# Treating Thyroid Despite Normal Labs

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The physician consultant opines that only patients with labs out side the normal range should be treated and to give thyroid support when this is not the case is outside of the standard of practice. This was stated despite a large number of studies given showing that this is not the case. This patient likely has a combination of secondary or tertiary and primary hypothyroidism (as discussed below). But, even if there was no central hypothyroidism involved, treatment is indicated.

Clinically, this patient had numerous signs and symptoms of hypothyroidism including:

1. A 40 lb weight gain with inability to lose weight
2. Elevated cholesterol
3. Severe fatigue
4. Periorbital oedema
5. Constipation
6. Severe widespread achiness / pain
7. Constipation
8. Arthralgias
9. Cognitive dysfunction
10. Dry skin
11. Paresthesias
12. Slow relaxation phase of the ankle reflex (SRPAR)

In a study published in the *Journal of Endocrinology and Metabolism*, the SRPAR was found in 77% of individual with tissue hypothyroidism and in only 6.5% of normals; dry skin was found in 76% of individuals with tissue hypothyroidism and in 36.2% of normals; course skin was found in 60% of individuals with tissue hypothyroidism and only 18.8% of normals; periorbital puffiness was found in 60% of individuals with tissue hypothyroidism and only 3.7% of normals; constipation was found in 48% of individuals with tissue hypothyroidism and only 15% of normals; and constipation was found in 48% of individuals with tissue hypothyroidism and only 15% of normals (150). The combination of these signs and symptoms is highly specific for the presence of thyroid dysfunction and a diminished end-organ thyroid effect. Another study published in the *British Medical Journal* also found that SRPAR was a better indicator of tissue hypothyroidism than thyroid function tests (TFT's)(153).

While treatment with thyroid hormone is clearly indicated in this patient and with treatment, the patient would be expected to have symptomatic improvement as well as a reduction of numerous disease risk, this certainly will not, on its own, be effective without addressing the multiple physiologic abnormalities present in CFS.

Numerous studies have demonstrated a central hypothyroidism in the overwhelming majority of patients with FM and CFS. For instance, a study published in the peer reviewed *Journal of Rheumatology* looked at the incidence of central hypothyroidism in patients with FM (6). They found, through the use of thyrotropin releasing hormone (TRH) testing, that all of the patients studied with FM had central hypothyroidism despite having baseline thyroid function tests (TFT's) in the normal range. They found that these patients with central hypothyroidism tended to have low normal TSH levels that averaged 0.86 vs 1.42 in normals with normal free T4 and free T3 levels. The free T4 levels were slightly higher in the patients with central hypothyroidism and the free T3 levels were slightly lower in patients with central hypothyroidism. With appropriate replacement, the TSH is usually low, undetectable or low normal so this is not by itself an indication of hyperthyroidism or over-treatment in this patient population. A TRH stimulation test would have been ideal to perform, but TRH is currently unavailable for clinical use.

Other studies confirm the fact that standard TFT's cannot be used to rule out central hypothyroidism, as they are generally undifferentiable from euthyroid individuals (6,8,119). One such study clearly demonstrating this fact was published in the *Journal of Clinical Endocrinology and Metabolism* where it was determined how often central hypothyroidism went undetected by standard TFT's (119). They found that 92% of patients with central

hypothyroidism would have remained undiagnosed using baseline TFT's. Thus, it is incorrect to conclude that thyroid replacement is not appropriate in this patient if he had TFT's in the normal range. Therefore, the utility of such testing is very low and would not be an effective means of directing treatment.

A study published in *The Lancet* performed thyroid biopsies in patients with chronic fatigue and found that 40% of these patients had lympocytic thyroiditis, with only half of these being positive for TPO or antithyroglobulin antibodies (thus going undetected). They also found that *"clinical response to thyroxine was equally favorable among patients with lympocytic thyroiditis, irrespective of initial thryoitropin (TSH) concentrations* (120)." This demonstrates that many of these patients with CFS and FM have a thyroiditis that is not detectable by standard auto-antibody testing and that such patients respond to thyroid replacement regardless of their baseline TFT's.

Another study published in the *Journal of Chronic Fatigue Syndrome* demonstrated that due to the hypothalamic and pituitary dysfunction present in FM patients, multiple hormone replacement, including thyroid, is appropriate, safe and effective despite baseline levels being in the normal range. Numerous other studies have also been published that support the appropriateness and safety of this treatment (13).

