November 2004 Issue | Raphael Kellman, MD

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Welcome to *Functional Medicine Update* for November 2004. What is one of the most significant, prevalent disorders that functional medicine professionals see in their practices? That is the theme we will be discussing in this edition of FMU. Our listeners may agree that this condition ranks high on their lists of the most prevalent clinical conditions seen in the rapid-paced world in which we live. I am speaking about functional, or borderline hypothyroidism.

According to epidemiological evidence, hypothyroidism is increasing in our culture, particularly in women as they age. It is potentially serious, often clinically overlooked, readily diagnosed by laboratory testing, and eminently treatable. Given that the majority of patients seen by general practitioners are females, and that we are an aging baby boomer population, it is not unexpected that virtually every practitioner in the field has had to deal with conditions related to functional, borderline hypothyroidism.

There is a large amount of information, both formal and informal, about the assessment and intervention in this condition. We felt it would be useful to focus the whole first section of FMU this month on the story of borderline hypothyroidism. As part of that, our Clinician of the Month has had extensive experience in this area, and he will share some of his own clinical takeaways from seeing several thousand patients with different aspects of thyroid dysfunction. Before we get to his interview, it is important to set the stage and define borderline functional hypothyroidism. How does it present and what clinical intervention protocols might be most useful for its management? Fortunately, there is a review paper that appeared in *The Lancet* this year that contains some good “news to use” about the thyroid gland and the state of hypothyroidism.[1] I am going to cite some of the information from that review paper.

History of Hypothyroidism
First, I want to talk about the history of hypothyroidism. When we look at the history of thyroid-related dysfunction, we see that knowledge about the condition is fairly recent. It goes along with the emerging theme of our understanding of the endocrine system. Only since the establishment of organic chemistry as a discipline, and application of that discipline to physiology, have the concepts of endocrinology advanced.

“In 1874, Gull described several previously healthy women who acquired clinical features similar to those in cretinism. 4 years later, Ord coined the term myxoedema to describe a syndrome in five women with coarse features, mental dullness, dry skin, hypothermia, and oedema. At much the same time, two Swiss thyroid surgeons, Kocher and Reverdin, independently described cachexia strumipriva, a cretin-like state developing after thyroidectomy. In 1883, the Clinical Society of London formed a committee to

investigate the connection between myxoedema, cretinism, and cachexia strumipriva; and 5 years later, the committee issued its landmark report linking the three conditions. In 1912, Hashimoto described autoimmune thyroiditis in four women with goitres that seemed to have turned into lymphoid tissue (struma lymphomatosa); and in 1956, Roitt and colleagues reported the presence of circulating thyroid autoantibodies in this disorder."

This suggested that the thyroid gland was being attacked as if the body was allergic to it.

"Treatment for hypothyroidism with sheep thyroid extract was first reported by Murray in 1891. Thyroid hormone was crystallized in 1914 by Kendall."

This treatment ultimately won the Nobel Prize in Medicine for Murray and his group.

"Reports of thyroxine's synthesis by Harington and Barger, and of its initial physiological testing both appeared in 1927. Triiodothyronine was discovered by Pitt-Rivers and Gross in 1952; and its endogenous generation from thyroxine was described by Ingbar, Sterling, and Braverman in 1970.

"In 1963, Condliffe purified thyrotropin (thyroid stimulating hormone), and soon thereafter Odell and Utiger both reported the first immunoassays for human thyrotropin. In 1971, Mayberry and Hershman simultaneously described use of thyrotropin immunoassays for diagnosis of hypothyroidism."

The field, as we are now describing it—the immunochemistry, physiology, and function of the thyroid gland, and the activity of the thyroid hormone components—is fairly recent (within the last 30 to 40 years), as it has contemporarily been developed. Through that period of time, the first discoveries were made about frank thyroid disease. This resulted in the naming of conditions like Graves' disease and Hashimoto's thyroiditis. Over the last decade or two, however, concerns about borderline hypothyroidism have become more prevalent. It appears there is a much wider range of thyroid dysfunction in the absence of overt pathology than was previously recognized. This can be connected to many signs and symptoms related to thyroid hormone function at the cellular or tissue level.

If we look at the prevalence of subclinical hypothyroidism in the United States population, the data suggest, based upon interpretations of thyroid stimulating hormone (TSH) levels, that five percent or more of the population probably presents with functional borderline hypothyroidism, or so-called subclinical hypothyroidism. The controversy that exists is whether the presence of borderline or subclinical hypothyroidism demonstrates the need for treatment, or whether it is just a marker for later-stage, more serious clinical conditions indicating further treatment. Would we be under-treating if we did not intervene in subclinical hypothyroidism or, if we did, would that constitute over-treatment? Those are interesting questions that have been discussed in both academic and intellectual circles, and that have now filtered down to the ground level. Some practitioners and certain medical and disciplinary boards have examined physicians who have intervened in borderline or subclinical hypothyroidism and determined that they were over-treating. I want to address that issue, because it is important for the patient and the practitioner from the standpoint of clinical and medical/legal issues.

Causes of Hypothyroidism

The most common cause of acquired hypothyroidism, either subclinical or overt, is autoimmune thyroiditis, commonly called Hashimoto's disease. This condition is seven-fold more common in women

than in men, and increases in incidence during middle life.[1] The role of autoimmunity in its pathogenesis is lent support by a histological finding of diffuse lymphocytic infiltration of the thyroid gland, presence of circulating thyroid autoantibodies in almost all patients, and in animal models created by immunization with thyroid antigens, suggesting that there is an immunological component. The finding that affected thyrocytes express the MHC class II proteins needed for antigen presentation to CD4 (helper) T lymphocytes, and evidence of activated CD4 T cells specific for thyroid antigens, appear to support the etiology of Hashimoto's thyroiditis. The questions are: Why are people, as they age, more susceptible to the production of antithyroidal antibodies? Why do they become allergic, in part, to their own thyroid gland? These questions are open to much controversy and discussion because, to date, there are no definitive, clinical answers.

