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Hypotheses

TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss

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Abstract. While many endocrinologists continue to debate the appropriate levels of TSH to use as boundaries for normal limits, we believe using TSH to assess thyroid function is counterproductive, particularly in those patients attempting to lose weight. From the published literature and our own clinical experience, we have come to understand that the set point for metabolism is adjusted downward in the hypocaloric state. The decrease in metabolism is often referred to as part of the "famine response." This metabolic response has been documented in several major vertebrate classes demonstrating its widespread importance in nature. In our current environment, the famine response limits the patient's ability to lose weight while consuming a hypocaloric diet and performing modest levels of exercise. Our own experience with the famine response is consistent with that found in the literature. Treating to normalize thyroid hormone levels and eliminate hypothyroid symptoms results in the suppression of TSH. This is understood as a normal part of treatment once we accept that the thyroid set point has been lowered. This is not an argument to use thyroid hormones to increase metabolism above normal to achieve weight loss. Our goal is to correct the hypothyroid response in a weight loss patient and return him/her to normal metabolism so that the patient feels normal and is better able to lose weight and maintain that loss.

Keywords Famine response ● Hypocaloric state ● Hypothyroidism ● Reverse triiodothyronine ● rT_3 ● T_3 ● TSH ● Triiodothyronine

Introduction

Major controversies regarding appropriate thyroid treatments are ongoing and are affecting the morbidity and most likely mortality in many populations. In his 2008 paper, Dommisse has extensively covered the disagreements in this area and presented arguments which challenge the views of the majority of the medical community.[1] While we agree with him, we bring a unique experience base to the discussion which, we believe, supports and adds to Dommisse's work.

The authors have the clinical experience over the past eight years of treating over 15,000 obese patients with a healthy low carbohydrate, low fat diet, supplements to correct any nutritional deficits from the low calorie diet, a program of light exercise, and various medications for appetite control used both on and off label. The weight loss in our clinic has averaged about 19% at 2 years for those who stay on treatment that long. Other benefits that we have observed with this treatment are improved blood pressure using fewer antihypertensive medications, improved glycemia, again with fewer anti-diabetic medications, improved lipids, and improved quality of life.

When using these highly effective appetite suppressants on our obese and overweight patients, we have found approximately one third of them suffer the common phenomenon of reaching a plateau while continuing our diet and exercise recommendations. These patients have accompanying symptoms of low thyroid which may include coldness, cold extremities, fatigue, joint aches, hair loss, constipation, and depression. Our clinical experiences have led us to believe that the inappropriate assessment of thyroid function using thyroid stimulating hormone (TSH) is an important factor contributing to the inability of many patients to lose weight and maintain the loss. TSH is considered the gold standard for evaluating

thyroid function because it responds in logarithmic fashion to subtle changes in thyroid hormone levels, decreasing dramatically in the circulation when thyroid hormone levels rise and increasing dramatically when they drop.

Thus, it would appear that the portions of the brain involved in metabolism are using this pathway to tightly defend a homeostatic level. While we certainly agree that this pathway is used, we will demonstrate that there are times when providers must choose to override the homeostatic set point and treat based on other available indicators of metabolism. The paradigm we are proposing shifts away from using TSH to assess medically appropriate treatment of hypothyroidism once this phenomenon is understood using a more global view of negative feedback systems in animals. Arguments about the appropriate range for normal TSH are rendered irrelevant by our view.

Much of what we will argue is already in the scientific literature but is unknown, not understood, or not accepted by most prescribers. These concepts apply both to hypothyroid patients already on thyroid treatment as well as those who are normal in both thyroid hormone levels and metabolism prior to attempting to lose weight.

1. The homeostatic set point for metabolism (mediated via thyroid hormones) is reset at a lower level in the hypocaloric state in some patients. The resultant lowered energy expenditure may be highly adaptive when food is scarce; but it hinders weight loss attempts in our obese and overweight patients. These patients may also suffer from symptoms of low thyroid such as coldness, cold extremities, fatigue, joint aches, hair loss, constipation, and depression.

2. The health care community is well aware of the concept of homeostasis but does not consider the well-studied concept of alterations of set points.

3. During weight loss attempts, when thyroid is carefully replaced to eliminate hypothyroid symptoms and restore normal circulating levels of thyroid hormones (free triiodothyronine [FT_3] and free thyroxine [FT_4]), TSH is suppressed (personal observation).

4. This suppression of TSH should be understood to represent part of the normal feedback mechanism by which the body decreases metabolism to maintain stored resources in the face of insufficient nutrition. This level of TSH should not be used to regulate thyroid dosing. If a provider regulates thyroid hormone dosing based on TSH in these circumstances, the patient's weight loss attempt will be severely hindered.

5. Reverse T_3 (rT_3), which increases in the famine state, may have a function in suppressing metabolism in humans.

6. We will critique arguments against thyroid treatment in the hypocaloric state.

7. Once the relative importance of TSH versus FT_3, FT_4, and rT_3 are reconsidered in the hypocaloric condition, it is appropriate to carry this argument to the non-dieter.