There is controversy as to the usefulness of follow-up TFT's, especially in patients with CFS and central hypothyroidism (13,152,153,119,121,122,123,124,125,154). A study published in the *British Medical Journal* found that for individuals who had overtly abnormal thyroid tests initially, but normal labs with treatment with thyroid replacement, the evaluation of clinical symptoms by doctors experienced in thyroid disease was a more accurate measurement of end-organ thyroid effect than TSH, free T4 or Free T3 levels (151). This is also especially and more certainly true of individuals with any degree of central hypothyroidism as in this case. The authors state, "*To establish their role in monitoring patients receiving thyroxine replacement biochemical tests of thyroid function were performed in 148 hypothyroid patients studied prospectively. Measurements of serum concentrations of total thyroxine, analogue free thyroxine, total triiodothyronine, analogue free triiodothyronine, and thyroid stimulating hormone, made with a sensitive immunoradiometric assay, did not, except in patients with gross abnormalities, distinguish euthyroid patients from those who were receiving inadequate or excessive replacement. These measurements are therefore of little, if any, value in monitoring patients receiving thyroxine replacement (151)."*

There are additional reasons that baseline and also follow-up TFT's are of limited use in treatment of patients with CFS and FM (127-143). For example, a low TSH does not necessarily indicate excessive thyroid therapy or hyperthyroidism, again showing that the reviewer's insistence that any one who relies on anything except the tests, including clinical signs and symptoms, is practicing outside of the standard of practice. Even in normal individuals without CFS or FM, a suppressed TSH requires clinical correlation. For instance, a study published in the *British Medical Journal* demonstrated that the false positive rate that a suppressed TSH indicates hyperthyroidism in someone on thyroid replacement is 80% (151).

The positive predictive value that a suppressed TSH indicates hyperthyroidism in normal individuals with primary thyroid failure is:

$$\text{Positive predictive value (PPV)} = \frac{\text{sensitivity x prevalence}}{((100\text{-specificity}) \times (100\text{-prevalence})) + (\text{sensitivity x prevalence})}$$

$$\frac{59 \times 20}{(100-51) \times (100-20) + (59 \times 20)}$$

$$\frac{1180}{49 \times 80 + 1180} = \mathbf{23\ \%}$$

Thus, a person on thyroid replacement with a suppressed TSH has only a 23% chance of being hyperthyroid. In addition, if a person has any degree of central hypothyroidism, as in this case, the suppressed TSH is meaningless (127,128,129,139,131,132,133,134,135,136,137,138,139, 140,141,142,143). The most

appropriate and accurate means of monitoring adequate replacement in these patients is a careful assessment of clinical response. For a given level of T4 and T3 in the serum, the pituitary and heart will always have a higher intracellular level of T3 than any other tissue (161,162). This is why the first change with subclinical and frank hyperthyroidism is a suppressed TSH (although meaningless with hypothalamic and pituitary dysfunction seen in CFS and FM) and an increase in heart rate (162,163). Excessive reliance on laboratory values and ignoring the clinical picture can lead to an improper assessment and inaccurate diagnosis.

Blindly treating a lab value without a thought of the underlying pathophysiology or clinical correlation does not exemplify the practice of good medicine. It is for that reason that I analyze the entire picture, identify all of the underlying issues, assess correlation and treat with a multiprong approach for the most effective outcomes.

In addition, it has been shown that these patients with central hypothyroidism secrete a TSH that is less bioactive than normal TSH (127-143,151,152,153). This decreased bioactivity is not detected on 3rd generation or other standard TSH assays. This results in a lower level of T4 and T3 for any given concentration of TSH. This is why the TSH is not reliable in central hypothyroidism and that you must suppress the TSH in order to even begin to achieve tissue euthyroidism (127-143,149,151,152,153). A landmark study by Escobar published in the *Journal of Clinical Investigation* measured the tissue level of T3 in 10 different tissues during T4 thyroid replacement. They found that all tissues except the brain (including the pituitary) required supraphysiolgic levels of plasma T4 to provide normal tissue levels of T3. Doses of T4 that normalized plasma T4 and T3 levels were insufficient to normalize the concentration of T3 in most tissues. A notable exception was the brain (pituitary), which showed a remarkable degree of independence from plasma T4 and T3 levels and other tissue concentrations of T4 and T3. As some amounts of T4 infused, the level of thyroid hormones in the pituitary was over twice that of other tissues, again demonstrating that pituitary levels and thus TSH secretion is not an accurate measure of tissue hypothyroidism. The authors conclude, "*It is evident that neither plasma T4 nor plasma T3 levels alone permit prediction of the degree of change in T4 and T3 concentrations in tissues… The current replacement therapy of hypothyroidism should no longer be considered adequate, and might possibly lead to the development of new strategies of therapy…(155)"*

It was originally believed that thyroid hormones enter the cells by passive diffusion, but it is now clear that cellular uptake is via a carrier-mediated process (156,157,158,159) and studies are demonstrating the presence of a thyroid resistance in CFS and FM, possibly secondary to a defect in the transport system, further limiting the utility of TFT's in evaluation of tissue levels of thyroid (121,122,123,124,125,126,165). Consequently, the multiple uncertainties and variables associated with a combination of primary hypothyroidism, central hypothyroidism and thyroid resistance make the most appropriate method of monitoring adequate tissue levels of thyroid a knowledgeable physician's clinical assessment (121-153,165). A number of double blind placebo controlled trials have demonstrated that follow-up TFT's are of little help in determining tissue euthryoidism in these patients and have demonstrated the superiority of clinical assessment over TFT in these patients (123,124,125,126,154,13,165).

Endocrinology texts are clear that if there is any degree of hypothalamic or pituitary dysfunction, as with this patient, the recommended method of monitoring thyroid replacement is by clinical assessment as the TSH is meaningless and should be suppressed with proper dosing (162,165,168).

**Footnotes and References**


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