No role for tri-iodothyronine (T3) testing in the assessment of levothyroxine (T4) over-replacement in hypothyroid patients

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ABSTRACT

Tri-iodothyronine (T3) is a sensitive marker of endogenous hyperthyroidism. In levothyroxine (T4)-induced hyperthyroidism, there is no reason for T3 to be elevated, but this test is often requested in over-treated hypothyroid patients. This study investigated how informative T3 levels are in these patients. Our hypothesis is that T3 measurement would not add anything to the assessment of T4 over-replacement in primary hypothyroidism. Over a 15-week period, consecutive thyroid function test requests in patients on levothyroxine had T3 levels measured if thyroid-stimulating hormone (TSH) was below the reference range (RR; <0.27 miu/L) and free T4 was within or above the RR (12–22 pmol/L). Those with fully suppressed TSH (<0.02 mu/L) and high free T4 (>27 pmol/L) were defined as being over-replaced, while those with low, but measurable TSH and a normal free T4 were defined as unlikely to be over-replaced (control group). Receiver operating characteristic (ROC) curve analysis was used to assess the discriminant power of T3 to detect over-replacement. Of the 542 patients examined, 33 were included in the over-replaced group and 236 patients in the control group. A total of 273 patients were excluded for not fulfilling the criteria for either of these groups. In the over-replaced group, none had a raised T3. The most discriminant T3 level, using ROC curve analysis, was 1.6 nmol/L (RR=1.3–2.6 nmol/L), with a corresponding sensitivity and specificity of 58% and 71%, respectively (P=0.16). T3 levels bear little relation to thyroid status in patients on levothyroxine replacement, and normal levels can be seen in over-replaced patients. Measurement of T3 in this situation is of doubtful clinical value.

What's already known about this topic?: Thyroid function tests are the way that adequacy of levothyroxine replacement is determined. Where the test is available, T3 is often requested together with T4 and TSH by clinicians. The question is whether T3 measurement adds any further information.

What does this article add?: The presented data supports the position that T3 measurement does not add anything to the interpretation of thyroid hormone levels in subjects with hypothyroidism on levothyroxine replacement therapy. Unnecessary testing could be avoided if this were more widely appreciated. In addition, over-replacement, with its attendant risks, would be more readily recognised and not wrongly excluded on the basis of a falsely reassuring normal T3 result.

KEY WORDS: Hypothyroidism.
Therapeutics.
Thyroxine.
Triiodothyronine.

Introduction

The main causes of hypothyroidism are chronic autoimmune disease (e.g., goitrous autoimmune thyroiditis [Hashimoto's thyroiditis]), atrophic autoimmune thyroiditis) or destructive treatment for hyperthyroidism, which may account for up to one-third of cases of hypothyroidism in the community. In the landmark Whickham survey,[1] 8% of women (10% aged >55 years) and 3% of men had subclinical hypothyroidism.

Thyroid function tests (TFTs) have become the mainstay for optimising levothyroxine (T4) replacement therapy. Both subclinical and overt thyroid hormone abnormalities can occur in patients on thyroid medication, indicating the usefulness of determining thyroid hormone status in patients on levothyroxine therapy and the need for monitoring patients at least annually.[2]

The recommended approach in primary hypothyroidism is to titrate levothyroxine therapy against the thyroid-stimulating hormone (TSH) level while assessing clinical wellbeing and other secondary metabolic abnormalities.[2] The primary target of replacement therapy is to make the patient feel well and to achieve a serum TSH within the reference range.[3,4] Free T4 measurement is considered to be of additional value in monitoring levothyroxine treated patients since TSH takes a while to respond to changes in therapy; clearly, a role exists in patients with pituitary problems on T4 therapy in whom TSH is unreliable. However, the rationale for measuring tri-iodothyronine (T3) as a useful marker to detect over-replacement with exogenous T4 therapy is questionable.

In patients with low endogenous production of thyroid hormones on levothyroxine replacement, little T3 is likely to be secreted by the thyroid and extra-thyroidal conversion of T4 to T3 is unlikely to cause high levels of T3 in plasma. Yet, many requests in these patients include a T3 level with the

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expectation that this will aid interpretation of TFTs, particularly when T4 and TSH levels suggest over-replacement. Moreover, in many laboratories, a T3 request is added if the free T4 and TSH concentrations suggest over-replacement, again in the belief that this will aid the interpretation of results.

Based on the fact that T3 is produced endogenously in primary and secondary hyperthyroidism, but only arises after conversion from T4 in patients on levothyroxine treatment, the hypothesis of this study is that T3 would not add any discriminative power to the determination of over replacement with levothyroxine over and above review of the TSH and free T4 levels.

