UNDERSTANDING THYROID HORMONE ACTION AND THE EFFECTS OF THYROID HORMONE REPLACEMENT – JUST THE BEGINNING NOT THE END.

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BACKGROUND

Thyroid hormone – the easiest hormone to replace?

L-Thyroxine is considered the treatment of choice for hypothyroid patients as it has a long half-life, is inexpensive to produce and provides stable levels of T4, T3 and TSH over 24-hour period. Indeed, this favourable pharmacodynamic profile linked with excellent bioavailability following oral administration and the ability to fine titrate dosing using sensitive TSH assays has led most endocrinologists to believe that, unlike all other hormones, thyroid hormone replacement is straightforward. An unwelcome challenge to this view is the proportion of hypothyroid patients that report that they are not back to their normal self despite doses of thyroxine sufficient to normalise TSH levels (1,2,3,4,5). We recently tried to quantify this problem in a community-based cross-sectional survey and observed a 6.7% absolute excess of psychiatric caseness (32.3 vs 25.6%) in patients on thyroxine compared to an age- and sex-matched control population from the same community. This difference persisted even in individuals on T4 with recent TSH levels in the laboratory reference range (6).

Is dissatisfaction on thyroxine replacement therapy related to thyroxine?

Thyroid dysfunction has two very important clinical features which distinguishes it from dysfunction in other endocrine glands: it is both very common (up to 5% of the population) (7,8) and very easy to detect. As a result there will inevitably be extensive overlap between patients with hypothyroidism and patients with other medical and psychological conditions. Hence one explanation for apparent dissatisfaction with thyroid hormone replacement is likely to arise from dysphoric patients being screened for thyroid dysfunction and then started on thyroxine for minor rises in TSH. If their symptoms were not due to hypothyroidism in the first place, they would not be expected to improve on treatment and the result will be a dissatisfied patient on thyroxine. Undoubtedly this accounts for a proportion of dissatisfaction on thyroxine and is consistent with the strong placebo effect in trials of alternative forms of thyroid hormone replacement (9,10,11). A second explanation may be that thyroid hormone at supraphysiological levels has a useful euphoric effect that is lost on dose reduction.
Thirdly, impaired psychological well-being may be related to thyroid autoimmunity, independent of the patients thyroid status as suggested by some epidemiological studies (14). At present this is difficult to quantify and the possible mechanism remains unclear. However, recent developments in the biology of thyroid hormone action and metabolism indicate that a fourth alternative explanation - relative tissue hypothyroidism – may explain at least some cases.

**Possible mechanisms resulting in tissue hypothyroidism despite normal TSH levels**

Although it has long been known that T4 needs to be converted to T3 for intracellular action, recent studies have emphasised the complexity of thyroid hormone action (see figure).

Possible sites of defective thyroid hormone metabolism

Abbreviations:

- T4 – Thyroxine; T3 – Tri-iodothyronine; TH – Thyroid Hormone;
- RXR – Retinoid X receptor; D1-3 – Deiodinases – Type 1-3; NTCP – Na+/Taurocholate co-transporting polypeptide; OATP – Organic anion transporting polypeptide; LAT1 – L-type amino acid transporter 1; MCT 8 – Monocarboxylate transporter 8

The presence of membrane thyroid hormone transporters amplifies hormone uptake by up to 10-fold (15,16). Following uptake, deiodination is carried out by not one but three selenium dependent deiodinases (D1 – D3) each with different catalytic specificity, tissue distribution and sensitivity to extracellular influences. As a result, the amount of intracellular T3 derived directly from circulating T4 rather than T3 can vary
up to 10-fold between tissues (17). In addition, thyroid hormone receptor action depends on many co-regulators (18) whose levels vary between tissues and operates via 9 different isoforms of 2 different thyroid hormone receptor genes (TRα and TRβ) whose levels also vary widely between tissues (19). Hence, although levels of circulating TSH in the reference range typically indicate normal levels of intracellular T3 in the hypothalamus and pituitary, there are several mechanisms by which such a normal TSH level may fail to indicate intracellular euthyroidism in other tissues, for example following thyroid hormone replacement (Table 1).
Major abnormalities in these pathways might result in a small subgroup of individuals being very dissatisfied with T4 replacement despite normal TSH levels, while common polymorphisms with more minor effects might result in a range of satisfaction with T4 in treated patients. Also, in the general population with an intact thyroid axis, such
common polymorphisms might represent predisposing factors for other conditions such as depression or anxiety.