Symptoms of Hypothyroidism

In patients with autoimmune thyroiditis, the thyroid gland can be nonpalpable, or diffusely enlarged (150-300{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of normal size). In patients with the fibrous variant, the thyroid gland is hard and markedly enlarged, but that is not necessarily a prerequisite or a clinical finding in individuals with borderline, subclinical hypothyroidism. Antimicrosomal or anti-thyroid peroxidase antibodies are present in 95{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of affected individuals, and this has often been used as a biochemical or laboratory marker. Anti-thyroglobulin antibodies, however, are present in only about 60{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of patients, and therefore appear to be less clinically specific or sensitive. Obviously, indications for hypothyroidism tests depend on the clinical indications and presentation in the patient. Many physicians are very skilled at evaluating and understanding the connection of symptoms to thyroid-adrenal-pituitary- hypothalamic function. Clinical signs include fatigue, cold intolerance, constipation, impaired memory, slowed mental processing, depression, ataxia, muscle weakness, muscle cramps, menstrual disturbances such as alteration of the cycle producing dysmenorrhea, infertility, goiter, hoarseness, and weight gain. All these symptoms are classic examples associated with hypothyroidism, and can be seen in different degrees and prevalence relative to borderline subclinical hypothyroidism.

Radiological and Laboratory Test Abnormalities of Hyperthyroidism

Radiological abnormalities often show pericardial and pleural effusions and pituitary gland enlargement in frank cases of hypothyroidism, but these are not necessarily to be seen in borderline cases. Laboratory test abnormalities often show elevated cholesterol as LDL cholesterol, lowered HDL cholesterol levels showing an elevated LDL-to-HDL ratio, low levels of plasma or serum sodium, and often hyperhomocysteinemia. This implicates some influence on the modulation of important amino acid metabolism, which is associated with vascular disease, dementia, Alzheimer's disease, certain forms of cancer, bone loss, and arthritis. Apparently, there is an interconnection between hypothyroidism and the folate cycle, renal function, and homocysteine metabolism and excretion.

Risk Factors for Hypothyroidism

When we look at the risk factors for hypothyroidism, we see conditions that would initiate autoimmunity, particularly focused on the thyroid gland, such as any type of precipitating event that might upregulate MHC class II antibodies against the thyroid. These could be allergens, stress factors, or toxins. Some environmental factors have been clearly implicated that may be associated with the appearance of autoimmune thyroiditis and borderline hypothyroidism.

I want to emphasize that there are genetic underpinnings of risk. Therefore, we cannot say that all people respond identically. Genomic concepts indicate that there is wide variation in the ways people respond to the environment through their neuroendocrine and immune systems and that these variations might translate into potential risk to hypothyroidism.

Treatment for Hypothyroidism

Once the condition has been diagnosed, how is it managed? The most common treatment is intervention with synthetic thyroxine (T4). In the literature, it is generally considered that the optimal dose of T4 for hypothyroid patients is related to body weight, trying to achieve about a 1.8 µg-per-kg dose in adults. I will speak more to that in a few moments. Generally, when physicians initiate thyroxine therapy, they start with a dose around 125 µg per day in the 70-kg individual, and laboratory monitoring for TSH is repeated some four to six weeks after initiation. That is the standard approach for frank hypothyroidism, but the question might be raised as to whether this is the best approach for managing a patient with borderline subclinical hypothyroidism.

There are many potential causes of TSH elevation related to things such as drugs and other covariant illnesses that may create alteration in thyroid function, sensitivity, and metabolism. I will be speaking about those in a moment because it is important to clinically evaluate other factors that may contribute to what appears to be a thyroid-related dysfunction.

Adverse Reactions to T4 Treatment

What are the adverse reactions to T4 treatment? The most common reaction is called subclinical thyrotoxicosis, with increasing risk to bone loss, and atrial tachyarrhythmias. These symptoms appear to be the most common in over-treatment with T4. It is also important to note that if the patient has borderline adrenal cortical insufficiency (often called hypoadrenocorticism), and ischaemic heart disease, over-treatment with T4 intervention can induce cardiac-related dysrhythmias. One has to be mindful of the fact that there is close communication between the adrenal glands through the hormones they secrete, particularly cortisol, and the thyroid hormone-modulated effects on cellular function, particularly the cardiocyte. Managing a patient with borderline hypothyroidism patient with T4 intervention needs to be accomplished skillfully and carefully.

Neuropsychological Deficits Associated with Hypothyroidism

The big advantage of using T4 is lowering the potential risk to either primary or secondary diseases. Often, the rationale for treatment in borderline subclinical hypothyroidism is reduction of later-stage problems. Then, the question is whether a combination of T4 and T3 needs to be used in primary prevention. That has been a long-standing debate, and there has been considerable controversy about it. We have discussed this in previous issues of FMU. We cited from a paper in *The New England Journal of Medicine* several years ago, indicating that neuropsychological deficits associated with hypothyroidism appear to be better managed by using a combination intervention with T3 and T4.[2] However, since that paper appeared, two others have evaluated that intervention in similar patients and, in both cases, investigators came to the conclusion that there was no advantage to using a combination of T3 and T4. These papers included studies by Walsh et al. and Sawka et al. that noted no improvements in well being, cognitive function, or quality of life with a combined treatment of T3.[3],[4]

There is still some controversy about the use of T4 by itself versus a combination of T3 and T4. I should point out that in the Bunevicius study, a ratio of T3 to T4 that was physiologically unnatural was used (a

very high level of T3 relative to T4). That may not duplicate the rhythmic effect these hormones have when secreted from the thyroid gland at normal ratios—90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} T4 and 10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} T3. It may have been a better trial if those ratios had been used, as they appear to be more compatible with normal physiology.

Notwithstanding that controversy, patients with mild hypothyroidism (borderline or subclinical hypothyroidism) may receive an advantage from primary or secondary prevention of things like cardiovascular disease (CVD), as well as dysphoria. First of all, the potential benefit is to prevent the progression to overt hypothyroidism with all the attendant risks. Second would be intervention for reducing future risk of CVD by improving lipid profiles, reducing inflammatory markers, and improving insulin sensitivity and glucose tolerance, all of which are interrelated with thyroid hormones through the web of the neuroendocrineimmune system. The general strategy in managing a patient with borderline subclinical hypothyroidism is not solely to reduce the symptoms associated with the condition, but also as secondary prevention for the improvement of cardiovascular and endocrine function, in general.

