Thyroid hormone replacement – a counterblast to guidelines*

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*cf *A Counterblaste to Tobacco*, a treatise written by King James VI of Scotland and I of England in 1604 in which he expresses his distaste for tobacco.

In the early 1990s I was involved in the initiation of guidelines in medicine, in the UK at least, when President of the Royal College of Physicians of Edinburgh. It was one of many errors of judgement in my long professional career. Their development was encouraged by government, during one of its recurrent financial difficulties, in order to deliver a higher level of healthcare throughout the country without having to replicate major teaching hospital services in smaller and often geographically remote hospitals. The unforeseen consequence is that guidelines have assumed a clinical and legal importance far beyond that which was ever intended by their protagonists. Although their consensus recommendations are rightly qualified by the acknowledged variability of the quality of evidence, it is the key statements which are seized upon by the non-expert, and not the reservations. It is as if guidelines, like the tablets given to Moses on Mount Sinai, have been carved in stone for a new generation of doctors that seems duty-bound to follow each edict slavishly. The impression is that young physicians have ceased to think, ceased to challenge received wisdom and ceased to recognise that patients come to the consultation as individuals, expecting to benefit from the opinion of an open-minded and experienced professional.

Simply because no two patients present in the same manner, guidelines, by their very nature, are the antithesis of the art of medicine. We cannot afford to underestimate the level of frustration among patients, exasperated by the 'one solution fits all' philosophy. It was put to me recently by a patient that, if governments wished to save money from their healthcare budgets, they should invest in flocks of African grey parrots, as these repetitive mimics could easily replace the current breed of doctor in the consulting room. She had a point.

Make no mistake, the guidelines produced by organisations, such as the American Thyroid Association (ATA) and adopted worldwide, are rightly considered as masterpieces within their genre, being comprehensive reviews of our current state of knowledge and marvellous educational resources. Somehow, however, there is a disconnection between the understandably conservative recommendations which will always be behind the times and the everyday problems faced by patients and clinicians. Of these, the longest standing and most pressing is surely how we treat patients with primary hypothyroidism. Ever since 1990, advice has been repeated time and time again that patients taking levothyroxine (LT4) for primary hypothyroidism should be rendered clinically euthyroid with a serum thyrotropin (TSH) concentration within the reference range,[1,2] despite the flawed evidence that a suppressed serum TSH is a risk factor for cardiovascular disease and reduced bone mineral density,[3] as serum triiodothyronine (T3) concentrations were not measured. It is conceivable that, among the heterogeneous group of patients with hypothyroidism, there were some, treated for Graves' disease with iodine-131 or surgery, with autonomously functioning thyroid remnants, insufficient to maintain euthyroidism, but in whom serum T3 concentrations were in the upper part of the reference range or raised as a result of LT4 therapy.

There is, at last, evidence of what clinicians and patients have suspected for some time; that simply restoring serum TSH concentrations to normal in patients taking LT4 is not the answer for everyone. My colleagues and I had been impressed by the proportion of patients who declined treatment with iodine-131 for Graves' disease as the rumour among them was that such treatment would result in excessive weight gain. Rather than continue to dismiss these anxieties, we investigated weight gain in patients in remission and with a normal serum TSH concentration after a course of antithyroid drugs for Graves' disease and compared it to that of patients rendered hypothyroid by surgery or iodine-131 and who were taking LT4 in a dose which resulted in a normal

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serum TSH. The weight gain was significantly greater in the LT4-treated patients. Interestingly, those patients in whom serum TSH concentrations were intentionally suppressed with LT4 had no weight change.[4] These findings were among the first to challenge the wisdom of adhering to the ATA guidelines and can perhaps be explained by resting energy expenditure being lower in LT4- treated patients with normal serum TSH when compared with normal subjects or those receiving suppressive doses of LT4.[5] Recently it has been shown that, in thyroidectomised patients, it is necessary to give sufficient LT4 to achieve a low serum TSH if pre-operative concentrations of serum T3 and thyroxine (T4) are to be restored.[6] National Health and Nutrition Examination Survey data have revealed that prescribing a dose of LT4 which restores serum TSH to its somewhat wide reference range is associated with lower serum T3 and lower T3:T4 ratios than euthyroid individuals not taking LT4. These biochemical disadvantages were associated with adverse objective and subjective parameters, such as increased body mass index, lipid profile and feelings of poor health.[7] There is also no evidence of increased cardiovascular or fracture risk in patients taking LT4 in whom serum TSH is low but not suppressed.[3] So, guidelines, with their understandable emphasis on high quality evidence-based medicine, have inevitably diminished the importance of listening to the concerns of the patient, one of the foundations of clinical medicine.

If we now begin to accept that our insistence upon recording a normal serum TSH concentration in patients taking LT4 for primary hypothyroidism is misplaced, for some patients at least, what are we to make of the increasingly strident calls for adjunctive liothyronine, either in synthetic form or as part of thyroid extract? Ever since Bunevicius and colleagues claimed a benefit in neuropsychological terms for hypothyroid patients taking both thyroid hormones[8] and the studies in rats suggesting that it was not possible to achieve satisfactory intracellular concentrations of T3 with levothyroxine alone,[9] there have been countless publications denying the benefit of additional liothyronine.[10] The negative results quelled the enthusiasm for adjunctive treatment with liothyronine and have done little to assuage the doubts of those who feel that their complaints of inadequate thyroid hormone therapy are not being listened to, let alone addressed. It is these same patients who were raising the possibility of impaired peripheral conversion of LT4 to T3 by the deiodinase-2 enzyme (D2), predating publication of the data which suggested that those who benefited from liothyronine, in addition to LT4, possessed polymorphisms of the gene encoding that enzyme.[11] Recently, it has been shown that the thyroidectomised patients on LT4 replacement who carry the Thr92Ala or Ala92Ala isoforms of D2 are at increased risk of reduced intracellular and serum T3 concentrations.[12] Once again patients were ahead of the game.

