Heart disease in patients with thyroid dysfunction: hyperthyroidism, hypothyroidism and beyond

Tiroid disfonksiyonlu hastalarda kalp hastalığı: Hipertiroidi, hipotiroidi ve ötesi

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ABSTRACT

The thyroid and the cardiovascular system are closely related, both in physiological and pathological conditions. The adverse consequences on the heart of overt thyroid disease are well-known and even subclinical forms of both hyperthyroidism and hypothyroidism are associated with increased cardiovascular mortality. In recent years, attention has shifted towards milder forms of thyroid disease, such as the so-called "low T3 syndrome", which is characterized by an isolated reduction in circulating levels of the biologically active form of thyroid hormone, triiodothyronine (T3). Furthermore, variations of T3 within the physiological range have been linked to coronary artery disease, one of the leading causes of morbidity and mortality worldwide. The present manuscript provides an overview of thyroid physiology and pathophysiology, with a particular focus on cardiovascular disease in patients with milder forms of thyroid dysfunction.
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Key words: Coronary artery disease, heart disease, prognosis, thyroid dysfunction

ÖZET

Tiroit ve kardiyovasküler sistem hem fizyolojik hem patolojik durumlarla yakından ilişkilidir. Aşikar tiroid hastalığının kalp üzerindeki olumsuz sonuçları iyi bilinmektedir ve hatta hem hipertiroidinin hem de hipotiroidinin subklinik formları bile kardiyovasküler mortalite artışı ile ilişkilidir. Son yıllarda, dikkatler triiodothyronine (T3), tiroid hormonunun biyolojik aktif formunun dolaşımdaki düzeylerinde izole olan reduksiyonu ile karakterize "düşük T3 sendromu" gibi söylenen tiroid hastalığının daha hafif formlarına doğru kaymıştır. Ayrıca, fizyolojik sınırlardaki T3'ün varyasyonları dünyada, morbidite ve mortalite nedenlerinin başında gelenlerinden koroner arter hastalığı ile bağlantılı bulunmuştur. Sunulan yazı tiroid disfonksiyonunun daha hafif formlu hastalarda kardiyovasküler hastalık üzerinde özellikle odaklanarak, tiroid fizyolojisi ve patofizyolojisini gözden geçirmeyi sağlamaktadır. *(Anadolu Kardiyol Derg 2013; 13: 62-6)*
Anahtar kelimeler: Koroner arter hastalığı, kalp hastalığı, prognoz, tiroid disfonksiyonu

Introduction

Thyroid hormone is secreted by the thyroid gland in its inactive form, thyroxine (T4). Production of T4 is regulated by thyroid-stimulating hormone (TSH) released by the anterior pituitary gland which, in turn, is under the influence of thyrotropin-releasing hormone produced in the hypothalamus. Homeostasis is maintained by a negative feedback loop of thyroid hormone which acts on both the hypothalamus and the anterior pituitary gland. Once T4 reaches the peripheral tissues, it is converted into its biologically active form, triiodothyronine (T3), by the deiodinase enzyme. Thyroid hormone has numerous effects on the cardiovascular system in physiological conditions which are mediated prevalently by intracellular

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receptors, but also through non genomic pathways. In particular, T3 increases heart rate and cardiac contractility, and reduces systemic vascular resistance by acting directly on smooth muscle cells. The fall in peripheral vascular tone causes a reduction in effective arterial volume which activates the renin-angiotensin-aldosterone axis with a subsequent increase in circulating volume, which is accentuated by thyroid hormone-stimulated secretion of erythropoietin. The summed effect of all these actions of thyroid hormone is an increase in cardiac output.

