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OPINION

The euthyroid sick syndrome: Is there a physiologic rationale for thyroid hormone treatment?

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Thyroid hormones play an important role in regulating a wide range of functions of the human body. In the context of classic endocrine feedback theory, this relationship can be viewed as bidirectional in that changes occurring in non-thyroid organ systems can have a significant effect on thyroid homeostasis. The complex set of these thyroid adaptations has been collectively termed as the "euthyroid sick syndrome" (ESS) (1). The ESS is marked by varying normal to low levels of serum thyroxine (T_4), normal to high free T_4, low triiodothyronine (T_3), but normal to low normal thyrotropin (TSH) levels. It is the TSH levels that make the strongest case for euthyroidism, because sick hypothyroid animals will still demonstrate elevated TSH levels. The precise etiology of these adaptations in all circumstances is still unclear as is the need for physicians to attempt to "normalize" the situation, specifically by replacement of thyroid hormones. Many studies have tried to clarify this dilemma for a wide variety of non-thyroidal illnesses, such as infections, cardiac diseases, pulmonary diseases, thermal injuries, or surgical and trauma patients. The most dramatic changes in thyroid function tests have been documented in critically ill patients. These are the patients in whom there is the strongest imperative to maximize all aspects of treatment in order to ensure their survival with the least amount of morbidity. Indeed, there appears to be a direct correlation between the most dramatic changes in the levels of thyroid hormones and ultimate poor clinical outcome.

Key-words: Triiodothyronine, euthyroid sick, non-thyroidal illness, critical care.

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If the profile of changes in thyroidal economy in the ESS represent a physiologic adaptive response, which some have referred to as "physiologic hypothyroidism", then treating with thyroid hormone could be potentially harmful for such a patient. On the other hand, if the changes represent a true "pathologic" hypothyroid state, then treatment with thyroid hormone could be of benefit. Therein lies the root of the controversy. In order to better understand the basis for the controversy, it will be of use to briefly review in greater detail how each component of the thyroid axis is influenced by non-thyroidal illnesses.

OVERVIEW OF THYROID AXIS ADAPTATIONS

Thyroxine (T_4)

T_4 originates exclusively from the thyroid gland. In general, serum T_4 levels decrease during ESS (also referred to as non-thyroidal illness - NTI). This could potentially be explained by either decreased synthesis or altered peripheral metabolism. According to a commonly accepted hypothesis, an inhibitory effect is exerted on the hypothalamic-pituitary-thyroid axis in the presence of stress, inducing a secondary state of decreased thyroid gland stimulation due to reduced TSH production. This is thought to represent an attempt of the organism to homeostatically conserve energy by suppressing the catabolic effects of thyroid hormone in the setting of acute stress, illness, or starvation. Another major determinant of serum T_4 concentration is the binding capacity and binding affinity of the principal hormone transport protein, thyroxine binding globulin (TBG). TBG is produced by the liver, and in most stress-related situations, its production is decreased as the liver diverts synthetic processes to the production of acute phase proteins. Because T_4 circulates almost 100% protein bound, a reduction in TBG level will result in a decrease in measured serum total T_4. Similar alterations in binding apply to the other principal thyroid hormone bind-

ing proteins, transthyretin [thyroid binding prealbumin (TBPA)] and albumin. In addition to the reduction in TBG binding capacity, there are compelling data for reduced TBG binding affinity due to circulating inhibitors to thyroid hormone binding, such as high levels of free fatty acids or various cytokines. Early in the onset of systemic illness, the reduced binding of hormone to its binding proteins will result in a higher proportion of hormone that is unbound or free. Subsequently, the high free T_4 levels drop, generally into the normal reference range. Because free T_4 represents the bioavailable form of the hormone, these high-to-normal free T_4 levels are interpreted by many as further evidence (along with the normal TSH levels) of the euthyroid state of these patients, and therefore as mitigating against treatment with thyroid hormones.