I would like to talk about some of the conundrums associated with subclinical borderline hypothyroidism. It is important to talk about what is said in the traditional endocrinological literature about the assessment of this condition. I am going to cite some of the treatment guidelines from the National Academy of Clinical Biochemistry and the Laboratory Support for the Diagnosis of Thyroid Disease, first published in 2003.[5] In this monograph, the authors discuss the kinds of discordances in the FT4/TSH blood chemical analysis that assesses thyroid function that lead us to see that there may be conditions where there are normal levels in the blood panel, but still some concern about abnormal levels in the individual. Let me cite some examples.

What happens if a person has a modestly elevated TSH, but a normal T4? For example, a TSH not high enough to be pathologic, but one which is just above the reference range, and a T4 level that is within the reference range. What should the practitioner do in this case? This is a classic example of mild borderline subclinical hypothyroidism. Clinical symptoms in the patient should be examined very carefully to see if any of them are associated with what would classically be called a thyroid-related function. In that case, anti-thyroidal antibodies to thyroid peroxidase should be measured, with confirmation of TSH levels after six weeks of intervention. These symptoms may carry the strongest connection between borderline hypothyroidism and later-stage concerns.

What about a normal T4 and a depressed TSH? Some people might call this mild hy*per*thyroidism. This would require looking for some kind of thyroid toxic effect that is inducing hyperthyroidism. It is clinically uncommon to see a TSH less than 0.5 with a normal T4, but in the scheme of looking at the range of thyroid function, this would be the other side of the coin—a hyperthyroid condition which might later become a hypothyroid condition based upon reserve and exhaustion of the gland and the system.

What about individuals with a normal TSH, but either a slightly elevated or slightly depressed T4? They are not driving the thyroid gland very hard with pituitary TSH, but they have either a low or slightly elevated T4 level. In those cases, we would look at the same symptom cluster. Is there evidence of thyroid-related dysfunction? Is there evidence of glucose intolerance? Is there evidence of lipid abnormalities in the plasma profile? We would need to try and pull together a web of understanding about the complex. Perhaps rather than being a cause, it is the effect of other disturbances in the

endocrinological system that need to be brought into balance. It could be estrogen, testosterone, or progesterone imbalances, cortisol imbalances, or insulin imbalances, all of which are interrelated in the communication with thyroid hormone.

Recall that the principal way T3 is produced is by extra-thyroidal conversion of T4 to T3 by a deiodinase enzyme that is selenium-dependent. Selenium deficiency can produce secondary symptoms of hypothyroidism. Sometimes, by increasing selenium intake, thyroid function can be improved by the enhanced extra-thyroidal conversion of T4 to T3. I am not talking about toxic doses of selenium; I am talking about 50 to 400 µg per day of an organoselenium source to see if it would influence the conversion of T4 to T3.

The intracellular activity of thyroid hormone comes through T3 cellular communication to the T3 receptor site. Therefore, the interconversion of T4 to T3 is very important in establishing tissue-specific activity of thyroid function. When the data from laboratory analysis is ambiguous for TSH and T4, and even T3, and one thing looks normal and another looks slightly abnormal, symptoms need to be correlated and nutritional and environmental factors need to be examined. Then, one can start to develop a whole picture of how these things may interconnect, giving rise to what appears to be only a slight imbalance in thyroid hormone function as it pertains to laboratory analysis.

What about TSH levels? TSH can be slightly elevated or slightly depressed, with normal levels of T4. In that case, pituitary level dysfunction is somehow regulated by compensation of the thyroid gland production level of T4. I would start looking at things like feedback processes from the adrenal glands. I would also look at cortisol and stress. These may be playing on organ reserve, where the web of interaction has been stressed, yet there is enough resiliency or reserve in that web to compensate by mobilizing the reserve. We may only be seeing the shadows of dysfunction by slight elevations or depressions of TSH, but the thyroid gland is still regulating itself adequately with reasonably normal levels of T4.

There can also be normal levels of TSH and elevated levels of T4 in the pathological range. There could be very high levels of T4. In that case, one would be getting into the concept of endocrinopathy, and should be looking at TSH-secreting pituitary adenomas, or something like that. In the case of marginal alterations in TSH, T4, or T3 levels, if they do not appear to make sense, I would start looking at imbalance and reserve situations, and the tissue specificity when tied with clinical symptoms.

Relationship of Serum TSH to T4

What about the serum TSH-to-T4 relationship? When the hypothalamic pituitary function is normal, there is a log linear inverse relationship between TSH and free T4. This means the log of the TSH levels is associated with a reduced level of free T4 because of negative feedback inhibition by pituitary TSH secretion by thyroid hormones. Thus, thyroid function can be determined either directly by measuring the primary thyroid gland product (T4), or indirectly by assessing the TSH level, which inversely reflects the thyroid tissue concentrations sensed by the pituitary gland. It follows that high TSH and low T4 is characteristic of hypothyroidism. That would be the general way it has been historically diagnosed as primary hypothyroidism. However, as I just mentioned, there are many conditions that reflect a borderline subclinical imbalance state that do not appear to be clear. In those cases, looking at other variables necessary to assess the state of the patient is important.

Variations in Hormone Levels

There are variations in thyroid hormone levels over age and over conditions. I have already talked about anti-thyroidal antibody conditions leading to hypothyroidism that increase with age, more commonly seen in women than men. There are hormonal effects from cortisol and from estrogen and testosterone that influence thyroid-binding hormones and thyroid metabolism. It would be safe to say that one needs to be very cautious in assessing thyroid hormone blood analyses by making sure all of the other variables are examined—age and gender of the patient, medications, and the presence of other illnesses. We know about the euthyroid sick syndrome that is sometimes seen in hospital patients. It is less common in ambulatory patients, but there are modifications based upon other illnesses that affect the way thyroid hormones are secreted, metabolized, and excreted. All of these variables need to be taken into account as we start evaluating whether the patient needs thyroid hormone replacement therapy.

Coefficient of Variation in Test Results

I want to say something about the tests. We often think when we get a number from a biochemical test from a clinical lab that the same number would be reproduced if we were to do it repetitive times. But every test has an interindividual variability, so-called coefficient of variation, or CV. T4 and T3 have fairly tight CVs in the range of 10-15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} inter-sample variation. But with TSH or thyroglobulin, we see a lot more potential variation, a higher CV, meaning there is more scatter in the test. It is important to recognize that the same number may not be reproduced every time, and one needs to look at both the laboratory variation, as well as the patient physiological variation, in applying a meaning and interpretation to that number. The reason I mention this is because I often hear individuals talk about very small changes in TSH and placing considerable amount of clinical importance on them. This is probably uncalled for, based on the variation in the test and the percent CV.

