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Case Reports

Hypothyroidism, Particularly Associated with Weight Loss: Evaluation and Treatment based on Symptoms and Thyroid Hormone Levels

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Abstract. Famine causes adaptive changes in thyroid function which helped individuals survive during times of low food availability. These changes in thyroid function and metabolism have become maladaptive as the induced hypothyroidism associated with intentional weight loss restricts the success of diet attempts and encourages weight regain. In our previous paper [1] we described the mechanisms and consequences behind maladaptive hypothyroidism associated with intentional weight loss. Here we give two specific patient examples of this syndrome and how the biochemical and clinical changes were managed for the clinical benefit of our patients. More broadly, we address the need to understand that there are limitations to our ability to detect every appropriate variable in any one patient, so that we do not overestimate the value of any particular lab reading in any one patient.

Keywords ● Famine ● Weight loss ● Maladaptive hypothyroidism

Introduction

As described in our previous paper, we find that assessment of patient symptoms, free thyroxine (FT_4), free 3,5,3'-triiodothyronine (FT_3), and 3,3',5'-triiodothyronine [reverse T_3 (rT_3)] is an effective approach to treating hypothyroidism, particularly that occurring during weight loss attempts. Our main rationale is that using thyroid stimulating hormone (TSH) as the primary determinant of thyroid function is misleading because the set point for circulating thyroid hormones is lowered in many patients in a hypocaloric state. A major consequence of weight loss is a change in thyroid function which is highly adaptive in a calorically restricted environment, but we consider to be maladaptive hypothyroidism in the context of our current environment of excess high fat, high calorie food, and little need to expend energy. These changes have been documented in other studies where thyroid function and basal metabolic rate have been measured in the presence of caloric restriction in humans and animals. See Rowsemitt and Najarian[1] for discussion and literature. A major concern of the authors is that a new era of medical treatment to control appetite and food cravings appears imminent, but that the accompanying weight loss-induced changes in thyroid function are not appreciated by most clinicians. We are not trying to raise a patient's metabolism above normal to generate weight loss; we are merely trying to return decreased metabolism to normal, thereby allowing a patient's weight loss behaviors to produce the desired effect. Not all weight loss patients suffer this decrease in metabolism. The clinician must evaluate symptoms and appropriate laboratory values to determine if treatment is needed.

Two other issues remain in addressing thyroid problems in the hypocaloric state: (1) Most recent studies discount the value of T_3 treatment.[2] We are taught that the prohormone T_4 is converted to adequate amounts of T_3, the active hormone, so that there is no need to administer T_3. T_3, which we believe is critical for treating our patients with maladaptive hypothyroidism, is not even available in pill form in the formulary of the United Kingdom Health Care System. Only T_4 is covered for treatment of hypothyroidism; T_3 is covered only as an injectable for myxedema coma, a severe form of hypothyroidism.[3] (2) We find that rT_3 has been discredited by most fellow clinicians. In this paper, we present our own clinical experience which demonstrates the importance of both T_3 and rT_3 for the evaluation and treatment of the hypothyroidism which occurs in many people during weight loss attempts.

In most studies of weight loss, whether with medications, bariatric surgery, or any other approach, a plateau in weight often occurs in the first six months

of treatment, sometimes with weight regain even while on treatment.[4,5] Along with any weight loss approach, symptoms of low thyroid are common. For example, bariatric surgery guidelines from the Mayo Clinic provide a list of possible symptoms during the first three to six months: "body aches, feeling tired, as if you have the flu, feeling cold, dry skin, hair thinning and hair loss, mood changes."[6]

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.