Given the critical nature of the obesity epidemic, we feel it is time to express these ideas in a thorough manner in hopes that providers will begin to work on bringing the patient's metabolism back to normal during weight loss attempts. Further, even in the non-dieting patient, evaluating symptoms, FT_3, FT_4, and reverse T_3 are of more value than TSH for improving patients' quality of life.

1. Resetting the Thyroid Hormone Set-Point: "The Famine Response"

Many studies have reported changes in metabolism in the hypocaloric state in humans. Early literature was reviewed in the seminal work of Keys et al.[2] in their experimental study of human starvation. Our own coverage of the literature is summarized in the Table. (This table is not designed as an exhaustive literature review, but rather to provide the reader an overview of the general findings in this field. We also provide limited information regarding details other than hormone blood levels. Again this is merely to provide the reader with a concept of what else has been studied.)

Almost without exception, experimental studies of fasting or low caloric intake in humans show decreases in circulating levels of total T_3 (TT_3) (all of the 22 studies) and FT_3 (all of the eight studies) with increases in rT_3 (16 of 17 studies). (There are two alternate pathways for T_4 metabolism: to the active hormone (T_3) or to rT_3. Most providers believe rT_3 is an inactive byproduct.) T_4 results are mixed.

For total T_4 (TT_4), four studies show increases, 10 no change, and four show decreases. Similarly, for FT_4, seven show increases, 4 no change, and one shows a decrease. The results for TSH are mixed, showing either decreases (six studies) or no changes (nine studies), but never an increase.

There are also a limited number of reports of other relevant variables in humans and laboratory rats (Table). These hormonal changes are similar to those found in euthyroid-sick syndrome[3] and, in fact,