Materials and methods

Study period and rationale

Over a 15-week period (August to November 2010), all TFT requests in patients on levothyroxine therapy had levels of total T3 measured if the TSH level was below the reference range (0.27–4.2 mu/L) and free T4 was above or within the reference range (12–22 pmol/L). Patients were identified using the Telepath laboratory information management system (iSOFT, Sydney, Australia).

The rationale behind the present study was that if the TSH levels were in the normal range there would be no reason to suspect hyperthyroid status and to request any further tests, including T3, to exclude this. As a result, only patients on levothyroxine with a TSH below the reference range were included in this study. Moreover, this had the added advantage of testing the diagnostic value of T3 in the context in which it would actually be used in clinical practice, rather than in patients with TSH levels within the reference range.

The patients with TSH below the reference range were then subdivided into two groups. The first of these groups contained patients with a fully suppressed TSH level (<0.02 mu/L) together with free T4 levels >27 pmol/L, which were defined as clear over-replacement of levothyroxine. The second of these groups contained patients with free T4 levels within the reference range combined with a low (but not suppressed) TSH level, which were defined as excluding T4 over-replacement and acted as a control group.

Exclusions

All patients with a recent history of hyperthyroidism, hypopituitarism, or thyroid carcinoma were excluded, as were individuals treated with T3 (whose T3 levels would reflect this), carbimazole, propylthiouracil, or radioactive iodine. The latter were excluded because of the potential for some of these to relapse to thyrotoxicosis with predominant T3 toxicosis, while patients with pituitary disorders were excluded as this condition invalidates TSH as a marker of thyroid status.

Laboratory analysis

Free T4 and TSH were measured by automated immunoassay on the Roche Modular system (Roche, Basel, Switzerland). Total T3 was measured by automated immunoassay using the Siemens Immulite 2000 analyser (Siemens, Munich, Germany). This manufacturer stated that this assay does not cross-react with reverse T3. Cost data for the measurement of serum total T3 in this study were based on the reagent costs for the Siemens kits combined with the estimated staffing costs.

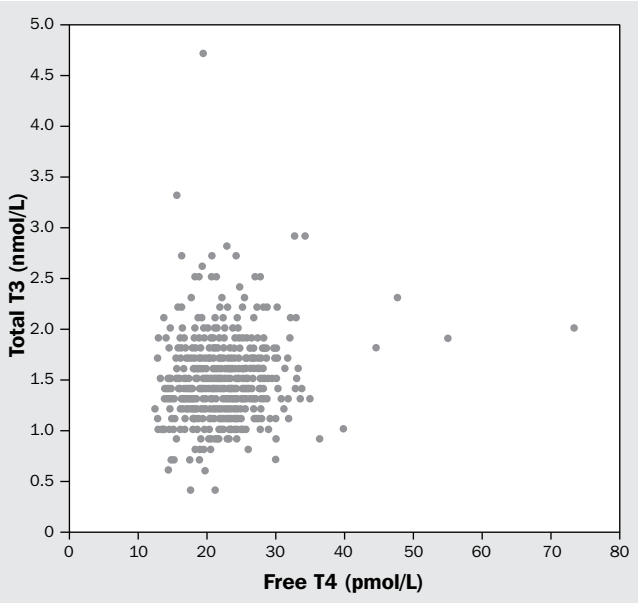

Fig. 1. Scatter plot of free T4 versus total T3 levels for all patients (n=542) included in the study.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS, Wacker Drive, Chicago, IL, USA). Receiver-operating characteristic (ROC) curve analysis was carried out to assess the discriminant power of T3 levels in determining over-replacement of levothyroxine therapy. ROC curves are used to define appropriate clinical cut-off points for different diagnostic tests. Sensitivity (probability of a positive test when disease is present) was plotted on the y-axis against 1-specificity (probability of positive test when disease is absent) on the x-axis. A ROC curve usually forms a stepped curve convex to the top left hand corner (the closer the curve is to this corner the better the test, and the corresponding sensitivity and specificity for the test). ROC curves have the advantage of displaying performance across the whole range of potential cut-off points, but they are a trade-off between sensitivity and specificity which can be visually appreciated to help decide the optimal cut-off value. Based on a power of 0.8 and P<0.05, a minimum number of 24 patients deemed to be over-replaced with levothyroxine and 142 patients not over-replaced was deemed to be required.

Results

A total of 542 patients with TSH levels below the lower end of the reference range and a free T4 within or above the reference range were included in this study. The distribution of free T4 versus T3 levels for the whole group is shown in Figure 1. No relationship was found between free T4 and T3 concentration in this group (r^2 = 0.06, n=542; P=0.25, on univariate linear regression).