Thus, blood T_4 concentrations in the ESS may be low because of both reduced TSH stimulation and reduced transport protein binding and affinity. There is yet another important mechanism influencing both serum T_4 and serum T_3 levels and that relates to altered metabolism of T_4 itself in starvation or illness. Under normal conditions, thyroxine is metabolized to T_3 (the "active" thyroid hormone) via a 5'-deiodinase, by what has been called the "activating pathway". Alternatively, there is an "inactivating pathway" governed by 5'-deiodinase by which T_4 is monodeiodinated or converted to reverse triiodothyronine (rT_3), an inactive metabolite. The suppression of the 5'-deiodinase enzyme explains the often dramatic lowering of serum T_3 levels and rise in rT_3 levels seen in the ESS.

Irrespective of serum hormone levels, whether or not there is transport of thyroid hormone to cellular receptors is yet another issue. Several studies have indicated that cells do not uptake thyroid hormone in the setting of systemic illness as they would in a more physiologic state (2), presumably related to altered nuclear T_3 receptor-binding capacity (3). In the absence of data, one can only speculate as to whether these changes represent a desired adaptation or a maladaptation to the stress, and whether further increasing serum hormone levels might have a beneficial or harmful effect. As suggested by Glinoer (4), correcting the serum levels would be useless if transport were impaired, but could increase tissue levels to a dangerously supraphysiologic hyperthyroid range if transport were not impaired.

Tri-iodothyronine (T_3), reverse tri-iodothyronine (rT_3)

The designation "low T_3 syndrome" is synonymous with ESS and is obviously based on the dramatic reductions seen in serum T_3 with illness, secondary to decreased conversion of T_4 to T_3 related to inhibition of 5'-deiodinase. Decreased conversion of reverse T_3 to its metabolites is also seen, as the same enzyme is responsible for these two metabolic processes. As a result, serum total and free T_3 concentration drop while that of rT_3 rises. All of the factors influencing the activity of these enzymes in health and disease (e.g. fasting, drugs, acidosis) are yet to be elucidated.

Thyroid Stimulating Hormone (TSH)

Under normal conditions, there is a tightly regulated feedback loop between the hypothalamus, the pituitary gland and the thyroid gland, keeping thyroid hormone and TSH levels in a relatively tight physiologic range for each individual. In the setting of nonthyroidal illness, TSH concentration is normal or slightly low, and several factors are known to suppress TSH in this setting, including steroids and dopamine. It has been speculated that the suppression may be related in part to the relative hypercortisolism occurring during stress, and other factors have been implicated including somatostatin, tumor necrosis factor and other cytokines. A diagnostic dilemma created by this drop of the TSH is the distinction of NTI from hyperthyroidism (typically presenting with low TSH as well). The advent of highly sensitive TSH assays with continually decreasing lower detection limits has offered the most useful tool for this purpose. In general, it would be very rare for TSH to fall below 0.05 μU/ml in the setting of NTI. Commonly, but not uniformly, TSH levels will be observed to rise, sometimes above the reference range, during the recovery phase of the non-thyroidal illness, followed by normalization of the thyroid hormone levels (5).

THE THYROID AXIS AND THE CARDIAC PATIENT

Proponents for the treatment of critically ill patients with thyroid hormone often use as justification several of the effects of thyroid hormone on the cardiovascular system and its possible salutary effects on hemodynamics in cardiac patients. In this context, some of these observations deserve review because the alterations in thyroid economy observed during cardiopulmonary bypass in humans are similar to those seen with other types of systemic stress. These changes include a decline of T_3 (as much as 75%), a rise of reverse T_3 (sometimes as pronounced as 300%) and a usually normal T_4, and have been noted in patients undergoing off-pump coronary artery bypass as well as in acute ischemic syndromes.

