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CENTER FOR HORMONE IMBALANCE, HYPOTHYROIDISM AND FATIGUE

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**O**BESITY 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 is 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 hypothyroid-

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ism 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,

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 re-

leased 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.

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