The heart in overt hyperthyroidism and hypothyroidism

Thyroid disease is frequent and has a prevalence that reaches 15% in adult females. Inter-gender differences may be explained considering the role of autoimmunity in the pathogenesis of the most common forms of hyperthyroidism and hypothyroidism, which are, respectively, Graves' disease and Hashimoto's disease (1). In hyperthyroidism, thyroid hormone has the same effects as those observed in physiological conditions, but they are amplified. For this reason, patients refer palpitations ascribable to tachycardia and cardiac output is even three times greater than in normal conditions. In certain cases, heart failure secondary to persistently elevated heart rate or direct myocardial involvement (i.e. hyperthyroid cardiomyopathy) (2) may be observed. A typical cardiovascular manifestation of hyperthyroidism is atrial fibrillation, which can be mitigated by beta-blocker therapy and cured definitively through normalization of thyroid function, with thyrostatics, surgical thyroidectomy or ^{131}I-radioiodine (3). Coronary artery disease (CAD), on the other hand, is not frequent in this setting in the absence of traditional coronary risk factors, although hyperthyroidism may aggravate preexisting CAD due to an increase in myocardial oxygen demand. In addition, coronary vasospasm has been described in patients with hyperthyroidism (1).

The hemodynamic changes that are present in hypothyroidism are opposite to those of hyperthyroidism and include bradycardia and narrowed pulse pressure. In contrast to hyperthyroidism, ventricular arrhythmias, favored by prolongation of the QT interval, are more frequent than atrial arrhythmias. In some cases, Torsade de Pointes have been reported (3). Hypothyroidism, contrary to hyperthyroidism, may accelerate the progression of CAD (3) through various mechanisms. For example, risk factors, such as arterial hypertension and dyslipidemia, have a higher prevalence in patients with hypothyroidism (4). Hypothyroidism may also lead to systemic inflammation, hyperhomocysteinemia, endothelial dysfunction, hypercoagulability, impaired fibrinolysis, and platelet abnormalities (4). Importantly, many of these alterations are reversible once thyroid function has been normalized (5, 6).

The heart in subclinical forms of thyroid disease

Subclinical thyroid disease has been the focus of numerous studies in recent years. Rodondi et al. (7), examining data from more than 3000 subjects enrolled in the Cardiovascular Health Study with a mean follow-up of 12 years, demonstrated that patients with subclinical hypothyroidism have an increased risk of heart failure and a higher prevalence of cardiac abnormalities at echocardiography, especially when TSH is greater than 10 mU/L. In particular, E wave velocity, an index of diastolic function, and left ventricular mass, which is an important determinant of diastolic relaxation, are higher in patients with subclinical hypothyroidism. Of note, in this study subclinical hyperthyroidism was not predictive of heart failure risk. Subsequently, the Thyroid Studies Collaboration (8) carried out in more than 55000 patients an individual participant data analysis which has two important advantages compared to traditional meta-analyses: they are not as subject to bias and they allow the performance of time-to-event analyses. In their study, the authors showed that subclinical hypothyroidism is associated with in an increased incidence of death and other adverse events secondary to CAD. Coincidentally, a TSH value of 10 mUI/L emerged once again as the ideal cutoff to identify patients at particularly high risk. A similar type of analysis performed by the same group, but this time in patients with subclinical hyperthyroidism, revealed that isolated reductions in TSH, especially if less than 0.10 mUI/L, may lead to atrial fibrillation, as well as to an increase in the risk of total and CAD related mortality (9).

Whether population screening for and treatment of subclinical forms of thyroid disease are advantageous from a cardiovascular standpoint remains a matter of debate (10). Recommendations for screening vary between professional societies and some have advocated its use only in high-risk individuals. The cardiac benefits of treating subclinical hyperthyroidism include a reduction in left ventricular mass index and in the incidence of atrial and ventricular arrhythmias (11). In subclinical hypothyroidism, replacement therapy improves endothelial function and coronary risk profile (5, 12), reduces carotid intima-media thickness (13), and prevents heart failure events (7). More importantly, a reduction in CAD related morbidity and mortality has also been documented in this context, such as in the Wickham Survey which included more than 2000 individuals with a follow-up of 20 years (14). However, in a more recent report by Razvi et al. (15), conducted in almost 5000 subjects with subclinical hypothyroidism followed-up to a median of 7.6 years, although levoT4 therapy reduced the incidence of CAD events, the benefits were limited to younger (less than 70 years old) patients.

