.

5. Sandra G et al. Serum leptin in children with obesity. Relationship to gender and development 1996;98:201-203.

6. Kozlowska L, Rosolowska-Huszcz. Leptin, Thyrotropin, and Thyroid Hormones in Obese/Overweight Women Before and After Two Levels of Energy Deficit. Endocrine 2004;24(2):147-153

7. Fekete C et al. Differential Effects of Central Leptin, Insulin, or Glucose Administration during Fasting on the Hypothalamic-Pituitary-Thyroid Axis and Feeding-Related Neurons in the Arcuate Nucleus. Endocrinology 2006;147(1):520-529

8. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS 1996 Role of leptin in the neuroendocrine response to fasting. Nature 382:250–252

9. Legradi G, Emerson CH, Ahima RS, Flier JS, Lechan RM. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. Endocrinology 1997;138:2569–2576

10. Zimmermann-Belsing T et al. Ciruclation leptin and thryoid dysfunction. European Journal of Endocrinology 2003;149:257-271.

11. Schwartz Mw, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature 2000;404;61-671.

12. Mantzoros CS, Moschos SJ. Leptin: in search of role(s) in human physiology and path physiology. Clinical Endocrinology 1998;49:551-567.

13. Fruhbeck G, Jebb SA, Prentice AM. Leptin: physiology and pathophysiology. Clinical Endocrinology 1998;49:551-567.

14. Flier JS, Harris M, Hollenber A. Leptin, nutrition and the thyroid: the why, the wherefore and the wiring. The Journal of clinical Investigation 2000;105(7):859-861.

15. Gon DW, He y, Karas M, Reitman M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta 3-adernergic agonists and leptin. Journal of Biological Chemistry 1997;272:24129-24132.

16. Cusin I, Rouru J, Visser T, Burger AG, Rohner-Jeanrenaud F. Involvement of thyroid hormones in the effect of intracerebroventricular leptin infusion on uncoupling protein-3 expression in rat muscle. Diabetes 2000;49:1101–1105.

17. Rosenbaum M, Godmsith R et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J. Clin. Invest 2005;115:3579-3586 .

18. Rosenbaum M, Muryphy et al. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulation concentration of thyroid hormones. JCEM 2002:87(5):2391-2394.

19. Leibel RL et al. 1995. Changes in energy expenditure resulting from altered body weight. N Eng JMed. 332:621-28.

20. Rosenbaum M et al. The effects of changes in body and thyroid function. Amer J Clinical Nutrition 2000;71:1421-32.

21. Ahima, R et al. Role of leptin in the neuroendocrine response to fasting. Nat. 1996;382:250-52

22. RosenbaumM. et al 1997 Effects of weight change on plasma leptin concentrations and energy expenditure. J Clin. Endocrinol. Metab 1997;82:3647-54

23. Legradi G et al. 1998. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid m neurons of the hypothalamic paraventricular nucleus. EndocrinoL 1998;138:2569-76.

24. Boozer C et al Synergy of leptin and sibutramine in treatment of diet-induced obesity in rats. Metab. 2001;50:889-93.

25. Campfield LA et al. Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. Sci 1995;269:546-48.

26. Farooqi I et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Eng J Med 1999;341:879-84.

27. Chehab F. Leptin as a regulator of adipose tissue mass and reproduction. Trends Pharmacol Sci 200;21:309-14.

28. Rosenbaum K et al. The role of leptin in human physiology. N Eng JMed 1999;341:913-15.

29. Naslund, E, et al. 2000. Associations of leptin, insulin resistance and thyroid function with long-term weight loss in dieting reduced-obese men. JIntMed, 248:299-308.

30. Doucette, E, et at. 2000. Appetite after weight-loss by energy restriction and a low-fat diet-exeriese follow up. Int J Obesisty 2000;24:906-14.

31. Roos A, et al. Thyroid function is associated with components of the Metabolic syndrome in Euthyroid Subjects J. Endocrinolgy & Metaoblism 2007;92(2)491-496.

32. Leibel R.L et al. 1984. Diminished energy requirements in reduced obese patients. Metabolism 1984; 33:164-70.

33. Lowell B, Spiegelman B. Towards a molecular understanding of adaptive thermogenesis. Nature 200;404:652-660.

34. Silva JE.Thyroid hormone control of thermogenesis and energy balance. Thyroid. 1995 Dec;5(6):481-92.

35. De Boer Jo, Van Es EJ, Roovers LC, Van Raaij JM, Hautvast JG. Adaptation of energy metabolism of overweight women to low-energy intake, studied with whole-body calorimeters. American Journal of Clinical Nutrition 1986;44;585-595,

36. Kok P, Roelfsema F et al. High Circulating Thyrotropin Levels in Obese Women Are Reduced after Body Weight Loss Induced by Caloric Restriction. Journal of Clinical 2005;90(8):4659-4663.

37. Weinsier RL et al. Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. Am J Clin Nutr 2000 Nov;72(5):1088-94.

38. Neeck G, Riedel W. Thyroid Function in Patients with Fibromyalgia Syndrome. J of Rsheumatology 1992:19-7:1120-1122.

39. Rose SR; Lustig RH; Pitukcheewanont P; Broome DC; Burghen GA; Li H; Hudson MM; Kun LE. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 1999 Dec;84(12):4472-9

40. Lowe JC. Thyroid Status of 38 Fibromyalgia Patients: Implications for the Etiology of Fibromyalgia. Clin Bull Myofacial Therapy, 2(1):47-64, 1997.