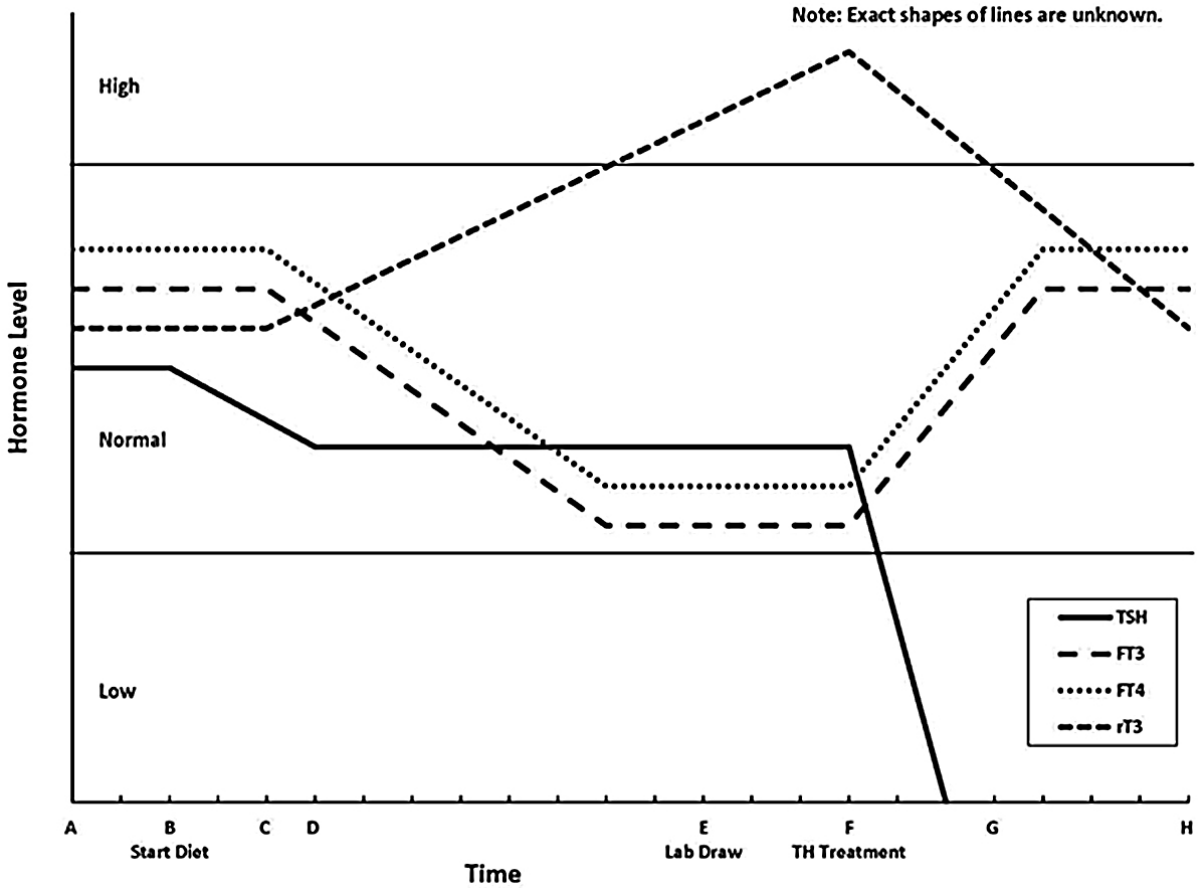

Figure. Hormonal responses to a hypocaloric state with subsequent treatment. Note: Time frames and shapes of response curves are unknown. Levels of all four hormones are normal before the diet (Time A). At time between time points B and D, TSH is dropping slightly to signal the thyroid gland to make less thyroid hormone. This drop is the mechanism to decrease metabolism in the hypocaloric state. At point C, free T_3 begins to drop as rT_3 increases. Also at time point C, different observations have been reported for changes in FT_4: in our experience, FT_4 also drops as indicated on the graph. In the literature, some report no change, whereas others report an increase in FT_4. By the time of the blood sampling (time E), in our experience, patients whose FT_3 and FT_4 have dropped to the low end of normal (with possible above normal rT_3 levels) are those experiencing symptoms of low thyroid. They may have any of the following symptoms: feeling cold, cold hands and feet, elevated diastolic blood pressure secondary to vasoconstriction, fatigue, depression, constipation, hair loss, dry skin, insomnia, as well as others. They have often hit a plateau of weight loss even though they have continued to maintain their hypocaloric diet and exercise program. At point F, we begin treatment with thyroid hormone (T_4 with T_3, T_3 alone, or desiccated thyroid, depending on the situation). Between points F and G, FT_3 and rT_3 (and FT_4 if it was administered) are returning to more normal levels, while TSH plummets, often to undetectable levels. At time point H, symptoms of low thyroid are resolved, the patient has no symptoms of hyperthyroidism, and if rT_3 had risen and was treated appropriately, rT_3 decreased.

the hypocaloric state has been used as a model to study these hormonal changes in severe illness. Our figure demonstrates these changes graphically.

Unfortunately, the famine response escapes detection by current laboratory evaluation of the thyroid. In our clinical experience, the differences found do not reach levels one observes in pathological states. Before dieting (Figure: times A – B) TSH, free T_4, and free T_3 are within normal limits. After dieting starts (times B – F), decreases occur in these three hormones in many patients, but the hormones remain within normal limits. Furthermore, clinicians are

looking for an increase in TSH to indicate a decrease in thyroid function, not a decrease in TSH. And the decrease that occurs is not enough to be noticeable on an individual clinical laboratory assessment. Only when data are available before and during a hypocaloric treatment can these differences be observed (Table).

Thus, when a patient presents with symptoms of low thyroid and is unable to lose weight despite serious caloric limitation, most clinicians test for primary hypothyroidism with a TSH assay. The likely result is a TSH at the lower end of normal (Figure: times D – F). The clinician interprets the TSH reading to mean that the thyroid hormones are within normal limits and, if anything, to assume that FT_3 and FT_4 are on the high end of normal. If the patient requests a FT_3 and FT_4, those are likely to be at the low end of normal or only slightly below normal (personal observation, TN and CR). The provider would be likely to conclude that there is nothing wrong with the patient's thyroid function despite the symptoms. The patient is often told to get more exercise and that s/he must be eating more calories than realized.

We would agree that there is nothing "wrong" with the patient's thyroid function. The hypothalamic-pituitary-thyroid (HPT) axis is performing in a highly evolved manner to help the patient live through the current caloric limitations. In the clinical setting, one is unlikely to have the comparison of pre-famine to famine hormone levels as has been documented in clinical research studies. The results of these studies conflict with our understanding of normal adult human homeostasis. Under our usual understanding of human endocrinology, we would not expect a decrease in FT_3 or FT_4 to occur simultaneously with a decrease in TSH. Rather, we would expect a decrease in FT_3 or FT_4 to be met by an increase in TSH as the feedback loop's mechanisms work to achieve maintenance of a stable set point.

2. But Is It Not Unusual to Alter a Homeostatic Set Point?

Actually, it is not unusual for set points to change. However, homeostasis is a major paradigm providing the framework for our learning of much of human physiology and endocrinology. This concept is generally the first idea taught in introductory human physiology class. We are not taught to think of humans as having set point changes except for the well-recognized differences in reproductive hormone levels before and after puberty. The concentrations of androgens and estrogens are regulated at low levels before puberty. An important way to think about this is that low concentrations of the reproductive steroids are sufficient to suppress production of GnRH, LH, and FSH during childhood, whereas much higher levels of these steroids are required to inhibit the relevant hypothalamic and pituitary hormones after puberty. By definition, this means that the hypothalamic and pituitary set points change during maturation. After puberty, these sites are much less sensitive to the gonadal steroids.