Indications of High T3 and T4 Levels

I want to discuss things that might influence T3 and T4. Many individuals have moved away from T4 and rely more on T3 levels. A high serum T3 level is often an early sign of recurrence of Graves' hyperthyroidism. High serum T3 usually precedes iodine-induced thyroid toxicosis. Serum T3 measurements are useful for distinguishing mild subclinical hyperthyroidism from T3 toxicosis. Looking at T3 levels to determine thyroid toxic effects may be better than looking at T4 levels. TSH and T4 measurements have historically been found to be most useful for picking up borderline functional hypothyroidism. T3 levels may be better for evaluating at the higher end of the normal range for potential thyroid toxicosis. The reason for that is because most of the T3 that is working at the cell physiological level is intracellular and not available for analysis, and we can be misled as to how much T3 is really functioning in the body. A high level of free T3 in the blood suggests thyroid toxicosis, and it normally occurs as a consequence of a drive from iodine or an increased conversion of T3, with drugs or disease being the principal reasons.

Drugs that Compete for Thyroid Hormone Binding

There are many drugs that compete with thyroid hormone binding and therefore displace thyroid hormone off the binding globulin, thereby liberating as free hormone into the plasma, making it more active. This can induce thyroid toxicosis by increasing availability to free hormone. The most common interactions occur from drugs such as Phenytoin, Furosemide, and some anti-psychotic and antidepressant medications. These can displace thyroid hormone from the binding globulin, increasing its availability and potential for activity, and also increasing the level in the plasma. One might be led to a false sense as

to where that hormone is coming from if these medications are not taken into account. By the way, blood-thinning medications like heparin may also increase potential for thyroid dysfunction. Serum from patients treated with heparin, including the low molecular weight heparin preparations, variously exhibits high free T4 levels secondary to heparin's effect on inducing lipase activity that increases free fatty acids, thereby altering the binding of T4 to the thyroid hormone globulin, and increasing its level. This is just a reminder to make sure that the patient's medications are evaluated when interpreting a thyroid hormone blood chemical analysis.

We have talked a little bit about T4 and T3 hormone replacement for assessment. In patients with mild subclinical hypothyroidism, starting at lower-dose interventions of either T4 or a combination of T4 and T3 is what has been called for.

Elevated Thyroid Hormone-Binding Globulin Autoantibodies or Thyroid Peroxidase Autoantibodies
What about patients with elevated thyroid hormone-binding globulin autoantibodies or those with thyroid peroxidase autoantibodies? This is an important part of the story because there are patients with borderline hypothyroidism for whom the etiology is not well recognized. Once antithyroidal peroxidase autoantibodies are assessed and an elevated level is observed, one begins to think of immune system dysfunction or autoantibody production against the thyroid gland as the etiological agent. When this is the case, one wants to lower the load of antigenic precipitators. These could be allergens, toxins, or various agents that induce upregulation of expression of the antibodies from B cells, the so-called Th2 component of the system, that try to reestablish a balance between Th1 and Th2 lymphocyte activity. Omega 3 fatty acids, various flavonoids, vitamin C, and vitamin E are immune-modulating substances that help restore balance to the Th1 and Th2 system. Lowering the load of various antigens, such as gluten from grain-based products, may be very important. Upon continued consumption of gluten, individuals with gluten sensitivity can suffer adverse effects in their immune systems that increase anti-thyroidal antibodies and produce what might look like Hashimoto's thyroiditis and altered thyroid hormone metabolism and function. I would urge evaluation of the potential of food-based antigens

That brings up the important role that insulin and insulin resistance may play, and their association with endothelial dysfunction, lipid abnormalities, and thyroid dysfunction. There is an interesting article in the *Journal of Internal Medicine* which examined associations among leptin from adipocyte fat cells, insulin resistance, and thyroid function in patients placed on a long-term weight-loss program. The investigators found an interesting correlation between insulin, leptin, body composition, and thyroid hormone metabolism.[6]

Often, patients with hypothyroidism also present with cholelithiasis and gallstones. The cholesterol gallstone is also often found in individuals with metabolic syndrome. Increasing saturation of the bile with cholesterol and its esters produces cholesterol gallstones. If insulin sensitivity is regulated, blood lipids managed, and thyroid function improved, the risk to gallstone formation may be significantly reduced. We see this most often in the postmenopausal woman, as well as a high prevalence of cardiac disorders, hypothyroidism, and Hashimoto's autoimmune thyroiditis. Again, looking at the web, these things tend to track together. If you want to know more about the metabolic syndrome and cholesterol gallstones, there is an editorial about their association in the *American Journal of Clinical Nutrition*.[7]

When putting a person into an insulin improvement program, stress management program, or a thyroid management program, one is starting to develop a comprehensive strategy toward the management of

what might be considered borderline subclinical hypothyroidism. Even patients with excess body fat who go into an appropriate weight-loss program—which lowers inflammatory biomarkers such as tumor necrosis *alpha* (TNFα) and C-reactive protein (CRP), improves serum lipid patterns, and improves insulin sensitivity—are those in whom improved thyroid function should also be observed.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: It's time for our Clinician of the Month. This month, we are fortunate to have a clinician who is actively involved in the area of functional and nutritional medicine. He has gained a wide and well-deserved reputation for understanding the interconnectedness, what we call the functional medicine matrix, and applying it successfully in clinical practice. Dr. Raphael Kellman is a medical doctor who completed his training at Albert Einstein College of Medicine in New York City. He has been involved in the development of what I call a "frontier level clinic" in New York City, one I hear a lot about from people as I travel on the East Coast. It is a great privilege to have Dr. Kellman with us this month. Raphael, welcome to Functional Medicine Update. Perhaps you would tell us about how you made the transition from your training to functional and nutritional medicine.