It is instructive to consider the history of thyroid hormone replacement in order to appreciate that many of our policies have, to some extent, been accidental rather than planned. Thyroid extract was first used some 125 years ago with good effect and remained in widespread use until the 1950s when a suitable synthetic LT4 preparation gradually supplanted it. The doses employed were 200–400 μg daily. Although T3 was discovered as the second thyroid hormone in 1952 it was not used to any extent therapeutically as patients seemed content with LT4 alone, long before the demonstration that circulating T3 was largely derived from deiodination of extrathyroidal T4. The seismic shift in the treatment of hypothyroidism, however, was the result of the development of sensitive assays for TSH which showed that, in order to restore serum TSH to normal, the dose of LT4 required was of the order of 75–150 μg daily. Higher doses caused suppression of TSH consistent with hyperthyroidism. The resultant dose reductions were tolerated by the majority of patients but this was the beginning of significant dissatisfaction with adequacy of the recommended treatment of primary hypothyroidism which remains problematic today. The previously high doses of LT4 would, by the law of mass action, have overcome any impaired D2 activity in affected patients. Little attention has been given to a study, important in retrospect, which showed that it was difficult to increase serum T3 into the hyperthyroid range with LT4 unless serum free T4 concentrations were markedly elevated at around 35–40 pmol/l.[13] This was an elegant demonstration that exogenous subclinical hyperthyroidism was a different entity from endogenous subclinical hyperthyroidism, even although serum TSH was suppressed in both conditions. In other words, a low serum TSH concentration in patients taking LT4 did not necessarily indicate overtreatment.

We started by prescribing thyroid extract, unaware that it contained T3, replaced it with what would now be regarded as high doses of LT4, without knowing of the existence of T3 or its derivation from T4 and, once synthetic liothyronine was available, we have been reluctant to sanction its use.

It has always seemed counterintuitive to continue to treat patients with a prohormone (LT4) alone when the thyroid gland secretes both the active (T3) and inactive hormones. One of the reasons for favouring hydrocortisone over cortisone acetate in the treatment of adrenal insufficiency is that there have been reports of impaired conversion of the inactive cortisone acetate to cortisol by the 11B-hydroxysteroid dehydrogenase type 1 enzyme.[14] The assumption that D2 activity is universally efficient appears to have been a naïve concept and, if we subscribe to attempting to reproduce the physiology of thyroidal secretion in patients with hypothyroidism, as I believe we should, liothyronine ought to be prescribed to compensate for the 20% of secretion which has been lost. But we continue to sit on our hands waiting for the results of perfect, large, properly controlled studies which will almost certainly not be forthcoming in the near future, if ever; and bemoaning the fact that a modified-release liothyronine is not available, despite being called for almost 20 years ago.[15] We claim that it is inconvenient for the patient to take the short-acting active hormone three times a day,[16] despite the fact that we advise our patients with adrenal insufficiency to take hydrocortisone with the same frequency until the currently available modified release hydrocortisone preparations have been adequately assessed.[17]

The facts of the matter are that the current guidelines for LT4 replacement therapy in primary hypothyroidism are not fit for purpose and the continued reluctance to approve additional treatment with liothyronine denies the patient the precision medicine which we are encouraged to adopt,[10] and which many patients crave. In the future, D2 genotyping may play a role in identifying those patients likely to benefit from treatment with both thyroid hormones.[18] In the meantime, I am so concerned about the state of advice on the management of primary hypothyroidism that I am increasingly reluctant to suggest ablative therapy with iodine-131 or surgery in patients with Graves' disease, irrespective of age or number of recurrences of hyperthyroidism. Treatment with a thionamide, in which the hypothalamic-pituitary-thyroid axis remains intact, making interpretation of thyroid status simpler, is currently a more attractive proposition. It is not that I am unprepared to disregard guidelines by prescribing 'a little too much' LT4 or combined thyroid hormone therapy, but I know that an increasing proportion of primary care physicians, advised by guidelines, will not accept my advice. Experience of managing more patients with thyroid disease than most over a period of some 40 years is being trumped by inflexible guidelines; truly a remarkable state of affairs. Others hide behind guidelines to avoid the cost of prescribing liothyronine, which in the UK is exorbitantly priced by the sole supplier at some £250 for two month's supply of 10 µg daily, when well-travelled patients can obtain supplies for a few euros in Italy and Greece and beyond.

As I see it, we have three choices for those patients convinced that their present LT4 treatment is inadequate.

1. We can carry on with the current advice and be plagued by patients who do not achieve their anticipated quality of life as a result, surely a non-starter.
2. We can prescribe doses of LT4 which do result in TSH suppression, but are associated with unequivocally normal serum T3 concentrations as I am unaware that this combination of results has ever been proved a risk factor for atrial fibrillation or reduced bone mineral density, and why should it if the level of the active hormone is normal?
3. We can prescribe a combination of LT4 and liothyronine, ensuring that serum TSH is normal.

If the last is the preferred choice, the very number of potential patients will surely stimulate the pharmaceutical industry to provide a modified-release form of the active hormone at last. I can but hope that I do not have to wait as long as King James did for my views to be accepted.

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