Broadening our view to include eco-physiological adaptations of other animals demonstrates obvious changes in set points. Body temperature set point alterations in hibernating mammals are well studied. Hibernating mammals do not simply allow body temperature to drop to ambient temperature; e.g., a hibernating bat will maintain a body temperature slightly above ambient.[4] Hummingbirds, which maintain a very high metabolic rate during the day, go into torpor [a dormant state of low metabolism] at night, resetting their temperature set point to produce a much lower metabolic rate during their inactive time.[5]

Probably the best studied change in set point is that occurring in seasonal breeders. Extensive studies of long-day breeders (rodents) and short-day breeders (sheep) have elucidated mechanisms in which feedback set points are seasonally reversible. See Bronson[6] for review. Males maintain large testes and high circulating testosterone levels during the breeding season; during the non-breeding season, testes regress and testosterone levels may be almost non-detectable. In mammals, the control of these variations by day length is well known. Seasonal decreases in mass and functioning of gonadal and accessory tissues are understood to be adaptations to minimize androgen-dependent energy expenses during the non-breeding season (e.g., mate-seeking, aggression, and maintenance of testes and accessory organs). Such hormonal differences could not be produced and maintained if the set point of the feedback for testosterone remained constant.

Seasonal and facultative responses are not so obvious for humans living with regulated household temperature, warm clothing for cold weather, and constantly abundant food. We are so buffered from the vicissitudes of the environment that it is easy for us to view modern adult *Homo sapiens* as being in a single homeostatic state rather than considering our own species as having the ability to adapt to

altered environmental conditions. For many circumstances, this view is adequate for our understanding of human systems. However, by considering ecological factors, we can sometimes increase our understanding of human physiological issues. The identification of seasonal affective disorder (SAD) approximately 25 years ago demonstrated a strong connection to seasonal day length changes in a subset of the population. SAD is now widely accepted as a disorder which can be treated with phototherapy.[7]

In light of this understanding of adaptive physiological responses in humans and a variety of other vertebrates, we can now view hypocaloric patients differently. Almost without exception, studies show that decreased caloric intake in humans caused decreased circulating levels of TT_3 and FT_3 with increased rT_3 (Table 1). These individuals are using the famine response to stay alive when food resources are inadequate. Similar responses have been reported in several vertebrates, including desert tortoises,[8] herring gulls,[9] and mink.[10] For review, see Eales, 1988.[11] The widespread nature of this response is explained either by its appearance prior to the evolution of these distinct vertebrate classes or its independent evolution many times. In either case, its importance becomes obvious.

For the patient in the hypocaloric state, we must now re-evaluate how we view the hypothalamic-pituitary-thyroid (HPT) axis. This complicates the question of the appropriate evaluation and treatment of thyroid dysfunction. Subtle decreases in TSH and borderline low values of free T_3 and/or free T_4 with increases in rT_3 are indicative of a low-metabolism state that inhibits desired weight loss. The famine response can be viewed as maladaptive in our current obese and overweight patients attempting to lose weight. While the adipocyte hormone leptin plays an important role in regulating thyroid hormones and other aspect of the famine response (Rosenbaum and Leibel for review),[12] our own work focuses on the thyroid portion as this can be treated currently and has shown profound effects for many of our patients.

3. In the Hypocaloric State, Treatment of Low Thyroid to Produce Normal Levels of FT_3 or Both FT_3 and FT_4 Results in Suppression of TSH without Symptoms of Hyperthyroidism

We have observed this phenomenon in our patients over the years: administration of both T_3 and T_4 to produce normal serum levels of both hormones causes suppression of TSH (Figure: times F – H). If only T_3 is administered, T_3 levels are normalized and TSH is suppressed. When FT_3 alone or both FT_3 and FT_4 are corrected, clinical symptoms of hypothyroidism are resolved.

Proof that this phenomenon represents a change in thyroid homeostatic set point is that, by definition, a deviation from the set point of circulating thyroid hormones will cause a change in TSH in response. When experimental subjects are given T_3 to eliminate famine-induced hypothyroid symptoms, TSH is suppressed with no symptoms of hyperthyroidism.[13-15]

4. Suppression of TSH Either in the Hypocaloric State or in a Non-dieting Hypothyroid Patient Treated to Optimize Well-being Should be Understood to Represent the Body's Response to its Altered Set-Point for Thyroid Feedback

This is most easily explained as we do for patients: *Your body has chosen to decrease metabolism (by decreasing thyroid hormone levels) to save your life in this time of limited resources. The fatigue and coldness you feel are the body's attempt to make you burn fewer calories by decreasing your optional activity and lowering the heat generated.* (When asked, patients realize that they do not shiver or horripilate [develop "goose bumps"] during these times of extreme coldness. This demonstrates that the body is not attempting to correct the coldness with its usual autonomic responses: increasing heat production [shivering] or attempting to save heat [horripilation].) *When we bring your metabolism back to normal by giving you thyroid hormones to produce normal circulating levels, your body's regulatory systems assess this as a higher metabolic rate than the body wants for the low calorie state. Your brain thinks your thyroid must be making more thyroid hormone than is appropriate, i.e., parts of the brain are saying, "I'll die of starvation if I maintain normal metabolism. I need to decrease thyroid hormone production and I do that by not making TSH; this allows my thyroid hormones to drop back to lower levels." So TSH can go to zero while the body attempts to bring thyroid hormone levels and metabolism back down to their new, energy-conserving levels. Since we are providing exogenous thyroid hormone, this presents a challenge for the body.* In terms of symptoms, the patient now feels normal without either the previous hypothyroid symptoms or any symptoms of hyperthyroidism. (See figure for a graphic explanation.)