A number of animal studies have reported a beneficial effect of T_3 administration on the heart such as

the positive inotropic effect by T_3 on isolated papillary muscle function. When animals undergo cardiopulmonary bypass, an increase of anaerobic metabolism products such as lactate is seen, together with a decrease in creatine phosphate and adenosine triphosphate (ATP). Removal of the aortic cross-clamp results in reversal of these changes. If T_3 is given, the recovery is faster and ATP levels are higher (6). This beneficial effect has been explained by proposing that T_3 facilitates recovery of the stunned myocardium by improvement in local and global contractile function, in ventriculoarterial coupling, and in improved energy efficiency (7). On the other hand, there is evidence to suggest that the low T_3 state is actually protective. There seems to be a close correlation between the fall of T_3 levels and a rise of catecholamines and the risk that therapeutic repletion with T_3 would increase adverse outcomes, likely because of thyroid-catecholamine interactions (8). While both schools of thought are interesting and provocative, we do not believe that it is possible to draw any concrete conclusions about this issue on the data extant, particularly because many of the studies were inadequately controlled.

Uncertainty about any role for thyroid hormone replacement is increased by the results of studies of patients undergoing cardiopulmonary bypass in whom there were no significant increases in TSH implying the absence of physiologic thyroid hormone deficiency (9) and the conclusion that these patients remain euthyroid. Other workers have concluded that there was a beneficial effect of T_3 in patients given iv T_3 during coronary bypass surgery in whom circulatory collapse seemed imminent (10). Because the models of cardiac dysfunction both in man and experimental animals have been so varied, it is possible that the effect of T_3 administration may depend on the underlying type and degree of cardiac dysfunction. In one study (11), a low (<30%) left ventricular ejection fraction (LVEF) was associated with a significant reduction in the need for inotropes and diuretics, but not with any improvement in the perioperative mortality during the first 24 h after surgery. An opposite effect was noted in patients with higher LVEF (>40%). Other evidence (12, 13) indicated that, although administration of iv T_3 improves cardiac index and lowers systemic vascular resistance, there is no change in either the outcome or the need for standard care for these patients. To further stress the conflicting nature of the available evidence, another recent study did show improved outcome with T_3 treatment (14), although myocardial contractility does not seem to be affected by the presence of low T_3 levels (15). It has also been suggested that patients with advanced congestive heart failure may benefit from thyroid hormone administration (16). While an improved cardiac index and decreased systemic vascular resistance may be the basis for this benefit, concerns remain regarding the well-described complications of T_3 administration, namely ischemia (even in the absence of any significant coronary disease), increased oxygen demand, coronary spasm and arrhythmia (17).

THYROID AXIS IN THE SETTING OF FASTING AND STARVATION

Most hospitalized patients with significant non-thyroidal illness will suffer from some degree of caloric deprivation. Hence, experimental models of the effects of starvation or malnutrition on thyroid hormone economy are relevant to our understanding of the pathophysiology of the ESS and possible need for treatment of these patients. In starvation, the serum T_3 level is low without any significant changes in the concentration of T_4 or TSH. A well-documented decline in the rate of protein catabolism has been observed during periods of starvation, as evidenced by a reduction of urinary nitrogen and 3-methyl histidine excretion (18). Unfortunately, conflicting evidence exists for the usefulness of thyroid hormone supplementation in this setting. Rather, there is evidence to suggest that T_3 administration in this setting results in increased nitrogen excretion, reflecting increased muscle breakdown. Treatment with doses of T_3 that result in supraphysiologic concentrations has an augmented negative effect on both fat and protein catabolism. This would suggest that the diminished serum T_3 seen in the fasted state may actually be physiologic and play a critical protective and homeostatic role in the conservation of muscle mass. Extrapolation of this precept to the administration of thyroid hormone to critically ill hospitalized patients who are frequently relatively poorly nourished implies that such treatment may be harmful and result in enhanced muscle breakdown. Conceivably, this could impair respiratory muscle function and prolong the need for mechanical ventilatory support. We are most impressed with the fact that negative nitrogen balance is not observed when T_3 is administered in the fed state, implying again that the reduction in T_3 plays a protective role during fasting.