We also have patients who have come to us seeking help who believe they have hypothyroidism due to their understanding of their classic symptoms which may include: fatigue, depression, feeling cold or having cold hands and feet, constipation, hair loss, dry skin, heavy menstrual periods, and insomnia. They may also have raised diastolic blood pressure, partly due to vasoconstriction. Vasoconstriction with resultant cold extremities is one way that humans and animals preserve body mass during times of inadequate caloric intake by reducing both heat loss and energy expenditure. Some of these patients have been trying to lose weight and do not desire a medical treatment, but believe that our approach to thyroid therapy will help them in their weight loss and maintenance attempts. These patients have struggled for years with signs and symptoms of hypothyroidism but have been repeatedly told by providers that their thyroid function is fine, based on TSH values. In these cases, providers have been bound by the conventional wisdom that TSH is the best tool to assess thyroid function. We feel this is extremely unfortunate because the providers are practicing in a manner they consider safe and appropriate while the patients feel insulted and stymied. Numerous patients have come to us with food diaries with the exact, measured amounts of what they have been eating for months, while getting some exercise. They report feeling demeaned by providers who clearly think they are keeping inaccurate food records. While this may be true in some cases,[7] many of our patients with a history of careful diary-keeping have found weight loss to be possible with our thyroid treatment.

We have seen these changes take place in thousands of weight loss patients. Many, but certainly not all patients, in our practice suffer from symptoms of maladaptive hypothyroidism. Initially, treatment with T_4 was tried, but failed to resolve the symptoms of hypothyroidism. Adding T_3 helped, but due to its expense, we replaced synthetic T_4 and T_3 with desiccated thyroid. Although many providers believe that the contents of desiccated thyroid are not well regulated, USP regulations are maintained with a ratio of T_4:T_3 of 4.22:1, such that 120 mg of desiccated thyroid contains 68.2 mcg T_4 and 17.8 mcg T_3.[8] Our procedure was to assess FT_4 and FT_3 levels several weeks into treatment. If a patient had low thyroid symptoms with low or borderline low hormone levels, we prescribed desiccated thyroid, with one-half dose for six days, then full dose. Dosage was dependent on age, symptoms, and hormone levels, but the usual full dose is 120 mg. Many patients do well on this treatment.

For many years we treated with desiccated thyroid with considerable success. However, for some patients, even treating to a borderline high level of FT_3 proved insufficient to eliminate hypothyroid symptoms including the weight plateau. Regardless of how hard they reported working out and limiting calories, the weight would not budge. While people attempting weight loss often eat more than they realize,[7] we do not believe this explained what was occurring with these patients. These were people with a history of success with us using medication to help with appetite and cravings, and who were known to have habits which tend to be more successful for weight loss and maintenance.[9]

When we became aware of the possible role of rT_3, we ran this assay on a patient with the problems described here and found her rT_3 to be 499 pg/mL (range: 90-350 pg/mL). Although rT_3 is commonly discounted as inactive, there is evidence for its binding to membrane receptors[10] and producing hypometabolic effects.[11] Given our increased understanding, we started to assess this parameter routinely. In some cases, lab results revealed a low FT_3 and an increased rT_3. For these patients, we correct the metabolic and thyroid functions using only T_3 in divided doses until

the rT_3 is low normal. We then continue to use only T_3 if the patient is doing well clinically. (FT_3 will usually be in the normal range while FT_4 is low.) Alternatively, if the patient still has symptoms of low thyroid, even when FT_3 is normal or high normal and rT_3 and FT_4 are below normal, we add a low dose of T_4.

After treatment with T_3 or a combination of T_3 with T_4, and after the patient is clinically euthyroid with normal values of FT_3, FT_4 and rT_3, we often find that TSH is below normal. We believe that this is because the set point for feedback of thyroid hormones has been decreased. Thus, the body acts as though the thyroid gland is over-active during the weight loss state in order to lower metabolism and prevent weight loss during caloric restriction. When thyroid function is corrected with T_3, the already decreased TSH production is turned off, just as the TSH would be if one gave thyroid hormone to a euthyroid patient. (For further discussion, see Rowsemitt and Najarian.[1])

The following case reports from our practice should help to delineate this hypothesis in actual practice. For thyroid testing, all patients are instructed not to take their morning dose of thyroid medication until after a morning blood sample. Symptoms of high thyroid are explained to the patient; the patient is advised to call our practice immediately for medication adjustment should any of these symptoms arise. Patients are also advised that a sudden increase in food intake can cause their own thyroid glands to increase hormone production, causing hyperthyroid symptoms.