In cases like this, the primary care provider often receives a laboratory report of a suppressed TSH and informs the patient that his/her thyroid is being over-treated and that s/he should stop the thyroid treatment. The provider ignores the information that FT_3 and FT_4 are within normal limits and that the patient has finally ceased having symptoms of hypothyroidism and has started to lose weight again.

5. Reverse T_3 May be Part of the Mechanism Suppressing Metabolism in Humans

While most clinicians believe that rT_3 is a waste product and merely a pathway the body uses for the elimination of T_4, the literature provides arguments for a role for rT_3. Changes in kidney function show intriguing results. In fasting, tubular reabsorption of T_4 and T_3 is decreased[16] whereas that of rT_3 is increased.[17] Such variation in kidney function suggests that manipulation of plasma levels of these components is being performed based on caloric intake. While we find it difficult to understand the rationale for Wilson's specific approach to treating high rT_3,[18] we can see the general logic of a role for rT_3 in decreasing metabolism since rT_3 is known to compete with both T_3 and T_4 for transporters and receptors.[19] rT_3 also inactivates and degrades D2, the enzyme which both converts T_4 to T_3 and degrades rT_3.[20,pp.50,54] rT_3 also decreases the activity of D1, another enzyme involved in the same two pathways.[20,p.54]

So in a hypocaloric state, there is a relatively higher concentration of rT_3 and lower concentrations of both T_3 and T_4; also the available rT_3 can inhibit the functions of T_3 and T_4. All of this suggests a role for rT_3 in decreasing metabolism.

6. Critique of Arguments against Thyroid Treatment in the Hypocaloric State

It would appear obvious to attempt to replace the decrement in thyroid hormone levels to return metabolism to normal in patients in a weight loss program. However, several issues have prevented the medical community from pursuing such treatments.

Misdiagnosis of Hyperthyroidism. Extensive literature has addressed the question of side effects of hyperthyroidism. In some cases, clinicians have diagnosed hyperthyroidism because of a suppressed TSH, without assessment of symptoms or FT_3 and/or FT_4 levels.

Osteoporosis Risk. There are many reports of increased risk of bone loss with thyroid replacement for post-thyroid cancer patients. Most of these reports focused on suppressed TSH. In a non-famine state, TSH suppression generally indicates high thyroid hormones. However, as the ideas presented here demonstrate, the hypocaloric state causes a decrease in TSH without FT_4 and FT_3 being above normal limits. In this extensive body of work showing that TSH suppression decreases bone mass, FT_4 and/or FT_3 levels are not presented.

In an account where the actual thyroid hormones are maintained within normal limits and calcium supplements are provided, osteoporosis is not a problem.[21] Our patients who have had routine bone scans have not seen diminution of their bone density. Others anecdotally report the same.[1] In one osteoporosis clinic, thyroid treatment is evaluated by symptoms and thyroid hormone levels. Often, TSH is suppressed to achieve optimal functioning. Bone loss has not been a problem. (M. Gonzalez, MD, personal communication.) A recent review[22,pp.684-686,696] covers literature demonstrating inconsistent conclusions of reviews and meta-analyses of thyroid effects on bone density. The authors suggest that most of the study interpretations are confounded by previous history of hyperthyroidism or hypothyroidism. This is a question with multiple parameters, but we are convinced from clinical evidence that, as long as FT_4 and FT_3 are within normal limits, bone density is being maintained.

Cardiac Risk. Both hyperthyroidism and hypothyroidism are cardiovascular risks.[23] Our patients are quite different. They can only be considered hyperthyroid based on one lab value (TSH) that does not accurately display the patient's condition. Their FT_3, FT_4, and symptomatology indicate normal thyroid function. On the rare occasion that a patient has heart palpitations or other symptoms of overtreatment, we discontinue thyroid treatment temporarily and usually restart at a lower dose.

Furthermore, one must consider the entire system: the famine response is a multi-level adaptation involving down regulation of cellular receptors and intracellular machinery (Table). Thus the available thyroid hormone often does not appear to be as effective as

in the non-famine condition. Others concur in finding a lack of hyperthyroid symptoms in their hypocaloric patients on high doses of T_3.[14,24-26]

Nitrogen Depletion. In some studies of thyroid replacement in the hypocaloric state, nitrogen loss was evaluated and found to be excessive. It was concluded that T_3 has catabolic effects on muscles.[13,27,28] However, the hypocaloric diet given in each case provided less protein than required for muscle maintenance under normal conditions. Bray et al.[13,p.719] commented that sufficient dietary protein may eliminate this problem. In one study, adequate protein (74 g/day) was provided. Nitrogen balance reached equilibrium at day 11.[29] In our private practice, our patients are advised to eat adequate protein and we do not see problems with muscle wasting. Several authors provide a more thorough discussion.[13,27,28,30]

7. Broadening the Concept to the Non-dieting Condition

While the most obvious use of these principles is in weight loss patients, our thoughts may apply to general hypothyroid patients as well. Silva's group[31] found that increasing the T_4 dosage while maintaining TSH within normal limits resulted in a significant increase in resting energy expenditure. The authors reported that this difference in daily energy expenditure would be significant for long term weight maintenance. A thorough discussion of this issue is available.[32] The ongoing arguments regarding the acceptable limits of TSH may be the result of vocal patients who realize they feel better when their thyroid dosage is higher. Patients without weight problems also come to us suffering many symptoms of hypothyroidism yet have been told they are euthyroid based on laboratory assessment. If we find low normal FT_3 or FT_4 or high rT_3, we will treat accordingly. Generally, symptoms are resolved with our approach.