The Thyrotropin-Releasing-Hormone (TRH) Stimulation Test

RK: Thank you, Jeff. It's a pleasure to be here. I'll tell you how it all started. When I first finished my residency in internal medicine, I was working for other doctors and noticed that many of the patients I was seeing had typical symptoms of low thyroid, yet their blood tests turned out to be in the normal range. I knew something was off. Other doctors had placed many of these people on antidepressants. They were told they needed to lose weight and they needed a vacation. Yet, they all had the textbook symptoms of hypothyroidism. I knew there was another thyroid test called the TRH Stimulation Test, which was recommended in the medical textbooks, and that when one was in doubt, meaning when the blood tests were borderline, one should do this test. Even though the blood tests were in the normal range, the patients seemed borderline in terms of their symptoms, so I thought we should do the TRH test. The doctor I was working with agreed to let me do it, and we didn't charge the first 100 patients. I began conducting the TRH Stimulation Test on patients who had typical symptoms of hypothyroidism, and they failed the test significantly. I started these people on thyroid hormone and saw that they got better, beyond the placebo response. This all happened in 1989, and it got me thinking in terms of functionality, that there isn't a sharp demarcation between sickness and health; that in fact, there must be some gradient. I was taught in medical school that you're either healthy or you're sick. You have a disease and, if you don't, you're totally healthy. Immediately, I got to see firsthand that the black-and-white type of thinking is not really up to date.

I started seeing the same principle with diabetes. There was a gray area where people actually didn't have diabetes, but they seemed to have all the symptoms of a diabetic. I also believe they probably had all the risk factors for diabetes. Of course, ten years later, most doctors know that to be true. The thyroid is just

lagging behind, but eventually they'll get it in that domain, as well. We have to think in terms of functionality and if the tests are not revealing functionality, then they are inadequate, not the patients. That's basically how I came to understand the human body in terms of functional medicine.

JB: That's a fascinating story. You have also done a nice job in describing that in your book, Total Renewal, which I found to be a very well-described premise about functional medicine and the difference between pathology and reduced function. You're to be complimented on the way you contextualized that. Let me ask you a question about the specifics of the TRH Stimulation Test. We have all studied that test in school in endocrinology classes, but most people who are not endocrinologists probably have not brought it into practice because they think it's only applicable to frank, primary, severe hypothyroidism. The concept of using it as a challenge test to evaluate organ reserve is a fascinating concept that you've developed. How do you do the test, and what would you consider to be an abnormal result?

Interpreting TRH Test Results

RK: I've probably done at least 7000 TRH tests. By now, I can tell you what the abnormal graph should look like. Part of it is experience. I've learned that even if it's something written in a textbook, you may have to take it with a grain of salt. You have to understand what you see in clinical practice. Frequently, it's not the same as what you might read in a textbook. You need to have self-confidence in what you're doing in your own practice. After you've done enough of these tests, you know what's normal and what's abnormal.

Let me explain the test. We inject TRH (a hormone which comes from the hypothalamus), into the vein and take blood 25 minutes later. We check for levels of TSH. If one's thyroid is low, the pituitary is going to be producing a lot of TSH in an attempt to wake up the thyroid to produce more thyroid hormone. Theoretically, that increase of TSH in the pituitary should be reflected in the blood on what I call a static blood test, a regular blood test. However, we're finding that's not always the case. Even though sometimes there's a lot of TSH in the pituitary, it might not actually show up in the blood for a number of reasons which unfortunately, we don't have time to get into. However, if you inject TRH, which challenges the pituitary, it has no choice but to reveal how much TSH it is building up in its system, in the gland. It will then spill out into the blood. You give the blood test, after which you get an inner view of what's happening in the pituitary, which is a reflection of what's going on in the thyroid. If you do this test and see that the pituitary secretes a TSH of, let's say 25, it's pretty conclusive (in a woman especially, but also in a man) that the thyroid is low. Anything in a woman above around 15, 17, or certainly 20, reflects hypothyroidism. In a man, it would be anything above a 12. That, in my opinion, after doing so many of these tests, is very suspicious of a hypothyroid. However, there are some cases where people don't have a brisk TRH response because the pituitary is malfunctioning, as well—the pituitary's level of functionality is declining and it can't produce a lot of TSH. That also has to be taken into account. For example, if someone has heavy metal poisoning, it will frequently not only affect the thyroid, but in some situations, it can also affect the pituitary. This type of test requires not only the science of medicine, but a hefty dose of the art of medicine, as well.

Pituitary versus Thyroid Problems

JB: You've raised some very interesting questions. Given that you are stimulating with TRH, which then stimulates the release of thyroid stimulating hormone from the pituitary, which subsequently influences the release of thyroxine from the thyroid gland, how do you differentiate clinically between a pituitary level problem versus a thyroid problem? Or, do you treat them both together?

RK: If the thyroid is very low, then the pituitary, under ordinary circumstances, would be producing a lot of TSH. Then you know that the thyroid is low. That's what we're finding in the vast majority of patients. There are a small percentage of patients that still have hypothyroidism, but the problem is coming from the pituitary. In that situation, you are not going to get a high TSH response when you inject TRH. Then, you are going to have to use more clinical judgment. In that type of situation, I find that the baseline TSH tends to be over 2.5, or maybe even 3.0. In that case, it tends to be higher than in people who have low thyroid from a thyroid abnormality, not a pituitary abnormality. What happens is that the difference between the pre- and post- tends to shrink. In my experience, in people who have only a pituitary abnormality, they're not going to secrete much TSH. Sometimes, it's a combination problem, meaning that the thyroid is slightly dysfunctional and the pituitary is slightly dysfunctional. Then you will see an effect where the pre- and the post- of the TSH will not be very different.

JB: Do you find there's any evidence of differential clinical signs or symptoms that are markers, or are the symptoms diffuse and don't give specificity?

RK: Unfortunately, the latter is true. It's difficult to differentiate.

Symptom Clusters in Hypothyroidism
JB: In your experience, over the 7000 people you've tested, some of whom have shown abnormal tests, what kind of symptom clusters are indicative of subclinical hypothyroidism?

RK: Frequently, they're going to complain of fatigue and weight gain. Not everyone has weight gain, and sometimes this can be misleading. Sometimes, you can have weight loss, even in hypothyroidism. The common complaint is that they wake up more tired in the morning than when they went to sleep or, after they wake up, they feel they need another night's sleep. Brain fog is common; constipation is frequent. People do not have bowel movements on a daily basis. Women tend to have irregular periods. There is muscle and joint pain. Unfortunately, a lot of people who are only in their 40s or 50s just assume that it's due to aging, which is absurd. Where they're getting this notion from is beyond me. I think it's coming from some doctors and our culture, but that needs to be changed. If someone in their 50s has joint pain, it's not due to aging. I always tell these patients that if they were 95 years old and they told me their joint pain was due to aging, I might accept it, but not at the age of 55. We find there is some functional problem based on the TRH test. When you start treating the thyroid, all of a sudden, the fatigue goes away, the brain fog goes away, and the joint pain goes away.