41. Wiersinga WM 2000 Nonthyroidal illness. In: Braverman LE, Utiger RD, eds. The thyroid. Philadelphia: Lippincott; 281–292

42. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone me¬tabolism. Clin Endocrinol (Oxf) 1993;39:499 –518

43. Wartofsky L, Burman KD 1982 Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome." Endocr Rev 3:164–217

44. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR 2002 Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 23:38–89

45. McIver B, Gorman CA 1997 Euthyroid sick syndrome: an overview. Thyroid 7:125–132

46. Van den Beld AW et al. Thyroid Hormone Concentrations, Disease, Physical Function and Mortality in Elderly Men The Journal of Clinical Endocrinology & Metabolism 2005; 90(12):6403–6409

47. Sechman A et al. The relationship between basal metabolic rate (BMR) and concentrations of plasma thyroid hormones in fasting cockerels. Folia Biol (Krakow). 1989;37(1-2):83-90.

48. Corsonello A et al. Plasma leptin concentrations in relation to sick euthyroid syndrome in elderly patients with nonthryoidal illness. Gerontol 2000;46;64-70.

49. Peeters RP, Wouters PJ,, Van Toor H et al. Serum 3,3',5'-Triiodothyronine (rT3) and 3,5,3'-Triiodothyronine/rT3 Are Prognostic Markers in Critically Ill Patients and Are Associated with Postmortem Tissue Deiodinase Activities. The Journal of Clinical Endocrinology & Metabolism 2005;90(8):4559–4565

50. Annewieke W. Van den Beld, Theo J. Visser, Richard A. Feelders, Diederick E. Grobbee, and Steven W. J. Lamberts Thyroid Hormone Concentrations, Disease, Physical Function, and Mortality in Elderly Men. J Clin Endocrinol Metab 2005 90: 6403-6409; September 20 2005.

51. Pittman J et al. Antimetabolic Activity of 3,3',5-triiodo-DL-thyronine in man. Endocrinology. Mar;64(3):466–468.

52. Robin P. Peeters, Serge van der Geyten, Pieter J. Wouters, Veerle M. Darras, Hans van Toor, Ellen Kaptein, Theo J. Visser, and Greet Van den Berghe. Tissue Thyroid Hormone Levels in Critical Illness. J Clin Endocrinol Metab 2005 90: 6498-6507.

53. Den Brinker et al. Euthyroid Sick Syndrome in Meningococcal Sepsis: The Impact of Peripheral Thyroid Hormone Metabolism and Binding Proteins. The Journal of Clinical Endocrinology & Metabolism 2005;90(10):5613–5620

54. Peeters RP, Van der Geyten, Wouters PJ, Darras VM et al. Tissue Thyroid Hormone Levels in Critical Illness. The Journal of Clinical Endocrinology & Metabolism 2005;90(12):6498–6507

55. Peeters RP, Wouters PJ, Kaptein E et al.Reduced Activation and Increased Inactivation of Thyroid Hormone in Tissues of Critically Ill Patients. The Journal of Clinical Endocrinology & Metabolism 2003;88(7):3202–3211

56. Chopra I. A Study of Extrathyroidal conversion of thyroxind to T3 in vitro. Endocrinology 1977;101:453-64.

57. Okamoto R, Leibfritz D. Adverse effects of reverse triiodothyronine on cellular metabolism as assessed by 1H and 3P NMR spectroscopy. Res Exp Med 1997;197(4):211-217.

58. Larson FC, Albright EC. Inhibitoin of L-thyroxine Monodejodination by Thyroxine Analogs. J Clin Invest. 1961 July; 40(7): 1132–1138.

59. Pittman JA, Tingley JO, Nickerson JF, Hill SR. Antimetabolic activity of 3,3',5'-triodo-DL-thyronine in man. Metabolism 1960;9:293-5.

60. Boelen A et al. Association between Serum Intrleukin-6 and Serum 3,5,3'-triiodothyronine in nonthryoidial illness. JCEM 1993;77(6):1695-1699.

61. Hashimot H et al. Ther relationship between serum levels of interleukin-6 and thyroid hormone in childeren with acute respiratory infection. JCEM 1994;78(2):288-291.

62. Yamazaki K et al. Interleukin-6 (IL-6) inhibits thyroid function in the presence of soluble IL-6 receptor in cultured human thyroid follicles. Endocrinology 1996;137(11):4857-4863.

63. Baralena L et al. Relationship of the increased serum interleukin-6 concentration to changes of thyroid function in nonthryoidial illness. J Ejdocrinol Invest 1994;17:269-274.

64. Yudkin JS et al. C-reactive protein in healthy subjects: Associations with obesity, Insulin resistance, and endothelial dysfunction. Atherioscler Thromb Vasc Biol 1999;19:972-978.

65. Henryk Zulewski, Beat Müller, Pascale Exer, André R. Miserez and Jean-Jacques Staub Estimation of Tissue Hypothyroidism by a New Clinical Score: Evaluation of Patients with Various Grades of Hypothyroidism and Controls. The Journal of Clinical Endocrinology & Metabolism 1997;82(3):771-776.

66. Meier C, Trittibach P, Guglielmetti M, Staub J-J, Müller B. Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. British Med J 2003;326:311-312

67. Escobar-Morreale et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats, J Clin Invest, 1995

68. De Giudice EM et al. Inadequate leptin level negatively affects body fat loss during a weight reduction program for childhood obesity. Acta Peadiatr 2002;91:132-135.

69. Naslund E et al. Associations of leptin, insulin resistance and thyroid function with long-term weight loss in dieting obese men. J Internal Med 2000;248:299-308.

70. Fleisch AF, Agarwal N et al. Influences of Serum Leptin on Weight and Body Fat Growth in Children at High Risk for Adult Obesity. J Endocrinology Metab 2007:92(3):948–954