Given this wide variety of adaptations preventing weight loss and encouraging regaining of weight, treatment must be explored to help patients. We must recognize obesity as a disease state that requires treatment. While many possible avenues for treatment are being explored, we believe that, for those with symptoms and FT_3, rT_3, and FT_4 levels indicative of the famine state, thyroid treatment is an important and safe approach.

Many patients and clinicians believe weight loss is an achievable long term goal through moderate diet and exercise. With our current knowledge of the highly evolved mechanisms to prevent weight loss discussed here and the intensive amount of work required for successful maintenance of weight loss,[34] it is our job as clinicians to educate our patients that their challenges with weight are not lack of will power but a highly evolved system which can be treated. To continue to view our patients' failures as a weakness of will power is to ignore the reality of this condition and do a major disservice to our patients and society at large.

Conclusion

In our clinical practice, we measure FT_3 and FT_4 and often find them to be at the low end of normal when a patient is suffering from a plateau in weight loss despite strict caloric limitation and exercise. This condition is accompanied by symptoms of low thyroid such as cold, fatigue, depression, constipation, and/or hair loss. rT_3 is often elevated as well. Using individualized approaches to thyroid treatment, we find we generally can eliminate hypothyroid symptoms, but suppression of TSH is the rule, rather than the exception. If a patient maintains a low calorie state and we have treated thyroid abnormalities associated with weight loss, the body will continue to suppress TSH because of the altered feedback set point.

Anecdotally, many patients complain of reaching a plateau when trying to lose weight. This patient observation is in keeping with the concept of an adaptive response to decreased food supply. We now understand that this famine condition is a multilevel neuroendocrine response involving brain centers, circulating hormones, cell membrane transporters, and intracellular receptors and enzymes (Table). But adaptations to a reduced caloric state are not found only in thyroid pathways. Once weight is lost, skeletal muscle becomes more efficient favoring weight gain. For review, see Rosenbaum and Leibel.[12] Neuronal activity in brain areas involved in regulation of eating and hedonic responses are altered after weight loss, making food more desirable.[33]

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Table. Human and rat studies showing objective changes in the hypocaloric or fasting state.

During hypocaloric or fasting state	Human Response: **I** = Increase; **D**= Decrease; **NC** = No Change (only statistically significant results in study reported)	Rat
TT_3	**D** 800 kcal diet x 10 days; overweight women.[35] **D** 12-week, 1245 kcal diet; obese women.[36] **D** at 1 week, very low calorie diet +/- exercise; obese women.[30] **D** starvation at 1 week; obese men and women.[37] **D** 10 days starvation (returns quickly after refeeding); normal weight men.[38] **D** low calorie (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women.[39] **D** 400 kcal 5 days; obese men[40] **D** long term free-living calorie restriction compared with controls; men and women[41] **D** during first 15 days of fasting, then increased until day 30, but not to baseline; after refeeding, increased to baseline by 14 days; obese men and women[42] **D** after 4 days of fasting; obese men and women[43] **D** fasting days 11-20; obese men[44] **D** on day 4, remained low throughout 7-day fast; rose during refeeding; 6 obese women, one each man and woman, non-obese[45] **D** 500 kcal 2 weeks; obese men and women[46] **D** 300 kcal 12 weeks; obese women[47] **D** 4-week fast; obese men and women[48] **D** 60-hr fast; normal weight men and women[49] **D** 6-week reduced calories; obese children[50] **D** 320 kcal up to 13 weeks, by end of week 1, further decreased by week 3 and remained low until re-alimentation; obese men and women[51] **D** during 7 day fast. After 4 days of 200 kcal glucose, increased to peak; obese men and women[52] **D** after 4 weeks starvation; obese men and women[53] **D** 30 hr fast, then **NC** after refed 800 kcal at 1900 hr and sampled for 5 hr; healthy men[54] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55]	**I** by 14 day of fast; male obese Zucker[56] **D** by 4 days of fast; male lean[56] **D** 72 hr starvation; adult males[57] **D** Fasting: in 1 day; males[58] **D** 15-day food restriction; males[59]