The Dysphoria Component
JB: How about dysphoria? Do you find there's a depressive component?

RK: Absolutely. A significant percentage of people with low thyroid have depression. They don't know why they're depressed. Their lives could be great, and yet they're depressed. Recently, I had a woman who said she just got married a year ago. She has a wonderful husband and a wonderful life. Money is not a problem, but she's depressed. She had a low thyroid proven on the TRH test. She started on thyroid hormone and all of a sudden, she's not depressed any more. Dysphoria, depression, anxiety, and mood swings are all quite common signs and symptoms of hypothyroidism.

JB: It's interesting, because these observations you've made beg the question of origin. Why the thyroid as a problem organ in the late 20th, early 21st century? Is it stress? Is it environmental factors? What

relationships have you seen between the ways a patient might present and the appearance of a thyroid problem?

Environmental Toxins

RK: These are good questions. There is a virtual epidemic of dysfunctionality, and it comes significantly from the thyroid, although that's not the only culprit. I believe that we're environmentally poisoned. It's not like we're in Bangladesh and it becomes quite obvious that we're being poisoned by arsenic because we're developing severe neurological symptoms. It's a lot more insidious; it's a lot more chronic; it's a lot more slippery here. It's not that the levels of these heavy metals, like arsenic, aluminum, and mercury, cadmium, and titanium are so high that it becomes obvious. It's more in the range where we don't really believe it could play a role. Why we don't believe it could play a role has to do with the way we were taught in medical school with the paradigm that was used to understand health and disease. The most important thing that I've accomplished is finding a way to uproot that way of thinking. That paradigm was instilled in us in medical school only ten years ago, and that is the non-functional perspective, a very limited way of understanding health. Now, I'm coming from a different paradigm and seeing health with a different pair of glasses. If I see a level of arsenic, or mercury, or aluminum that's even slightly elevated, it's shocking to me and red lights go off. Ten years ago, I probably would have just dismissed it as nothing. I would hesitate even bothering to do the test. But that paradigm has shifted. Now, I believe that when someone has even low, low levels of these heavy metals, it's a significant problem. It's going to affect our health in ways that will not lead to a specific diagnosis, but might lead to debilitating problems that will consistently elude the typical medical doctor.

Intervention for Toxicity and Thyroid Dysfunction

JB: If you have identified in a patient's history that there may be an underlying toxicity relationship with their thyroid dysfunction, what type of intervention do you use? Obviously, you're going to support the thyroid, but there may be other mitigating triggers.

RK: It can be approached on two levels. First, you can treat the symptoms. If they have low thyroid, I always use a combination of T4 and T3, meaning I would use Armour thyroid frequently, or any preparation that has a combination of the two. There were some small studies and reports in The New England Journal of Medicine showing that adding T3 does make a difference, especially with cognitive/emotional/psychological issues. Clinically, I find that to be true—it's necessary to add T3. If the thyroid gland makes 10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} T3, why not try to mimic what the body is doing? That's what I do, so we use a combination of T4 and T3. It's also necessary to look into the underlying causes. Why did this happen in the first place? In addition to understanding the psychological/emotional/stress components, you can evaluate with neurotransmitter testing. You can evaluate it, of course, through the patient's history; and you can evaluate using adrenal saliva testing that we frequently do. You can evaluate the person's response to the stress. There are definitely ways of modulating that with supplements, nutrients, and herbs, even on a purely physical level. However, we also look into other potential causes like heavy metal toxicity. I frequently look into that, certainly with urinalyses. Of course, some people feel that hair analysis should be done. In New York, it's a little more difficult to do hair analysis. You also want to look into gastrointestinal (GI) function. Even if someone doesn't have GI complaints, when you look at the body from a holistic perspective, you need to look into what's happening in the gut. Gut toxicity could certainly cause thyroid problems. I have many stories about that, so I know it to be true. You may want to clean up the gut with a number of different programs.

You always want to look for the causes. However, it could take time until the condition is cured. In the meantime, placing patients on thyroid hormone helps. They see significant improvement. Then, over time, you can get them off of it. I tell them they don't have to be on it for life. They go on it for a week, a month, perhaps six months, and then we can try to get to the underlying causes.

Psychological/Psychogenic-Related Stress Factors

JB: As you're talking, it reminds me of the web of interconnectedness. We have the hypothalamus/pituitary, the adrenal, and the thyroid axis all speaking to each other and communicating with the outside environment. There is a big receptor system taking in information by way of sight, sound, touch, feel, and taste, and then translating it into hormonal messages that regulate cellular function. It sounds to me like what you do is functional endocrinology. You've moved way beyond just trying to find the disease, to trying to find the nature of the dysfunction in that web. When you do that, do you find that the psychological/psychogenic-related stress factors are a major component? How would you weigh that in your experience?

RK: It certainly plays a role. Sometimes it's the cause; sometimes it's the effect. It's difficult to be completely emotionally and psychologically stable when you have so many physical symptoms. Again, I think it forms a web. I think it's even beyond what we imagine, that it is such a complete web that you have to begin everywhere. The whole idea of cause and effect actually begins to get rather blurry. It all happens simultaneously. Any way you can intervene, you can make a difference. That's why sometimes you find people get completely better when you intervene on just a psychological/emotional level. That doesn't mean there isn't something going on physically, as well, but it seems to be such an interconnected web that I look at it as a simultaneous happening. The way you intervene can make a difference. I like to intervene on a few levels. I look at it more from a systems theory perspective, in that you never know what's going to cause the body to make that quantum leap to a healthier state. That one new variable you might throw in today that you didn't throw in yesterday gives the body additional incentive or push to make that quantum leap.

A Case History

JB: Maybe the best way to get this across to our listeners would be for you to give us a case history, one that you think exemplifies how this looks from the assessment through the treatment program and the outcome, just to give us a reality check.