Of the 542 patients, 33 were defined as being over-replaced with levothyroxine (free T4 >27 pmol/L and/or TSH <0.02 mu/L), and 236 were considered unlikely to be over-replaced (acting as the control group), with free T4 levels within the reference range combined with a low (but

not suppressed) TSH level. They were defined as excluding T4 over-replacement and acted as a control group.

A total of 273 patients were excluded for not matching these criteria because they had a TSH level within or above the laboratory normal range or free T4 below the laboratory normal range. irrespective of TSH level.

When data from suspected over-replaced (Group 1) and not over-replaced (Group 2) groups were analysed, no relationship was found between free T4 and T3 concentration in either group. (Group 1: $r^2 = 0.04$, $P=0.25$; Group 2: $r^2 = 0.07$, $P=0.18$ on univariate linear regression). Thus, measurement of T3 added little discriminant value in these patients.

None of the 33 patients in the over-replaced group had a raised total T3 level (reference range 1.3–2.6 nmol/L), while two out of the 236 patients in the control group had a high T3 level.

ROC curve analysis exploring the value of total T3 as a discriminator between cases of levothyroxine over-replacement and those classified as biochemically euthyroid revealed a gradient close to one (i.e., effectively a useless test). This analysis also identified the most discriminant T3 value as 1.6 nmol/L with a corresponding sensitivity and specificity of 58% and 71%, respectively (Fig. 2; $P=0.16$).

The total cost of each serum total T3 test was calculated to be approximately £3.75, and, therefore, the estimated cost of measuring this marker in the 542 patients included in this study was £2032 over the 15-week period (and £7046 annually). This cost includes costing for staff time and for reagents.

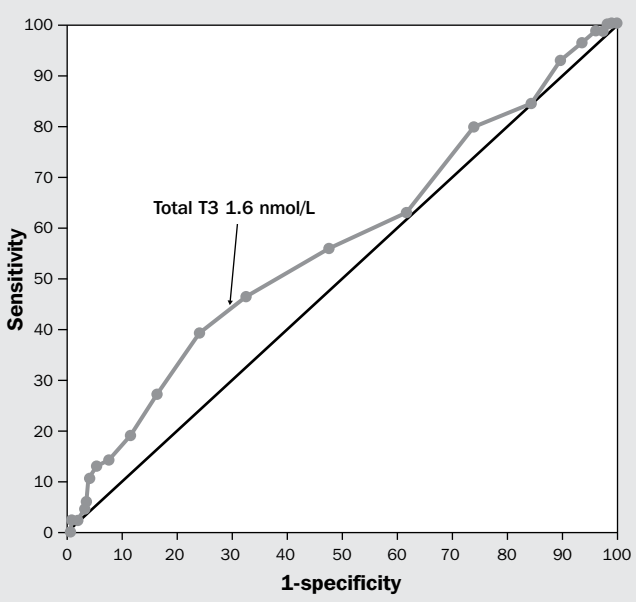

Fig. 2. Receiver operator characteristics (ROC) curve analysis for total T3 as a discriminator between cases of levothyroxine over-replacement ($n=33$) and cases that are biochemically euthyroid ($n=236$). The ROC curve is close to x=y with the greatest distance at total T3=1.6 nmol/L, with a corresponding 58% sensitivity and 71% specificity.

Discussion

This study has shown that measurement of T3 in patients on levothyroxine replacement adds little to the meaningful interpretation of TFT results. The data presented suggest that T3 levels are a poor indicator of levothyroxine over-replacement in patients with primary hypothyroidism, with a ROC curve close to the 45° line (being considered a useless test), and not a single high T3 result in the over-replaced group. Moreover, T3 is at its most discriminant at a value in the middle of the reference range. With a sensitivity and specificity of 57.6% and 71.2%, respectively, it is a poor test when used in this context, performing only marginally better than tossing a coin. Consequently, the present authors suggest that there is no rationale for T3 as a useful marker of over-replacement in patients who are on exogenous T4 therapy.

If TSH were in the reference range, it follows that there would be no reason to suspect hyperthyroid status and to request any further tests, such as T3. Therefore, patients on levothyroxine therapy with a TSH below the reference range, along with a normal or raised free T4, were deliberately chosen to be included in this study. Of these, patients with significantly elevated free T4 levels and suppressed TSH levels were defined as being over-replaced, and patients with free T4 levels within the reference range combined with a low (but not suppressed) TSH level were considered not to be over-replaced.