T3: from variations in the physiological range to "low T3 syndrome"

To exert its effects, thyroid hormone must be converted into its biologically active form, T3, by the deiodinase enzyme localized in peripheral tissues. "Low T3 syndrome" is characterized by an isolated reduction of T3, with normal serum levels of TSH and T4, and is caused by inhibition of the deiodinase enzyme. Although

low T3 syndrome (also known as non thyroidal illness syndrome and euthyroid sick syndrome) was once considered a beneficial adaptive mechanism under conditions of stress (16), several studies have shown that the syndrome has an adverse prognostic impact in various clinical contexts, ranging from chronic heart failure to acute myocardial infarction (17-19). In patients with heart failure, low T3 syndrome alters cardiac function directly and several mechanisms - from abnormal expression of genes encoding myocardial contractile proteins and cardiac ion channels to QT interval prolongation (20) - have been implicated in the process. Interestingly, the antiarrhythmic drug amiodarone, which is notoriously recognized for its side effects on the thyroid, leads to an isolated 20-25% reduction in T3 levels in most patients with normal thyroid function due to inhibition of the aforementioned deiodinase enzyme. Coceani et al. (21) have recently advanced the hypothesis that amiodarone may have an adverse impact on survival in patients with heart failure due to the induction of a iatrogenic low T3 syndrome. The clinical implications of such an effect, if confirmed in future studies, are potentially significant considering that amiodarone is the only antiarrhythmic drug which may be used in patients with heart failure, for example to maintain sinus rhythm and prevent ventricular arrhythmias in implantable cardioverter-defibrillator carriers (22). Amiodarone will continue to maintain this exclusive role in the near future because other commonly employed antiarrhythmic agents cannot be administered in this particular context. Even dronedarone, the novel iodine-free amiodarone derivative, is now contraindicated in heart failure in light of the disappointing and unexpected results of the ANDROMEDA study (23).

In patients without a history of either thyroid or cardiac disease, Coceani et al. (24) have demonstrated that free T3 levels are inversely correlated to the presence of CAD and that low T3 syndrome confers an adverse prognosis, even after adjusting for traditional coronary risk factors. TSH and T4, instead, were not associated with the presence of CAD in this study. Similar observations had been made previously by Auer et al. (25), although it should be kept in mind that the latter study enrolled a relatively small group of patients whose characteristics were not well defined. In particular, the prevalence of myocardial infarction and revascularization was not specified. Perhaps more importantly, the mean left ventricular ejection fraction of the population was not described, an important limitation considering the strong link which exists between heart failure and thyroid dysfunction (17, 18).

In a recent observational study by Ertas et al. (26), T3 levels within the physiological range were once again found to be inversely correlated with the presence and severity of CAD. The authors enrolled 119 consecutive patients with stable angina pectoris scheduled for coronary angiography. Exclusion criteria included acute coronary syndrome, a history of thyroid disease, amiodarone therapy and significant extracardiac illness. The population, therefore, was highly selected and homogenous, as in the study of Coceani et al. (24). Furthermore, thyroid hormone was measured before coronary angiography, an important precaution in view of the potential interference of iodinated contrast media with thyroid metabolism, and coronary angiographies were reviewed by two blinded interventional cardiologists, which limited potential bias in the analysis of data. The authors of the present paper went one step further compared to Coceani et al. (24) in so far as CAD severity was evaluated through the Gensini score, a widely accepted and validated coronary angiography scoring system. In particular, coronary lesions fall into one of six categories, ranging from contour irregularities to a complete occlusion, and the score of each lesion is then multiplied by a factor that takes into account its site in the coronary tree, with higher values reserved for more critical positions (for example, the left main coronary artery is assigned a corrective factor of 5, whereas the distal left anterior descending coronary artery has a factor of only 1). The final score is obtained by summing the final values of all the lesions identified at coronary angiography. In their study, Ertaş et al. (26) divided the population into two groups (mild and severe CAD) according to the Gensini score.