RK: Of course . A few weeks ago, I showed this case history to someone to illustrate functional medicine in practice. I had a lady who came in complaining of fatigue. She was in her mid 50s, and this had been going on for over ten years. She had a strong family history for diabetes, and had numbness and tingling in her hands and legs. She also had gained 25 pounds over the last two or three years. She had experienced brain fog, impaired memory, decreased libido, and irregular periods for a number of years, along with decreased mood. She had gone to a few doctors and all her blood tests were normal. Her PFT thyroid function tests were in the normal range. The TSH tests (she did three of them) reflected 2.3, 2.8, and 1.4. I could see that they widely differed. These were done in one year on the same patient. Her glucose was in the normal range. Her liver function test was slightly abnormal. There was no treatment done. One doctor put her on Paxil and, of course, her libido got worse, so she was switched to Effexor®. At that point, she came to see me. Her blood pressure was 130/84; pulse 60. She was obese. Her thyroid was not enlarged. There was a little bit of fluid retention in her extremities, but that was about it. In terms of routine testing, her cardiogram was sinus bradycardia. The R waves were somewhat diminished on the

cardiogram, but it was nothing significant. In terms of the workup, we did a TRH Stimulation Test. The pre-TSH, the first TSH, was around 2.4, similar to what she had in the past. The second one we did 25 minutes later after injecting TRH went up to a 33, which is very low. We also did an adrenal test. It's very important to do both, not just treat the thyroid and ignore the adrenals. Sometimes you can actually make people worse if you're not looking at things holistically. We did an adrenal saliva test and her adrenals were very, very low in the morning, in the afternoon, and at night. Her DHEA level was very low, both in the blood and in the saliva. We also did an ACTH stimulation test, which I do in certain cases with someone who has had chronic fatigue for a number of years. That test also revealed a blunted response, which is another discussion. I also did a glucose tolerance test and even though her glucoses were in the normal range, her fasting insulin was around 16 or 17. It spiked up to almost 100 in the first and second hour. In the third hour, it still remained elevated, even though her sugars were in the normal range on all the tests. We started her on Armour thyroid. I also did a little bit of work on her adrenals with pregnenolone, a little bit of DHEA, and licorice root at low dose because she had a little bit of borderline hypertension.

She came back two weeks later saying that it was the first time in ten years she was able to think clearly. That was after only two weeks. In a month, her energy was significantly better. It wasn't even close to anything that she had done in the past. Her body spoke to her about her low thyroid. She was convinced that she felt it in her bones. We did a followup TRH a month later. We had to tweak it a little bit; we had to raise the dose a bit. She started feeling even better. I addressed her glucose tolerance test, as well; to me, it's abnormal when you have a high insulin level. Plus, I discussed diet and told her she was at risk to diabetes. I told her that pre-diabetes is a disease, too. That was one of the causes of her tingling and numbness. Actually, both low thyroid and glucose intolerance can cause numbness and tingling. I started her on things that could help that directly—B12, folate, glutathione, or N-acetylcysteine as a precursor. Those are some of the things we did to try to alleviate that, but just improvement in the glucose tolerance test will help with numbness and tingling. And I started her on some supplements that can improve insulin sensitivity. When you put people on a comprehensive program, their lives turn around. This is what happened to this person. She lost weight. I tell people that thyroid hormone is not going to be a magic pill, that they have to work at it. They have to change their diets and they have to exercise. But the point is that this woman's TRH normalized, her tests normalized, and her energy improved. Now, a few months later, she's completely better. Also, when we retested, her insulin was down to less than 10 and her TRH test was within the normal range. Her blood pressure also began to drop. We now know that 130/84 or 85 is abnormal, too, and we saw hers come down to 118/74. That's the blood pressure we like to see. Hypothyroidism can elevate blood pressure, as well, and certainly insulin resistance. That's a typical story, not that uncommon. We see it over and over and over again. That's why this information needs to be widely disseminated across America.

JB: That's a brilliant clinical case example. What you have done so eloquently is describe many of the components we touch upon in Functional Medicine Update. What we might call borderline hypertension based on the new guidelines is probably related to some endothelial dysfunction. The endothelial dysfunction is related to insulin resistance. The insulin resistance is related to cortisol imbalance. The cortisol imbalance is related to thyroid imbalance, and those are related to the fact that your patient is in her 50s and probably starting into perimenopause. She may very well have an estrogen/progesterone imbalance. When you deal with all these issues, as you've done in a weblike sense, it's amazing how all of what may appear to be disparate clinical signs start to come in line and improve.

RK: It's fascinating, and it's just looking beneath the tip of the iceberg. It's amazing. People come in and everything's fine, the doctor said. All of a sudden, you're looking at it from a different angle and you may find 10 or 15 variables that are abnormal, and they're all interconnected, as you said. Even glucose intolerance and insulin resistance are not only related to cortisol abnormalities, but also to hypothyroidism. If the thyroid is low, just a slight dysfunctionality, it will also cause one to be more susceptible to insulin resistance.

JB: I want to thank you, Dr. Kellman, for sharing this with us. This is extraordinary and it's a magnificent application of functional medicine as we have thought of it over the last 15 or so years. And I really liked your books, Gut Reactions and Matrix Healing. For people who want to follow up and get more information about these books, I presume they can contact you at your office.

RK: Of course.

JB: Thank you for being such a tremendous clinician and for sharing this important information with us.

RK: I want to thank you, too, Jeff, for working in the same way.

JB: We'll talk to you soon.

Dysphoria and Dementia in Postmenopausal Women

I would like to follow up on Dr. Kellman's clinical comments about borderline subclinical hypothyroidism and its importance in health care, and talk about dysphoria and later dementia in postmenopausal women. The thoughts Dr. Kellman shared with us about the role thyroid metabolism plays in central nervous system (CNS) function is germane to the increasing number of women in the current postmenopausal age group who have historically been candidates for taking conjugated equine estrogens (CEEs) and synthetic progestins—also called hormone replacement therapy, or HRT—for the management of postmenopausal health risks. Women were told that CEEs would reduce risk to bone loss, lower the risk to cardiac disease, improve cognitive function, and lower the risk to dementia. It was a clinical approach that appeared to be the "be-all and end-all" for managing problems associated with postmenopause.