Table. Human and rat studies . . . *Continued*

T3 production	**D** 4-week fast; obese men and women[48]	
FT_3	**D** 60 hr fast; hypothyroid men and women[60] **D** after 4 days of fasting; obese men and women[43] **D** fasting days 11-20, decrease %FT_3 and absolute FT_3 with absolute FT_3 returning toward normal during days 24-42; obese men[44] **D** 500 kcal 2 weeks; obese men and women[46] **D** 4-week fast; obese men and women[48] **D** during 7 days of fast, then increased during glucose ingestion; obese men and women[52] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55] **D** after 4 weeks starvation; obese men and women[53]	
rT_3	**I** 800 kcal diet x 10 days; overweight women[35] **I** after 800 kcal diet produced 10% weight loss; obese and normal men and women[61] **I** starvation at 1 week; obese men and women[37] **I** starvation 4 weeks; obese men and women[48] **I** 10 days starvation (returns quickly after refeeding); normal weight men[38] **I** starvation at 1 week; normalized after 4 days refeeding; obese women[17] **I** at 1 week; very low calorie diet +/- exercise; obese women[30] **I** 400 kcal 5 days; obese men[40] **I** significant by day 2 of 400 kcal increasing daily; obese women[62] **I** from detectible in 1/7 pts to detectible in 4/7 pts after 60 hr fast; hypothyroid men and women[60] **I** during first 2 weeks, then return toward normal by day 18; obese men.[44] **I** 30 hr fast, then nonsignificant increase after refed 800 kcal at 1900 hr and sampled for 5 hr; healthy men[54] **I** 500 kcal 2 weeks; obese men and women.[46] **I** 320 kcal up to 13 weeks, rT_3 peaked at 1 week remained statistically elevated until week 7; obese men and women[51] **I** during 7 days of fast. Decrease by day 5 of 200 kcal glucose ingestion; obese men and women[52] **I** during first 15 days of fasting, then decreased to approximately baseline at day 30, then stable after refeeding for 14 days; obese men and women.[42] **D** after 4 days of fasting; obese men and women[43]	**NC** Fasting; males[58]

Table. Human and rat studies . . . *Continued*

Free rT_3	**I** during 7 days of fast. During glucose ingestion, decrease; obese men and women[52]	
Plasma clearance rate of rT_3	**D** fasting 7 day; obese women[17]	
T_3:rT_3	**D** 800 kcal diet x 10 days; overweight women[35] **D** at 1 week; very low calorie diet +/- exercise; obese women[30]	
TT_4	**I** after 4 days of fasting; obese men and women[43] **I** 320 kcal up to 13 weeks, increased by 1st week, but returned to baseline by 3rd week and remained there; obese men and women[51] **I** 400 kcal 5 days; obese men[40] **I** after 4 weeks starvation; obese men and women[53] **NC** 12-week, 1245 kcal diet; obese women[36] **NC** very low calorie diet +/- exercise; obese women[30] **NC** 60 hr fast; hypothyroid men and women[60] **NC** longterm free-living calorie restriction compared with controls; men and women[41] **NC** 7-day fast; 6 obese women, one each man and woman, non-obese[45] **NC** in 30 days fasting followed by 20 days re-feeding; obese men and women.[42] **NC** 500 kcal 2 weeks; obese men and women[46] **NC** 4-week fast; obese men and women[48] **NC** 6-week reduced calories; obese children[50] **NC** 60-hr fast; normal weight men and women[49] **D** Fasting days 11-20, with recovery days 24-42; obese men[44] **D** 6 mo calorie restriction; healthy, sedentary men and women[63] **D** 10 days starvation; normal weight men[38] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55]	**I** by 14 day of fast; male obese[56] **D** by 4 days fast; lean male[56] **D** 72 hr fast; adult males[57] **D** after 1 day fasting; adult male[58] **D** 5 days of food restriction; adult males[59]
T_4 half-life	**I** 300 kcal 12 weeks; obese women[47]	
TT_3/TT_4	**D** 12-14 hr into fast; mildly obese females[64] **D** low cal (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39]	
TrT_3/TT_4	**I** 48 hr into fast; mildly obese females[64]	

Table. Human and rat studies . . . *Continued*

FT_4	**I** 400 kcal 5 days; obese men[40] **I** after 4 days of fasting; obese men and women[43] **I** 500 kcal 2 weeks; obese men and women[46] **I** during fast with nonsignificant change during glucose ingestion; obese men and women[52] **I** 4-week fast; obese men and women[48] **I** 320 kcal up to 13 weeks. I by week 1, then returned to baseline; obese men and women[51] **I** slight after 4 weeks starvation; obese men and women[53] **NC** Fasting days 11-20, no change in absolute FT_4 - increase % FT_4; obese men[44] **NC** long-term free-living calorie restriction –27% sedentary[41] **NC** 60 hr fast; hypothyroid men and women[60] **NC** low cal (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39] **D** at 2 weeks on very low calorie diet; obese men and women[37]	**NC** by 14 day of fast; obese males[56] **D** by day 4 of fast; lean males[56]
TSH	**D** very low cal diet or fasting at 2 weeks; obese men and women[37] **D** slight. 10 days starvation; normal weight men[38] **D** to < 1 mU/L; after 30 hr fast. After refed 800 kcal at 1900 hr and sampled for 5 hr, nonsignificant increase; healthy men[54] **D** low calorie (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39] **D** during days 1&2 fast combined versus 2 days pre-fast, with gradual increase starting on day 3; 6 obese women, one each man and woman, non-obese[45] **D** after 4 days of fasting; obese men and women[43] **NC** after 60 hr fast; hypothyroid men and women[60] **NC** 400 kcal 5 days; obese men[40] **NC** at 2 weeks +/- exercise; obese women[30] **NC** 60-hr fast, TSH did not change (however, 60 hrs = 2.5 days so exact opposite time in day for reading and TSH has a diurnal rhythm, so numbers are not comparable); normal weight men and women[49] **NC** Fasting days 11-20; obese men[44] **NC** 6-week reduced calories; obese children[50] **NC** 320 kcal up to 13 weeks; obese men and women[51] **NC** 4 weeks starvation; obese men and women[53] **NC** 1-3 months after bilio-pancreatic by-pass surgery; men and women[55]	**D** 72 hr starvation; adult males[57] **D** 15 days of food restriction; adult male[59] **D** fasting in 1 day; males[58]