**Evidence that tissue specific variation in T4 action is clinically important – studies of combined T3/T4 replacement**

At present, the evidence that mechanisms such as those described in Table 1 have clinically important effects on thyroid hormone replacement is largely circumstantial. Note that in many cases these pathways are not easy to study in vivo and variations would result in differences in intracellular thyroid hormone levels (difficult to detect) without changes in serum levels. For example, deiodinase activities are located intracellularly and may not be reflected in serum levels. However, several studies have indicated that replacement therapy with T4 alone titrated to achieve normal TSH levels results in levels of T4 in the high reference range while levels of T3 remain in the low reference range (10,11,20,21,22). This is consistent with the relatively high levels of D2 in the pituitary making it sensitive to circulating T4 levels. If the local deiodinase (D2) activity in the pituitary were low, normalisation of TSH production would only be achieved when circulating T3 levels had returned to normal levels, irrespective of T4 levels (mechanism 1, table 1). Interestingly, treatment of patients with subclinical hypothyroidism with T4 alone frequently lowers circulating T3 levels, despite normalising TSH and T4 levels (23). This is almost certainly because the up-regulation of deiodinase levels in the thyroid that occurs in thyroid failure results in increased intrathyroidal T4 to T3 conversion and this effect is lost after exogenous T4.

In the light of these observations, and consistent with mechanisms 1 and 2 in table 1, one explanation for the apparent failure of T4 replacement alone to satisfy some patients is that satisfactory T3 levels are not restored in all tissues, especially those with low deiodinase levels (24,25). This has lead to an interest in combined replacement with T3 and T4 to mimic the production by the intact thyroid gland. Earlier studies on combined T3/T4 therapy did not attract attention as many patients felt the side effects of excessive T3. The doses used in these studies would now be considered excessive (26). In 1999, the study of Bunevicius et al rejuvenated the debate in this area with encouraging results (27). However, this has been followed by several further studies published recently refuting this finding (28,29,9,30,31,32).

Why have these later studies not replicated the findings of Bunevicius et al? One explanation is that these studies used different T3/T4 combinations in different regimes (Table 2).
In addition, several reviewers have commented that the original study by Bunevicius et al used a heterogenous population on high doses of thyroxine replacement and that the substitution was for a short period of time (5 weeks) without a washout period before the cross-over (33). However, it remains possible that there is beneficial effect of