THYROID HORMONE AND TRANSPLANTATION

An extraordinarily large number of studies have explored a possible role for thyroid hormone thera-

py in the brain dead organ donor, many of whom ostensibly demonstrate improved transplant graft survival and reduced post-transplantation complications with T_3 therapy. Many of these studies have been strongly criticized because the supporting data were not collected in a controlled fashion. On the contrary, the only well-controlled evidence collected from human subjects that is available today (19, 20) would suggest no benefit from T_3 administration in transplantation.

THYROID AXIS AND PULMONARY DISEASES

Most of the available data about the role of thyroid hormones in pulmonary diseases in the intensive care unit (ICU) setting come from *in vitro* studies or the study of either animal models or newborns with, or at risk of, respiratory distress syndrome. Thyroid hormone receptors are present on type II pneumocytes and have been implicated in the regulation of pulmonary function. Based on animal studies, T_3 administration is thought to attenuate sepsis-induced surfactant dysfunction. It causes favorable changes in the transcription of surfactant apoproteins and increases the presence of surfactant in the lung resulting in less alveolar consolidation and greater maintenance of lung integrity. In humans, maternal administration of T_4 does not improve fetal thyroid hormone status, but there is an increase in surfactant activity when T_3 is given to the fetus in utero. There are data suggesting that maternal administration of TRH (which crosses the placenta), together with steroids, may yield a greater degree of improvement in surfactant production, with fewer newborns developing respiratory distress syndrome. When T_3 is given to intubated preterm infants, the only benefit appears to be a smaller FIO2 requirement to maintain an adequate arterial oxygen partial pressure. While a benefit of T_3 therapy in fetal respiratory distress syndrome may be possible, extrapolating all this evidence to critically ill adults is not possible, and further studies are needed in this patient population. At present, there would not appear to be any indications for thyroid hormone therapy in order to improve lung recovery in critically ill adults.

THYROID HORMONE IN SEPSIS, BURNS AND SHOCK

Patients with septic shock may have the most profound demonstration of abnormal thyroid function tests comprising the ESS and hence constitute a particularly interesting group of patients in whom to examine potential benefits of T_3 therapy. Early animal data suggested that there is not only no benefit from thyroid hormone replacement, but moreover, a harmful effect is seen manifested as a reduction in the time to death and a significant increase in the total number of deaths (21, 22). On the positive side is one study that suggested improvement of renal function and a faster weaning time from pressors in septic patients treated with iv T_3 (23). There are some animal data available to suggest that administration of T_3 minimizes the sepsis-induced decrease in anti-thrombin III concentration (24), a phenomenon observed during disseminated intravascular coagulation (DIC).
Patients with profound changes of the ESS suffering from severe thermal injury and burns constitute another population of the critically ill with high mortality rates from pneumonia and sepsis for whom T_3 therapy has been proposed. In studies to date, administration of thyroid hormone in the form of T_3 in this setting seems to have little to no effect on rates of recovery or mortality (25). Other data suggest that there is a significant role of catecholamine metabolism underlying the metabolic changes seen in those burn patients that are largely independent of the thyroid axis.

CONCLUSIONS: SHOULD WE TREAT SICK PATIENTS WITH T_3?

We believe that the decreased conversion of T_4 to T_3 that is the hallmark of the thyroid changes in nonthyroidal illness has selectively evolved to promote survival. Replacement with thyroid hormone, as either T_4 or T_3 in shock, sepsis, trauma, bypass surgery, heart failure, myocardial infarction, or starvation implies some compulsion to reverse the metabolic responses which have been activated during illness to give the host an adaptive advantage during times of stress. We do not believe that there are any conclusive studies indicating that administration of thyroid hormone to the critically ill patient results in long-term benefit, improved morbidity or mortality. Rather, well-conducted studies performed on fasting patients have provided evidence that the decrease in T_3 is a protective measure that spares muscle breakdown. Actions of T_3 that may improve metabolic and hemodynamic outcomes in the patient with myocardial ischemia, improve surfactant production in the patient with respiratory distress, and improve recovery in the patient with renal failure are mostly unproven. Certainly, the potentially detrimental effects of thyroid hormone administration on the heart and bones when given to clinically euthyroid patients must be borne in mind. Moreover, while total T_3 is reduced in the ESS, Chopra (26) observed normal free T_3 in 83% of ESS patients and concluded it was likely to be responsible for maintaining the euthyroid state.