Case Reports

Patient Number 1. The first patient example is a 67-year-old female; height: 5'2"; weight: 268 lbs; body mass index (BMI): 49 (range: 19-24; overweight; 25-29; obesity: ≥ 30). Baseline blood pressure was 110/74, blood sugar (BS) was 153 mg/dL 10 days after her first visit. Her medical problems at baseline included obesity, type 2 diabetes mellitus (DM2), high blood pressure (HTN), fatigue, depression, and asthma. Her medications included glipizide 10 mg daily, amitriptyline 50 mg daily, metoprolol 50 mg daily, furosemide 40 mg daily, potassium chloride, lisinopril 10 mg daily, Advair Discus 500/50 twice daily (bid), and montelukast 10 mg daily.

She was started on our comprehensive program. Five months after starting her weight loss treatment, she developed symptoms of hypothyroidism with constipation and fatigue. She had lost 28 lbs by this time and was having difficulty losing more weight even though she was eating less than she was before her weight loss treatment began. At the start of treatment, her FT_4 was 0.9 ng/dL (range: 0.7-1.48). At the time of her low thyroid symptoms, her FT_3 was 2.9 pg/mL (range: 1.71-3.71) and her FT_4 was 0.91 ng/dL (range: 0.7-1.48). She was then treated with thyroid hormone (desiccated thyroid with a ratio of T_4:T_3 of about 4:1) at 60 mg daily for 6 days to acclimate, then increased to 120 mg daily. Since her low thyroid symptoms were only partially improved, her thyroid hormone dose was increased to 150 mg daily 5 months later, with resolution of the constipation and fatigue. After two years on her weight loss treatment, her weight was 231 lbs. Nearly 3 years after the start of her weight loss treatment, while on 150 mg of thyroid hormone, she felt cold and constipated, with another weight loss plateau. We had just started testing for rT_3 at this point. Her labs on the 150 mg dose of desiccated thyroid were: rT_3 394 pg/mL (range: 90-350), FT_3 3.94 pg/mL (range: 1.71-3.71), and FT_4 1.24 ng/dL (range: 0.7-1.48). The task of bringing down her rT_3 was then addressed. Over a period of a few months, her desiccated thyroid hormone was discontinued and instead the patient was given gradually increasing doses of T_3 only, starting at 20 mcg daily and gradually increasing the T_3 to 60 mcg bid. Five months after starting on T_3 with increasing doses, her weight had dropped to 209 lbs. Her BP was 118/66 mmHg with pulse of 74 on lisinopril 10 mg daily, metoprolol 50 mg bid, and furosemide 40 mg daily. Instead of glipizide, she was taking metformin 500 mg bid. She was clinically euthyroid on the T_3 only. Her most recent labs on 60 mcg bid of T_3 were FT_3 3.8 pg/mL (range: 1.71-3.71), FT_4 0.64 ng/dL (range: 0.7-1.48) and rT_3 137 pg/mL (range: 90-350). Four months prior to this visit her BS was 125 mg/dL.

Comments. This example makes the important point that three years into the program, with FT_3 above normal and FT_4 in the reference range, the patient had difficulty losing weight and had low thyroid symptoms. We believe that this was due to her elevated level of rT_3. The only way to lower rT_3 in this setting is to avoid giving any T_4 (since T_4 is the source of both T_3 and rT_3) and to replace T_4/T_3 with T_3 only. Over a period of a few months, both the rT_3 and T_4 will fall while the T_3 should remain in the normal range.

Another point is that there are wide reference ranges for thyroid tests. Some patients feel optimally well when their thyroid levels are on the high side and some when the thyroid levels are lower in the normal range. For example, a patient with a history of an anxiety disorder or sensitivity to stimulants such as caffeine may feel better when thyroid levels are on the low sides of their ranges. Some require treatment at the high end of normal to eliminate constipation, cold extremities, and/or other symptoms of low thyroid. We think that optimizing symptoms is a good guide along with complete thyroid testing including FT_4, FT_3, and rT_3, especially during caloric restriction. One can optimize symptoms of constipation or diarrhea, feeling too cold or hot, depression or anxiety, or feeling fatigue (which can result from high or low thyroid), etc., by appropriate dosing of T_3 with or without T_4.