**TABLE 2: COMPARISON OF STUDIES USING COMBINED T4 / T3 THERAPY**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mean T4 dose</th>
<th>Mean FT4 Levels (pmol/L)</th>
<th>TSH Levels (mU/L)</th>
<th>T3 dose used (mcg)</th>
<th>Wellbeing</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
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<td>Before</td>
<td>After</td>
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<tr>
<td>Bunevicius 1999</td>
<td>175</td>
<td>25.7</td>
<td>23.1</td>
<td>0.8</td>
<td>0.6</td>
<td>12.6 od</td>
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<td>(n=33)</td>
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<tr>
<td>Siegmund 2004</td>
<td>130</td>
<td>22.1</td>
<td>20.1</td>
<td>1.72</td>
<td>0.5</td>
<td>14:1 T4:T3</td>
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<tr>
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<tr>
<td>Saravananan 2003</td>
<td>127</td>
<td>21.1</td>
<td>13.73</td>
<td>0.94</td>
<td>2.28</td>
<td>10 od</td>
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<tr>
<td>Bunevicius 2002</td>
<td>115</td>
<td>20.7</td>
<td>12.3</td>
<td>1.02</td>
<td>0.47</td>
<td>10 od</td>
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<td>Clyde 2002</td>
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<td>15.83</td>
<td>10.7</td>
<td>2.6</td>
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<td>Saska 2003*</td>
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<td>15.7</td>
<td>10.55</td>
<td>1.75</td>
<td>1.8 - 2.4</td>
<td>19* as bd</td>
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<tr>
<td>Walsh 2003</td>
<td>136</td>
<td>15.3</td>
<td>11.4</td>
<td>1.5</td>
<td>3.1</td>
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* T3 dose is titrated. Other studies used fixed doses of T3.
combined substitution that is smaller than that originally suggested by Bunevicius et al or that affects a small subgroup of individuals and hence was missed in the other studies (3). Our own study based on power calculations from our previous cross-sectional study (6), involved 697 individuals and showed a modest beneficial effect after 3 months (10). Interestingly, thyroid function "drifted" between 3 and 12 months of follow-up (with a fall in the T3/T4 ratio) and the effect was lost (11).

**What might be the effects of hypothyroidism in some tissues despite normal TSH?**

It is well known that thyroid hormone is important for a variety of bodily functions including thermogenesis, basal metabolic rate, memory, skeletal and myocardial muscle contractility and sleep. In subclinical hypothyroidism problems with lipid profiles (34,35,36), left ventricular contractility (37), neuromuscular conduction (38) and psychological well-being are well established. It is not clear whether these functions are completely normalised after thyroxine replacement. Small defects in any or all these functions could result in significant morbidity.

**Evidence that thyroid hormone levels are important determinants of mood?**

The motivation for reconsidering our approach to thyroid hormone replacement has come from patients who describe low mood and lack of energy on current replacement regimes. Studies in animals indicate some evidence that thyroid hormones can raise cortical serotonin levels (39). Evidence in adult humans is more limited. There is also an extensive though somewhat controversial literature concerning the use of thyroid hormone, often in supraphysiological amounts (up to 300ug/day) in treatment-resistant depression as well as reports relating to impaired response to selective serotonin reuptake inhibitors in hypothyroidism (13,40). A recent large cross-sectional study failed to show an association between thyroid hormone levels and depression and anxiety ratings although only TSH and T4 levels were compared. A correlation was observed between previously diagnosed thyroid disease and psychological ratings independent of thyroid function, which may represent evidence for a link with thyroid autoimmunity (41).

**Is it safe to "over-replace" thyroid hormone?**

While it is clear that endogenous TSH suppression in thyrotoxicosis is harmful (42,43,44), evidence is more limited if the TSH is suppressed due to exogenous thyroxine. However, several studies have shown deleterious changes in echocardiographic parameters on suppressive doses of thyroxine which are reversed by dose reduction (45,46,47,48,49,50). Recent evidence also suggests that at least in the post-menopausal women, who are the majority of patients on thyroxine replacement, bone density is reduced (51,52) and the fracture risk increases significantly on suppressive doses of thyroxine despite correcting for related variables (53). This might
also be true in men on thyroxine replacement (54). However, the relationship with TSH was not studied in that epidemiological study. There are no long-term studies of patients on T3. These studies provide evidence that increasing thyroid hormone levels to “compensate” for relative tissue hypothyroidism in some tissues, is not without risks.

FUTURE DIRECTIONS

Where do we go from here?

