Commentary

The role of thyroid hormone therapy in acutely ill cardiac patients

Kathleen L Wyne

Assistant Professor, Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Author for correspondence: Kathleen L Wyne, kathleen.wyne@utsouthwestern.edu

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Abstract

The presence of a 'low T_3 syndrome' in the setting of nonthyroidal illness has long been recognized as the 'euthyroid sick syndrome', with the recommendation to observe and not treat with thyroid hormone replacement therapy. That approach has recently been challenged in the setting of critical cardiac illness. Research demonstrating that thyroid hormone therapy may improve hemodynamic parameters has rekindled interest in the use of thyroid hormone therapy in critical illness. Continued improvements in survival after critical cardiac illness provokes the question of whether thyroid hormone therapy would provide further incremental benefit.

The question of whether thyroid hormone supplementation should be provided to critically ill patients without a known history of thyroid disease is not a new debate [1]. Analysis of such patients led to the recognition of the euthyroid sick syndrome, which is characterized by low normal thyroxine (T_4) levels, low normal 3,5,3′-tri-iodothyronine (T_3) levels, variable thyroid-stimulating hormone (TSH) levels and elevated 3,3′,5′-tri-iodothyronine (reverse T_3; rT_3) levels. The physiologic changes that lead to these alterations are the body's attempt to conserve metabolism during illness. T_4 is normally metabolized through sequential deiodination to T_3 then to 3,3′-di-iodothyronine (T_2), which is then rapidly degraded to monoiodothyronines and thyronine [2]. Normally, about 40% of secreted T_4 is monodeiodinated in the 5′ position to yield T_3, and a similar fraction is monodeiodinated in the 5 position to yield rT_3. The body responds to illness by shunting T_4 disproportionately towards rT_3, which cannot be converted to the biologically active form of T_3 but only deiodinated to T_2.

Although this process makes sense teleologically as a form of conservation of energy, these authors raise the question of whether this could actually impair the body's response to the acute illness, namely the myocardial ischemia [3]. Unfortunately, they initially try to create an argument that the acute episode was associated with relative hypotension to the hypothalamic–pituitary axis leading to a 'low T_3 syndrome', although they are not able to offer any proof that such ischemia occurs in their cohort. They do mention the more likely etiology, which is cytokine-mediated suppression of T_3 production. Cytokines, including IL-6, IL-1, and tumor necrosis factor-α, contribute to the suppression of the 5′ deiodinase, thus shunting T_4 into rT_3 [4]. Cytokines can also contribute to the suppression of TSH. This raises an interesting question of whether the level of TSH, either in itself or in how it changes over the illness, has any prognostic information. Critically ill patients with the euthyroid sick syndrome can have a very low TSH level or it can be as high as 20 μIU/ml [5]. It is very possible that the higher TSH level represents recovery manifested as an asynchronous return of the hypothalamic–pituitary and thyroid axes to normal. Thus, as they recover from the acute illness they seem, transiently, to have a form of primary hypothyroidism. Because one does not know what phase of recovery a patient has reached, we have focused on maintaining the T_4, which is the 'storage form' of the hormone, in the normal range.

This study of patients with acute cardiac illness is of interest because the authors are proposing that as we are able to resuscitate many of these acutely ill patients they will then have increased T_4 requirements, and the 'low T_3 syndrome' might actually hinder our efforts. If this is a true 'low T_3 syndrome' due to hypothalamic–pituitary ischemia, combination T_4/T_3 therapy might be of value during the period of decreased production. This could be differentiated from the euthyroid sick syndrome by measuring reverse T_3 levels. If it were truly a simple deficit in T_3 production, reverse T_3 should also be low. If reverse T_3 is high, then what these authors are describing is truly the euthyroid sick syndrome. Although the traditional approach is to not treat the euthyroid sick syndrome with levothyroxine because it will all be

IL = interleukin; rT_3 = 3,3′,5′-tri-iodothyronine (reverse T_3); T_3 = 3,3′,5-tri-iodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

shunted into rT_3, the authors ask whether we should consider treating cardiac patients who have the euthyroid sick syndrome with T_3 (and not T_4) to facilitate cardiac recovery.

There is now evidence that the provision of T_3 improves hemodynamic parameters after open-heart surgery [6-8]. Studies in animals have shown that T_3 administration after an acute myocardial infarction is associated with a better left ventricular ejection fraction, which is very thought-provoking because left ventricular function is an important indicator of outcome after an acute myocardial infarction [9]. Although there will be resistance from the endocrinology community to trials of T_3 therapy in acutely ill patients, one must carefully consider whether it might have utility in a specific subset of patients – as these authors propose – who have an acute myocardial event. For that reason, this issue might need to be considered seriously in a prospective randomized trial.

Competing interests

The author(s) declare that they have no competing interests.

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