Now that the data from the Women's Health Initiative (WHI) studies have been published, we know that panacea was not realized. There is now a more cautious view of the role of mixed CEEs. It is not that they have no value; it is that the kind of excessive support for their application has diminished considerably in light of some of the more recent evidence. That also holds true as it relates to estrogen and dementia. Recently, in the *Journal of the American Medical Association*, two back-to-back papers were published that discussed the issue of HRT and dementia or mild cognitive impairment in postmenopausal women.[9],[10] The editorial that followed those two articles sums it all up. The author states that there is no evidence from the WHI data that the implementation of mixed CEE intervention did, in fact, help protect against the loss of cognitive function. The author further states that there may be some evidence that CEE intervention increased the loss of cognitive function.[11] That was not good news. The final message appears to be—do not use CEEs to try to improve cognitive function in postmenopausal women, whether alone or as part of HRT.

Nutritional Intervention in Postmenopause

What are the alternatives? How do we keep mood, mind, memory, and behavior intact? Some individuals have suggested that nutritional intervention with soy proteins containing phytoestrogens that function as selective estrogen response modulators (SERMs) may be an alternative. There is a paper in the Journal of the American Medical Association, titled "Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density, and Plasma Lipids in Postmenopausal Women."[12] In this trial, 25.6 grams of soy protein containing 99 mg of isoflavones were taken daily versus milk protein as an alternative. The authors conclude that this double-blind randomized trial does not support the hypothesis that the use of soy protein supplements containing isoflavones improves cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women, when started at the age of 60 years or later.

I do not want to throw out the baby with the bath water with this study. Clearly, there is a considerable body of literature that indicates there are many benefits in terms of improved endocrinological function, using diets that include soy protein and isoflavones at normal dietary cultural levels. But soy isoflavones, at least at that level, are not a panacea to help protect against the loss of function that occurs postmenopausally. What other nutritional associations are linked to bone loss, cardiac function, lipid panels, and CNS function? Once we ask that question, it comes back to looking at thyroid function. Therefore, intact thyroid function is very important. There is an estrogen/thyroid connection, a connection of calcitonin and thyroid function, and a connection of T3 to CNS function. The story begins to evolve as a functional web to support continued high-level CNS function in postmenopausal women.

We should look at things that might lower thyroid activity—food allergies, and gluten and its association with autoantibodies against the thyroid gland. We should look at selenium in the diet to make sure there is adequate conversion of T4 to T3. We should look at zinc, another important mineral for the proper sensitivity and metabolism of thyroid hormone. We should look at iodine to make sure it is adequate but not excessive in the diet to support proper thyroid hormone formation. We should look at things in the diet related to support of proper adrenal function. We should look at exercise, stress management, and things that help lower excessiveadrenal output of cortisol. We should look at things that help to stimulate insulin sensitivity because that will have a salutary benefit on thyroid hormone metabolism and sensitivity. We have discussed some of those things in previous issues of FMU, such as a diet with a lower glycemic load; cinnamon for improving insulin sensitivity; and lipoic acid, another insulin-sensitizing or supportive nutrient. What I am speaking to here is, as Dr. Kellman pointed out, broadening our perspective—moving from a slit to a window of opportunity. Often in medicine, we go from big and are trained to think small, rather than starting with small and going to big, and connecting the issues that may control the outcome of the variable we are analyzing in a patient.

There are many nutritional associations we should be attending to in conditions of bone loss, dyslipidemia, and CNS dysfunction in postmenopausal women that go beyond estrogen. Thyroid function, metabolism, and activity, and its interrelationship with insulin, cortisol, calcitonin, and things relating to parathyroid function, are all extraordinarily important. Parathyroid function takes its message, in part, from the calcium and phosphorus ratio of the diets. Women who drink a lot of soda pop and other synthetically sweetened beverages, may be getting a fairly high dose of phosphorus as the phosphates in cola drinks, but fairly low levels of calcium. They have an interrupted calcium-to-phosphorus dietary ratio that may induce secondary hyperparathyroidism, having an adverse effect upon thyroid hormone balance and calcitonin.

All of these things are interwoven. That is the excitement of functional medicine—putting the system into a context for clinical management so the whole person is being treated, not just the disease. The challenge is that it requires making a lot of thoughtful connections that may be more complicated than simply jumping to the conclusion of a diagnosis. I hope that Dr. Kellman's message came across strongly—that the payoff for that cerebral process for developing those relationships, is better patient outcome and solutions to complex, chronic age-related dysfunctions that are not amenable to polypharmacy.

There is an interesting paper in the American Journal of Clinical Nutrition which examines nutritional associations beyond soy isoflavones, having to do with bone loss, serum lipids, and CNS functioning in the postmenopausal transition.[13] These are things like calcium, flavonoids from fruits and vegetables, and various vitamins and minerals, as I have previously described.

Asking the Right Questions

A lot can be done once we ask the right questions. There is a common theme that comes through in every discussion we have had to date in FMU and that is, the questions you ask determine the answers you receive. If you do not ask the question, it is unlikely you will receive the answer. In functional medicine, one of the principal components of our teachings involved in gaining competency is learning how to ask the right questions. Once you ask the right questions, there are a multitude of places where you can find the answers. With the advent of the worldwide web, and accessibility of Medline and PubMed to virtually anybody with a computer, we can now find answers if we know what questions to ask. The difficulty in medicine has historically been to distill down the number of questions to a very few so that one will get "the right answer." That lowers reinforcement for asking questions and begins to make it a disadvantageous part of a daily practice. The fewer questions one asks, the better off and more efficient and effective one should be. That is antithetical to the functional medicine model, which basically states that the more questions one can ask to help connect important strategies for the management of complex symptoms in the patient, the more successful one will be in the outcome. That is what Dr. Kellman was referring to regarding how he approaches thyroid-related dysfunctions.

Thyroid function is an example of both the complexity and simplicity of functional medicine. There is a tremendous amount of information about the thyroid. We have only scratched the surface. We could discuss the topic for tens of hours. But through drilling deeper into the understanding of the thyroid, we start to explore and understand other connections as well, such as those of insulin, cortisol, testosterone and progesterone, and estrogen, which help us to understand how the body functions to improve the efficacy of patient outcome.

I hope I have provided you with some good takeaway information about using the thyroid panel and how to evaluate patients with subclinical borderline hypothyroidism.

We will see you in December.

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