Table. Human and rat studies . . . *Continued*

TSH diurnal rhythm	Eliminated within 24 hr of onset of fasting; 6 obese women, one each man and woman, non-obese[45] Eliminated after 30 hr fast; healthy men[54]	
Resting metabolic rate	**D** 800 kcal diet x 10 days; overweight women[35] **D** 6-week reduced calories; obese children[50]	
Basal metabolic rate	**D** 300 kcal 12 weeks; obese women[47]	
Core body temperature	**D** calorie restriction x 6 mo; +/-exercise for 24h temperature; healthy, sedentary men and women[63] **D** calorie restriction x 6 mo; +exercise for night temperature; healthy, sedentary men and women[63] **NC** very low calorie diet; healthy, sedentary men and women[63]	
24-hr energy expenditure	**D** calorie restriction x 6 mo. +/-exercise or very low calorie diet; men and women[63] **D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
Sleeping metabolic rate	**D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
24-hr respiratory quotient	**D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
Mononuclear leukocyte nuclear T_3 binding sites	**NC** (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[63]	
TSH response to TRH stimulation	**NC** after fasting at 2 weeks, then increased after 30 days of realimentation; obese men and women.[42] **NC** after 4 weeks starvation; obese men and women[53] **NC** 300 kcal 12 weeks; obese women[47] **D** peak and integrated response after 60 hr fast; hypothyroid men and women[60] **D** Peak after 4 days of fasting; obese men and women[43] **D** 7-day fast; obese men and women[52] **D** after 3-9 weeks of fasting; obese men[44]	
TT_3 response to TRH stimulation	**NC** in delta TT_3 after 4 days of fasting; obese men and women[43] **NC** after 4 weeks starvation; obese men and women[53] **NC** after 7-day fast: i.e., no change in delta of response but starting from lower baseline; obese men and women[52]	

Table. Human and rat studies . . . *Continued*

T_4/TBG	**I** during 30 days fasting, then remained elevated during re-feeding; obese men and women.[42]	
T_3/TBG	**D** during first 15 days of fasting then increased during next 15 days, and continued to increase during re-feeding; obese men and women[42]	
Free T_3 index	**D** 320 kcal up to 13 weeks, decreased by week 1 and remained low until refeeding; obese men and women[51]	
FT_4I	**I** 320 kcal up to 13 weeks, increased by week 1, then returned to baseline; obese men and women[51]	
Serum TBG	**NC** 320 kcal up to 13 weeks; obese men and women[51]	
Thyronine-binding globulin	Inconsistent at 2 weeks +/- exercise; obese women[30] **D** 500 kcal 2 weeks; obese men and women[46]	**I** by 14 day of fast; obese males[56] **I** by 14 day of fast; lean males[56]
T_4 binding prealbumin	**D** 500 kcal 2 weeks; obese men and women[46]	
Albumin	**NC** 500 kcal 2 weeks; obese men and women[46]	
T_3 Metabolic Clearance Rate	**NC** 4-week fast; obese men and women[48]	
T_4 Metabolic Clearance Rate	**NC** 4-week fast; obese men and women[48]	
T_4 production rate	**NC** 4-week fast; obese men and women[48]	
HepaticT_4 to T_3 conversion		**D** 2-day starvation; adult males[67] **D** 2-day starvation, then add carbohydrates: **I**; adult males[67] **D** 2-day starvation, then add amino acids: **I**; adult males[67] **D** 2-day starvation, then add lipids: **NC**; adult males[67]
Tubular reabsorption of T_4 and T_3	**D** 3-day fast; healthy adult men and women[16]	

Table. Human and rat studies . . . *Continued*

Hepatic T_3 production		**D** fasting; males[58]
Hepatic rT_3 degradation		**D** fasting; males[58]
Hepatic uptake of T_4 by cell membrane transporters	**D** 600 kcal diet for 10-14 days; euthyroid obese subjects (gender not stated)[68]	**D** fasting x day 3; **NC** if provide liver with T_4[69]
Pituitary nuclear T_3 content		**D** fasting 72 hr; adult males[57]
Pituitary nuclear receptor		**D** fasting 72 hr; (results in equal or greater receptor occupancy than controls); adult males[57]

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