Patient Number 2. The second patient example is a 46 year old female, 5'2", weight 150 lbs, BMI 28 (range: 18.5-24.9; overweight 25-29.9; obesity ≥ 30), with HTN. Her blood pressure was slightly elevated at 148/85 (on lisinopril 5 mg daily). Her medical problems at baseline included history of Hashimoto's thyroiditis, borderline high TSH, elevated lipids, and HTN. Her medications were lisinopril 5 mg daily, estradiol 2 mg daily, and rofecoxib 25 mg daily for osteoarthritis of her large joints. She was started on our comprehensive program. Thyroid treatment was started as well because of initial low thyroid symptoms of fatigue, constipation, and feeling cold along with a TSH of 3.41 uIU/mL (considered elevated by some, but not all groups who set limits for TSH). Desiccated thyroid was prescribed at 60 mg for six days to adjust to the medication, and then advanced to 120 mg daily. Over a period of several years thyroid hormone dose was reduced to 45 mg as dictated by clinical and lab results, and she was feeling relatively well. Her weight remained between 119 lbs and 130 lbs. Her blood pressure and pulse remained in the normal range (100/60-138/78, pulse 64-72) with no antihypertensive medications. Four years into her treatment, desiccated thyroid became unavailable so she was switched to levothyroxine at 75 mcg daily. Within a few weeks she began to feel tired, cold, and depressed and developed constipation and hair loss. Her FT_3 was 2.3 pg/mL (range: 2.2-4.0), FT_4 1.07 ng/dL (range: 0.93-1.70), and TSH was 0.91 uIU/mL. Her levothyroxine was increased to 100 mcg daily and T_3 was added at 5 mcg bid. Two months later, her first test of rT_3 was 379 pg/mL (range: 90-350), FT_4 1.12 ng/dL (range: 0.93-1.70), FT_3 2.4 pg/mL (range: 2.2-4.0). Over the next 4 months her levothyroxine dose was gradually reduced to zero, and she was placed on gradually increasing doses of T_3 only, ending on 25 mcg bid. Her weight was 125 lbs, BP 122/80 on no medications, and pulse was 72. She no longer suffered from hair loss; her bowels were normal, she felt well, and she stated that for the first time in her life she was not cold. Her lipids were also improved compared to baseline. On this regimen her rT_3 was 193 pg/mL (range: 90-350), FT_3 2.5 pg/mL (range: 2.2-4.0), and FT_4 0.67 ng/dL (range: 0.93-1.70).

Comments. This patient failed to achieve her optimum health until her rT_3 was mid-normal on T_3 replacement only. In addition, correcting peripheral vasoconstriction results in improved comfort, better sleep, and improved blood pressure, especially diastolic blood pressure. Patients with untreated hypothyroidism may have elevated blood pressure, especially diastolic hypertension, due to peripheral vasoconstriction. After the T_3 treatment to reduce rT_3 levels, a change from T_3 to desiccated thyroid or other ratio of T_4:T_3 dosing would be an option.

Discussion

By the early 1970's, TSH became the gold standard for assessing thyroid function. Part of its prominence as a diagnostic tool appears to have arisen because TSH levels change logarithmically when the levels of circulating thyroid hormones are higher or lower than the set point. However, several issues of basic endocrinology allow one to realize that using TSH alone will have severe limitations. TSH levels will not necessarily distinguish secondary hypothyroidism (of pituitary cause) from normal. A PubMed search of (intracellular) thyroid receptor mutations produced 598 citations and a search for mutations of the proteins which transfer thyroid hormones across cell membranes produced 65 citations. Clearly, this area of research is deemed important and these are only two portions of the pathway involved in generating a metabolic change via thyroid hormones. So assuming normal pituitary function, TSH does not really provide us with information about the desired result: metabolism. It only provides us with the information that the thyroid hormones are circulating at a level within the limits set by higher brain levels. As

pointed out by Dr. David Derry:

> If you remember it was a long time before the medical profession admitted that there were two new diseases to appear in the world that were not there before. Chronic fatigue and fibromyalgia were non-existent before 1980. This is seven years after the 1973 consensus meeting. So where did these two new diseases come from? The symptoms and signs of chronic fatigue and fibromyalgia were described in the literature in the 1930's as one way that low thyroid could be expressed. Treated early it was easily fixed with thyroid in adequate doses. But even then the clinicians had noticed that if a patient has low thyroid (chronic fatigue and fibromyalgia) for too long then it became more difficult to reverse all signs and symptoms regardless of what they were.[12]

Clinicians have relied strongly on TSH. Yet there has been an ongoing discussion of what range should be considered normal. Prior to the TSH assay and availability of commercial levothyroxine, patients were treated with desiccated thyroid with the dosage increasing until signs and symptoms were resolved. So two things had changed: (1) newer treatment trends involved using lower doses of pure T_4 and (2) the active hormone, T_3, was not given directly to patients. As has been known for years, T_3 is less available in the hypocaloric state.[1]

Numerous studies of weight loss treatments (whether from very low calorie diets, weight loss medications and diet, or bariatric surgery) often list as side effects the same spectrum of symptoms such as fatigue, depression, constipation, hair loss, feeling cold, and insomnia. We believe the insomnia may be related to the coldness of the body core and/or extremities. Many of these symptoms are likely due to the diet-induced hypothyroidism which is maladaptive in our current environment. Testing TSH, FT_4 or total T_4 will miss the diagnosis, since the changes in metabolism and thyroid function consist of only a slight lowering of TSH. Reported changes in total T_4 and FT_4 are inconsistent.[1] If the appropriate labs are run, an increase in rT_3 is found, accompanied by a decrease in FT_3. The syndrome of hypocaloric-induced hypothyroidism can be diagnosed only by evaluating changes in rT_3 and FT_3 as well as careful assessment of thyroid symptoms. Correction of diastolic hypertension, improvement of lipids and clinical symptoms, with return of rT_3 and FT_3 to normal after replacement of T_3 will confirm that the condition was present and treated appropriately. While many clinicians discount rT_3, our clinical results show its importance for patients whose systems use this pathway to decrease metabolism.

The assessment of thyroid status in clinical practice is generally based on a number which represents only one aspect of the system: a circulating hormone level. The clinician is not measuring the ability of that hormone to function by assessing metabolic rate or other signs and symptoms. A direct measure of metabolism would be a more meaningful approach. Since the symptoms are often vague, they may be dismissed by providers. In our litigious society, numbers give us comfortable boundaries with which to determine when to treat and when to tell a patient, "No, there's nothing wrong with your thyroid. If you are depressed, let's try an antidepressant. If you can't lose weight, try eating less and exercising more." We must also realize that there are false negatives and false positives for all tests, including lab tests. Thyroid function tests have a wide range of normal reference ranges. Reference ranges are determined by testing large numbers of "normal" patients and arbitrarily calling the highest 2.5% elevated and the lowest 2.5% as below normal.[13] Values outside these ranges often do not mean disease, and in fact may indicate improved health, such as an HDL level above normal. In certain mountainous areas in Europe with low iodine availability, cretins were born due to low thyroid hormones prenatally.[14] If such a population were used to determine the normal values of thyroid tests before the cause of cretinism was understood, the test population would have included the cretins. This would have produced reference lab ranges with lows for FT_4 and FT_3 that are considered markedly hypothyroid today.

When considering reference ranges for all of the thyroid labs, we find it particularly interesting that our patients with multiple low thyroid symptoms typically reach the low end of the ranges for FT_4 and FT_3; in some patients, these values go below the lower end of the range. To determine what values constitute the reference range, blood samples are obtained from clinically "normal" people. We have come to assume that many people included in the "normal" sampling are probably those in a hypocaloric state with some symptoms of low thyroid function. When you consider the percentage of people who are trying to lose weight at any point in time, this subset of the population must be skewing the

reference range to include those who are actually mildly low thyroid by symptomatic criteria.