New developments in thyroid hormone biology have indicated multiple levels at which variations in the pathway of thyroid hormone action shown in figure 1 could have clinically important effects but at present evidence of clinical relevance is limited. To make progress in this area and determine whether inter-individual variations in the pathway of thyroid hormone action contribute to psychological morbidity, predispose to other conditions and/or determine failure to respond adequately to thyroid hormone replacement in some individuals is a complex task. Progress is required in 4 areas: (1) There is a need for new markers of thyroid action in different tissues. In particular, it will be important to determine whether individuals who respond poorly to thyroid hormone in terms of psychological well-being fail to improve in any more objective measures that could relate to thyroid hormone action e.g. sleep pattern or serotonergic responses. These could then be used to monitor response to intervention more objectively. (2) Studies are required to identify any variations or polymorphisms in elements of the pathway of thyroid hormone action- e.g. T3/rT3 ratio, deiodinase or transporter polymorphisms - which predict the psychological response to thyroid hormone or correlate with other potentially thyroid hormone related effects (eg sleep parameters, echocardiographic changes or changes in bone turnover). (3) Future intervention studies with T4 alone or in combination with T3 should be large in order (a) to carry sufficient power to see any clinical significant effect, (b) to allow correlations to be drawn between response to therapy and baseline measures of thyroid hormone action or metabolism and (c) to be sufficiently long-term enough to enable assessment of the risk to the heart and skeleton of potential overplacement. Such studies also need to be very carefully blinded to distinguish placebo effects from effects attributable to the intervention. (4) Future studies involving T3 replacement will require careful attention to dosing, dose titration and dosing ratios with T4. We have shown that despite chronic combined T3/T4 therapy wide fluctuations persist in the free T3 levels (55). Thus, use of new low-dose and slow-release preparations to allow careful monitoring and physiological replacement will be particularly valuable (56,33)

CONCLUSIONS

Despite 100 years of thyroid hormone replacement, controversy still exists about the optimum replacement therapy for hypothyroid patients. Several recent studies have
given insight into the complex thyroid hormone metabolism. These support the hypothesis that serum and tissue levels of thyroid hormones may diverge significantly and vary between tissues. The dissatisfaction experienced by some individuals on thyroxine replacement despite normal TSH levels may in part relate to this. If so, it should be seen as a pointer to greater understanding of the action of thyroid hormone and its predisposing effects on morbidity in many conditions rather than an unwelcome clinical frustration. If so, we are at the beginning of a road of discovery rather than at the end of an unsuccessful chapter in thyroid hormone replacement.

REFERENCES

2. Walsh JP Dissatisfaction with thyroxine therapy - could the patients be right? Curr Opin Pharmacol 2: 717-722, 2002
3. Kaplan MM, Sarne DH, Schneider AB In search of the impossible dream? Thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients. J Clin Endocrinol Metab 88: 4540-4542, 2003
4. Cooper DS Combined T4 and T3 therapy--back to the drawing board. JAMA 290: 3002-3004, 2003
19. O'Shea PJ, Williams GR Insight into the physiological actions of thyroid hormone receptors from genetically modified mice. J Endocrinol 175: 553-570,2002
20. Rendell M, Salmon D 'Chemical hyperthyroidism': the significance of elevated serum thyroxine levels in L-thyroxine treated individuals. Clin Endocrinol (Oxf) 22: 693-700,1985
23. Meier C, Staub JJ, Roth CB et al. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 86: 4860-4866,2001
27. Bunevicius R, Kazanavicius G, Zalinkevicius R et al. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N


31. Siegmund W, Spieker K, Weike AI et al. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol (Oxf) 60: 750-757, 2004


33. Wartofsky L. Combined levothriiodothyronine and levothyroxine therapy for hypothyroidism: are we a step closer to the magic formula? Thyroid 14: 247-248, 2004

34. Yildirimkaya M, Ozata M, Yilmaz K et al. Lipoprotein(a) concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. Endocr J 43: 731-736, 1996


43. Sawin CT. Subclinical hyperthyroidism and atrial fibrillation. Thyroid 12: 501-
503,2002


61. Kung AW, Lau KS, Fong GC et al. Association of novel single nucleotide polymorphisms in the calcium channel alpha 1 subunit gene (Ca(v)1.1) and thyrotoxic periodic paralysis. J Clin Endocrinol Metab 89: 1340-1345, 2004