In order to validate the use of TSH as a marker in this classification, all patients with a history of pituitary or hypothalamic disorders were excluded. Other patients excluded were those with a history of hyperthyroidism or thyroid carcinoma, and individuals treated with liothyronine (exogenous T3), carbimazole, propylthiouracil, or radioactive iodine. The latter were excluded because of the potential for some of these to relapse to thyrotoxicosis with predominant T3 toxicosis.

Patients not on levothyroxine therapy, but in whom measurement of T3 was considered useful, especially in the presence of a low TSH, were also excluded to ensure the data obtained related to the question being asked. Clearly, there is a role for T3 measurement in patients receiving exogenous T3 in the form of liothyronine alone, or in combination with levothyroxine (only a small minority of patients in the UK), or in whom endogenous production is a concern, for example, recurrence of hyperthyroidism following surgery or radioactive iodine treatment.

When assessing thyroid status in patients treated with levothyroxine for primary hypothyroidism, the results presented in this study lead us to recommend the measurement of T4 and TSH, but not T3.

In this study, the use of a high free T4 along with a suppressed TSH to define the over-replaced group, combined with the use of a normal free T4 with low (but unsuppressed) TSH to delineate the group unlikely to be over-replaced, will have reduced the likelihood of error in allocating patients to the affected and control groups, respectively. It is important not to miss subclinical hyperthyroidism because of the associated increased mortality in older individuals.[6] This also applies to patients on levothyroxine replacement. The current study shows that these patients could be missed if a normal T3 is taken to exclude over-replacement with levothyroxine, as even in quite marked over-replacement (resulting in very high free T4 levels), T3 levels remained normal.

The recommendations in the review by Vaidya and Pearce[5] that measurement of serum TSH be the cornerstone

of monitoring levothyroxine replacement therapy is acknowledged, and a strong argument can be made for measuring free T4. However, T3 measurement is only needed when looking for recurrence of hyperthyroidism, for example, in patients following surgery or radioactive iodine treatment, when one is looking for evidence of excess endogenous thyroid hormone production.

Thyroid disorders are common and so the number of TFTs performed reflects this, with approximately 10 million requests each year in the UK, at an estimated cost of £30 million. Therefore, it is important that unnecessary measurements are prevented, as part of better testing and managing demand.[7] When money is saved on inappropriate testing, such as re-testing too often or on obsolete tests, it allows other new and useful tests to be resourced. This includes the proper use of T3 measurement in clinically appropriate situations, as described earlier. The estimated total cost of measuring this marker in the 542 patients included in the current study was £2032 over the 15-week period, which equates to £7046 annually for our laboratory. Of course, it is acknowledged that there can be difficulty identifying what thyroid medications patients are being treated with from a laboratory point of view and clinicians can help by making it clear as to which form of replacement therapy the patient is on when submitting TFT requests.

With respect to diagnosis of hypothyroidism, the British Thyroid Association Guidelines[2] state "If the serum TSH is greater than 10 mu/L and the serum free T4 concentration is low, then the subject has overt hypothyroidism and should be treated with levothyroxine. If the serum free T4 concentration is normal, but the serum TSH concentration is greater than 10 mu/L, then treatment with levothyroxine is recommended". No mention is made of total T3 as relevant to the diagnostic process. The findings presented by the current authors strongly support this position. It is worth mentioning that some hospital laboratories measure free T3 not total T3. We speculate that the findings would be similar for free T3 in terms of not adding anything to the interpretation of thyroid hormone levels in people with hypothyroidism on levothyroxine replacement therapy.

It is of note that in the Colorado Thyroid Disease Prevalence Survey, of the 1525 subjects taking thyroid medication, 17.6% had subclinical hypothyroidism, 0.7% were overtly hypothyroid, 20.7% had subclinical hyperthyroidism even though >90% had seen a healthcare provider in the previous year.[8] Similar data have been shown in UK community studies.[9,10] This all points to the importance of measuring TFTs annually in individuals on levothyroxine replacement with a corresponding change in thyroxine dose to ideally bring the TSH within the reference range.[2]

In summary, the presented data support the position that T3 measurement does not add anything to the interpretation of thyroid hormone levels in subjects with hypothyroidism on levothyroxine replacement therapy. Unnecessary testing could be avoided if this were more widely appreciated. In addition, over-replacement, with its attendant risks, would be more readily recognised and not wrongly excluded on the basis of a falsely reassuring normal T3 result.

In conclusion, T3 levels bear little relation to thyroid status in patients on levothyroxine replacement therapy, and normal T3 levels can be seen in patients who are over-replaced. Therefore, there is no role for T3 testing in assessing over-replacement of T4 therapy in hypothyroid patients. □

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