In addition to the information provided above, we have seen evidence of other adaptations to altered thyroid hormone levels. Many patients will do fine when maintained on their initial dose of desiccated thyroid. However for others, after several months of treatment, the patient reaches a plateau of weight with the return of low thyroid symptoms. When lab values are obtained, these patients usually have FT_3 and FT_4 which have returned to their previously low pre-thyroid-treatment levels. This demonstrates the body's ability to increase degradation rates of T_3 and T_4 which the body recognizes as being at hyperthyroid levels in the face of a hypocaloric diet. Also, in patients with high rT_3 who have been treated with T_3 only, we generally add some T_4 to the T_3 treatment after rT_3 has decreased to normal levels. Anecdotally, we have noticed that some of our patients with the most challenging weight struggles are those whose rT_3 levels rise dramatically as soon as any T_4 is added to their T_3 dose.

In the larger view, we must accept the fact that scientific knowledge evolves over time and both our understanding of what should be measured and the meaning of the resultant measurements can change. Consider cholesterol. Initially, we assessed total cholesterol with higher levels indicating increased cardiovascular risk. As time went on, we learned of HDL-cholesterol and LDL-cholesterol. Limits were set for each, with higher HDL being protective and lower LDL healthier. As the years have gone on, further refinement of the cholesterol parameters have been elucidated as has the importance of inflammatory markers.[15] These refinements are based on clinical outcomes. We should fully expect to see changes in both the parameters assessed and their acceptable values as our understanding increases.

But we will never argue for the dominance of a lab test when signs and symptoms are available. In considering thyroid lab values, we must also be cognizant of known biochemical variants such as receptor and transporter abnormalities which may cause a lab result to be at odds with the signs and symptoms.

It is possible that lifestyle changes in our society have affected thyroid function so that our normal values might be different when compared to people who lived thousands of years ago. Among the environmental changes that may lead to differences in thyroid levels are the amount of food eaten (increases in weight may raise thyroid levels and decreases in weight may lower thyroid levels)[1] and ambient temperature (warmer environments such as heated living and working spaces may lower thyroid levels). It is possible that our "normal" values, especially for those who are trying to lose weight, are in fact lower than what would have been determined from a population of normal people from thousands of years ago. Our "normal" ranges for thyroid tests might tend to be misleading in the same way that testing a population of "normal" people in areas of iodine deficiency hundreds of years ago would have been misleading in guiding people who needed to be treated to improve individual health. Normal values needed to be based on more than two standard deviations outside the range of "normal" people. We need to critically look at the health of those "normals" to see whether a different reference range would better serve the health of our patients. Certainly clinical health must be taken into account as has been done in our evolving understanding of cholesterol and inflammatory markers for cardiovascular disease risk.

While we have arrived at our current approach to thyroid treatment by years of working with patients to find the best approaches, we believe the research community should address these issues with our findings in mind. Controlled experiments studying thyroid treatment during weight loss should be performed monitoring rT_3 and treating with this paradigm (T_3 treatment) versus both untreated control and thyroxine groups.

While 10% weight loss is helpful at decreasing co-morbidities such as hypertension and type 2 DM, attaining normal weight seems out of reach of many obese people. This is partly due to the plateau created by maladaptive hypothyroidism. Ideally, we would like to be able to help many patients reach and maintain normal weight. Given our current environment with freedom from vicissitudes of food availability, this goal is harder than it would otherwise be. In our experience of having a combination of medications to suppress appetite and enhance satiety paired with the ability to fight this weight retaining thyroid response, we have been able to assist many people to reach and maintain normal weight. We submit these ideas hoping that others will join us in re-evaluating thyroid treatment when maladaptive hypothyroidism occurs during weight loss attempts. Clinicians must use clinical skills and patient-centered concerns in the optimum evaluation and treatment of their patients and

not succumb to blindly following an arbitrary system of defined normal lab values in making therapeutic decisions that greatly affect the well-being of their patients.

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