The authors reported that free T3 levels were significantly lower in subjects with CAD compared to those without CAD (4.0±0.7 vs. 4.6±0.6 pmol/L, $p<0.001$). Moreover, free T3 was lower in patients with severe compared to mild CAD (3.9±0.7 vs. 4.5±0.6 pmol/L, $p<0.001$). The importance of T3 was confirmed at logistic regression analysis. Indeed, free T3 maintained its predictive value for both the presence (OR 0.266, 95% CI 0.097-0.731, $p=0.01$) and severity (OR 0.238, 95% CI 0.083-0.685, $p=0.008$) of CAD. As in the study of Coceani et al. (24) free T4 and TSH were similar in patients with and without CAD. The authors also performed receiver operator characteristic analysis, which showed that a free T3 value below 4.2 pmol/L predicted the presence of CAD with a sensitivity of 69% and specificity of 71% (area under the curve 0.744, 95% CI 0.653-0.834, $p<0.001$), whereas in the case of CAD severity, sensitivity and specificity were 75% and 67%, respectively (area under the curve 0.733, 95% CI 0.642-0.824, $p<0.001$). Although statistically significant, it should be noted that the values of area under the curve were relatively low and, as a result, the predictive value of T3 should be considered modest at most. In addition, the authors should have provided measures of calibration, discrimination, and reclassification, rather than rely solely on the c statistic (27).

All of the studies examining the relationship between T3 and CAD have several limitations. Specifically, thyroid hormone was measured only once generally and, as a result, eventual variations in T3 levels over time, and their consequences on cardiovascular morbidity and mortality, remained undetected. Perhaps more importantly, any definitive statement regarding the causal role of T3 in CAD cannot be made until an appropriately designed study demonstrates that T3 supplementation in patients with low T3 syndrome slows the progression of CAD. To this end, basic science studies would also be needed to investigate the potential underlying pathophysiological mechanisms. However, consider-

ing that hypothyroidism, even if subclinical, increases the risk of CAD and that T3 therapy has proven benefits in diverse forms of heart disease (28, 29), any reduction in T3 should not be viewed as a simple marker of cardiovascular disease.

Notwithstanding the aforementioned limitations, clinicians should not ignore thyroid function, which should always be assessed in patients at risk of CAD. In this way, one may also exclude latent hyperthyroidism prior to coronary angiography as well as dyslipidemia secondary to hypothyroidism, for which statins do not represent a first-line therapy. Furthermore, measurement of thyroid hormone, particularly if compared to that of other biomarkers, is simple, inexpensive, highly reproducible, may be performed in most laboratories, and is easy to interpret even by non specialists. In Figure 1, the correlations between thyroid function, coronary risk factors, and CAD are summarized.

Conclusions

The thyroid plays a fundamental role in the maintenance of cardiovascular homeostasis. Not surprisingly, thyroid disease is associated with several adverse consequences on the cardiovascular system. Numerous studies have demonstrated that the distinction between normal and abnormal thyroid function is not as clear-cut as was once believed. Indeed, mild forms of thyroid disease and even variations of thyroid hormone within the physiological range have been linked to adverse cardiovascular prognosis. For this reason, thyroid hormone should not be considered dichotomously but, on the contrary, clinicians need to examine thyroid testing results as a continuous variable, in a similar manner to accepted coronary risk factors, such as blood pressure, glycemia and cholesterol. In the future, dedicated studies will need to establish which patients with mildly abnormal thyroid function need a targeted medical therapy.

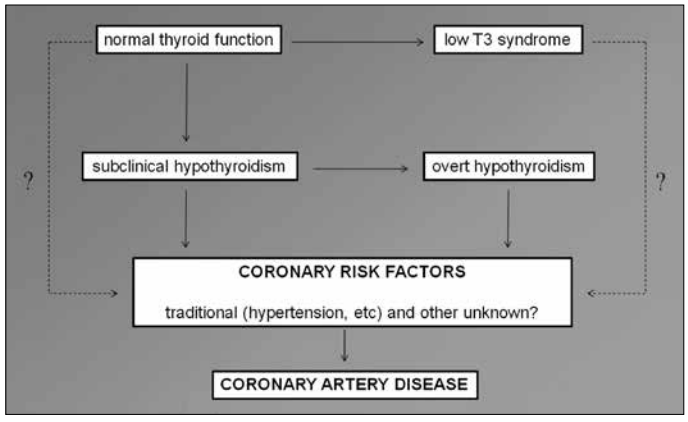

Figure 1. Hypothyroidism, both overt and subclinical, predisposes to CAD through traditional coronary risk factors (full lines). Physiological variations in T3 levels, as well as low T3 syndrome, have also been linked to the presence and severity of CAD, although the precise mechanisms underlying these associations remain unknown at the present time (dotted lines). It is conceivable that nontraditional coronary risk factors may be involved in the process

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