It is untenable to be dogmatic on this issue, because there are several important impediments to making a fully informed decision as to whether any patients with non-thyroidal illness should receive T_3 or T_4 therapy. The literature on this topic typically reported on small numbers of patients, often with marginal results that may not be widely applicable. Clearly, the animal models cannot be directly extrapolated to man. Moreover, it is difficult to know which end points are relevant, other than mortality which in ICU patients is often due to multifactorial causes. Given these caveats, a practising physician must make clinical conclusions with little experimental support. Our philosophy that therapy is not warranted is based upon the premise that patients with ESS are usually euthyroid (with normal TSH, free T_4 and free T_3 concentrations) with little convincing evidence of the presence of hypothyroidism. This rationale is supported by the fact that TSH levels do indeed rise to above the normal range in sick hypothyroid patients.

The approach to the ICU patient with abnormal thyroid function tests compatible with systemic illness should include a clinical assessment in addition to an examination of the blood test results. To determine whether there might be some underlying thyroid disease, it could be useful to obtain history of a prior overactive thyroid, thyroid surgery or radioiodine therapy, family history of thyroid disease, or prior thyroid function studies. On physical examination, the physician should look for evidence of previous thyroid surgery and the presence of signs suggestive of hypothyroidism. Attention should be paid to any history of administered medications in the ICU setting which interfere with thyroid function, such as phenytoin, dopamine, iv contrast agents, and high dose corticosteroids.

For all the reasons discussed above, we believe that there is no indication for the use of thyroid hormone supplementation in critically ill patients whose thyroid hormone abnormalities are consistent with the ESS. On the other hand, we would initiate a judicious trial of therapy with T_4 or T_3 if the TSH is elevated greater than 5 μU/ml, and especially if the Free T_4 is also decreased. An argument may be made for using T_3 rather than T_4 because the sick patient will only slowly convert the T_4 to T_3 due to the inhibition of 5'-deiodinase. One study employing T_4 treatment of critically ill patients showed no benefit of therapy (27). And finally, the patient with hypothalamic-pituitary disease may be encountered in the ICU, and such patients will have central hypothyroidism complicating their critical illness with inability to raise their serum TSH. These patients also require thyroid hormone replacement, a decision that may be based upon history of pituitary disease, MRI or CT findings of a pituitary tumor, low free T_4, or other clinical grounds. Our reluctance to consider T_4 or T_3 therapy would be lessened as well in pregnant patients at high risk for pre-term delivery and the respiratory distress syndrome. Another exception may be patients with prolonged systemic illness (particularly those in coma) which may lead to relative hormone deficiency as a result of persistently low TSH levels with secondarily reduced thyroidal stimulation. Our opinions are at variance with recognized expert thyroidologists such as Dr. DeGroot[1] and it is likely that such differences in opinion and approach to T_3 treatment of patients with non-thyroidal illness will continue until some proof of therapeutic efficacy is demonstrated.

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[1]My good friend, Les DeGroot, is a conservative Republican in his politics and I am a liberal Democrat. However, in the case of the issue of thyroid hormone treatment of non-thyroidal illness, our roles are reversed. He would aggressively treat with T_3 while I would conservatively await evidence of benefit, adhering to the time-proven dictum of *primum non nocere*. Leslie would classify me as a proponent of the school of thought that he has named "nature's wisdom – don't treat" (28). Indeed, there are countless examples of the folly of going against nature's wisdom and believing that we men and women of medicine know better. A recent example of a possibly analogous misguided attempt to improve upon Mother Nature is the finding of the Womens' Health Initiative (WHI) in the USA that hormone replacement therapy in postmenopausal women was more harmful than beneficial (L.W.)

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