Maturitas 87 (2016) 72–78

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Clinical challenges in thyroid disease: Time for a new approach?

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ARTICLE INFO

Article history:
Received 19 December 2015
Received in revised form 30 January 2016
Accepted 1 February 2016

Keywords:
Thyroid disease
Treatment
Diagnosis

ABSTRACT

Thyroid disease is common, and the prevalence is rising. Traditional diagnosis and monitoring relies on thyroid stimulating hormone (TSH) levels. This does not always result in symptomatic improvement in hypothyroid symptoms, to the disappointment of both patients and physicians. A non-traditional therapeutic approach would include evaluation of GI function as well as a dietary history and micronutrient evaluation. This approach also includes assessment of thyroid peroxidase (TPO) antibodies, T3, T4, and reverse T3 levels, and in some cases may require specific T3 supplementation in addition to standard T4 therapy. Both high and low TSH levels on treatment are associated with particular medical risks. In the case of high TSH this is primarily cardiac, whereas for low TSH it is predominantly bone health. This article discusses these important clinical issues in more detail, with some practical tips especially for an approach to the "non-responders" to the current traditional therapeutic approach.

Contents

1. Illustrative cases 73
   1.1. Case 1 73
   1.2. Case 2 73
2. What we know 73
3. Thyroid laboratory testing 73
4. What we think we know 74
5. Hypothyroidism controversies 75
   5.1. Does treatment affect outcomes? 75
   5.2. Does over-treatment matter? 75
   5.3. Persistent "hypothyroid" symptoms 75
6. The role of nutrition 76
7. The role of the gastrointestinal (GI) tract 76
8. Where does that leave us now? 76
9. Case follow up 76
   9.1. Case 1 76
   9.2. Case 2 76
10. Practice points 76
11. Further research 77
12. Conclusion 77
    Contributors 77

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http://dx.doi.org/10.1016/j.maturitas.2016.02.001
0378-5122/

Conflict of interest 77
Funding 77
Provenance and peer review 77
References 77

1. Illustrative cases

1.1. Case 1

A slim (BMI 19), active, 86 year old woman playing tennis regularly till the age of 83 was discovered to have an elevated TSH (4.5 mIU/L) (normal range 0.2–4.0 mIU/L) on routine bloodwork. She had no symptoms of hypothyroidism, and was feeling well. Nonetheless, she was started on levothyroxine. This resulted in insomnia for which she was started on clonazepam. This led to daytime confusion, fatigue and poor balance but fortunately no falls. She could now only manage walking in her building corridors using the handrails. She noticed that she felt stronger in the afternoon and evening when the clonazepam was wearing off.

1.2. Case 2

A 52 year old lady has a long history of thyroid disease since her 20's. She has multiple symptoms of hypothyroidism including fatigue, weight gain, thinning hair, and cold intolerance. She has been on ever increasing doses of levothyroxine, with the recent addition of cytomel. Her TSH is currently 0.03 mIU/L (normal range 0.2–4.0 mIU/L). She has had no improvement in her symptoms. Her bone density confirms osteoporosis.

2. What we know

The prevalence of spontaneous overt hypothyroidism is 1–2%, ten times more common in women than men, and increases with age. 8% of women and 3% of men have subclinical hypothyroidism [1]. Studies have reported that those with higher baseline serum TSH values and/or elevated anti-thyroid antibodies have a higher propensity to progress to overt hypothyroidism [2,3].

Thyroid hormone supplement is one of the most frequently prescribed therapies in the United States and Europe, and several studies of primary care practices indicate increasing levothyroxine prescriptions over the past few decades [4,5]. If left untreated hypothyroidism can be associated with significant morbidity, particularly in the elderly, where typical symptoms may be absent or may be erroneously attributed to normal aging or coexisting disease [6]. As abnormalities of thyroid function impact all organ systems, it often manifests predominantly in the most impaired organ system, particularly in those patients with comorbid conditions [7].

Increasing epidemiological evidence suggests subclinical hypothyroidism is associated with increased risk of coronary heart disease events, heart failure, cardiovascular mortality, and perhaps cognitive impairment, depression and fracture risk [8]. At the other end of the spectrum, two recent studies (from the UK and USA) report a cumulative rate of *over-treatment* of 9.6–16% over 5 years. [9,10] This raises the questions: is there a lack of symptomatic improvement; or are the risks of over-treatment unappreciated; or is deliberate generous treatment thought to improve symptoms? The latter possibility is also suggested by Taylor et al. who found that over-treatment was more likely if prescriptions were started for fatigue or depression [9]. It is important to remember that subclinical *hyper*thyroidism is also associated with significant health issues [11], as well as an increased risk of fracture [12].

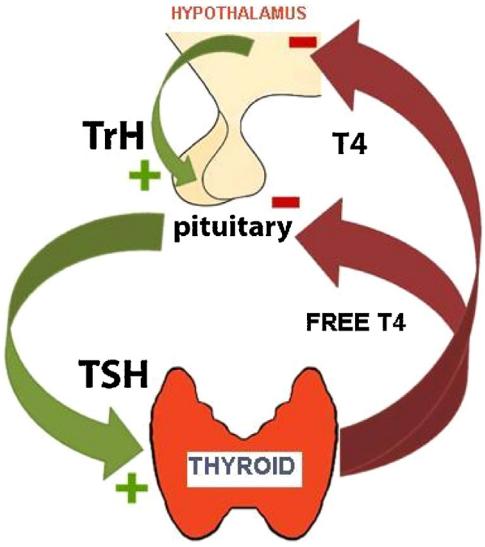

Fig. 1. Normal physiologic thyroid function (TrH: thyroid releasing hormone; TSH: thyroid stimulating hormone; T4: tetraiodothyronine).

3. Thyroid laboratory testing

Isley [7] suggested that "it is also essential to be able to distinguish between test abnormalities that indicate primary thyroid dysfunction and those that reveal an adaptive response to nonthyroidal illness".

A rational approach to the evaluation of thyroid function requires an understanding of the normal physiology of the thyroid gland. (see Fig. 1). TSH promotes thyroid gland growth and hormonal secretion. The level of TSH is regulated by circulating tetraiodothyronine/thyroxine (T4) levels. Thyroid releasing hormone (TrH) stimulates release of TSH, which then induces production of thyroxine (T4). The level of T4, influences the amount of triiodothyronine (T3) produced and both the hypothalamus and the pituitary alter production of TrH and TSH, respectively dependent on T4 levels. Elevated free (unbound to throxine binding globulin) T4 inhibits production, while low free T4 stimulates production. The thyroid secretes 90% T4, with 50% of this being deiodinated to T3. T4 is deiodinated to T3 in many cells of the body, particularly the liver and kidneys. The remainder is converted to reverse T3 (rT3). This is an inactive form of T3, and it is therefore a regulatory mechanism. More rT3 is created when the body needs to reduce the action of T3 and T4. Although both triiodothyronine (T3) and tetraiodothyronine (T4) are secreted by the thyroid gland, 80% of the circulating T3 is produced by extra thyroidal deiodination of T4. *T3 is the major active component* as it interacts with the nuclear T3 receptors in multiple tissues and subsequently affects promoter regions of genes that are positively or negatively regulated by thyroid hormones.

Nearly all T4 (99.96%) and T3 (99.6%) is bound within the circulation. The majority is bound to thyroxine binding globulin (TBG) (70%) with additional portions bound to transthyretin (10%) and albumin (15%). *Only free T3 and free T4 can enter cells to exert their actions.* The hormones are further deiodinated to diiodothyronine and monoiodothyronine in the liver and kidneys. Iodine is recycled or excreted in the urine.

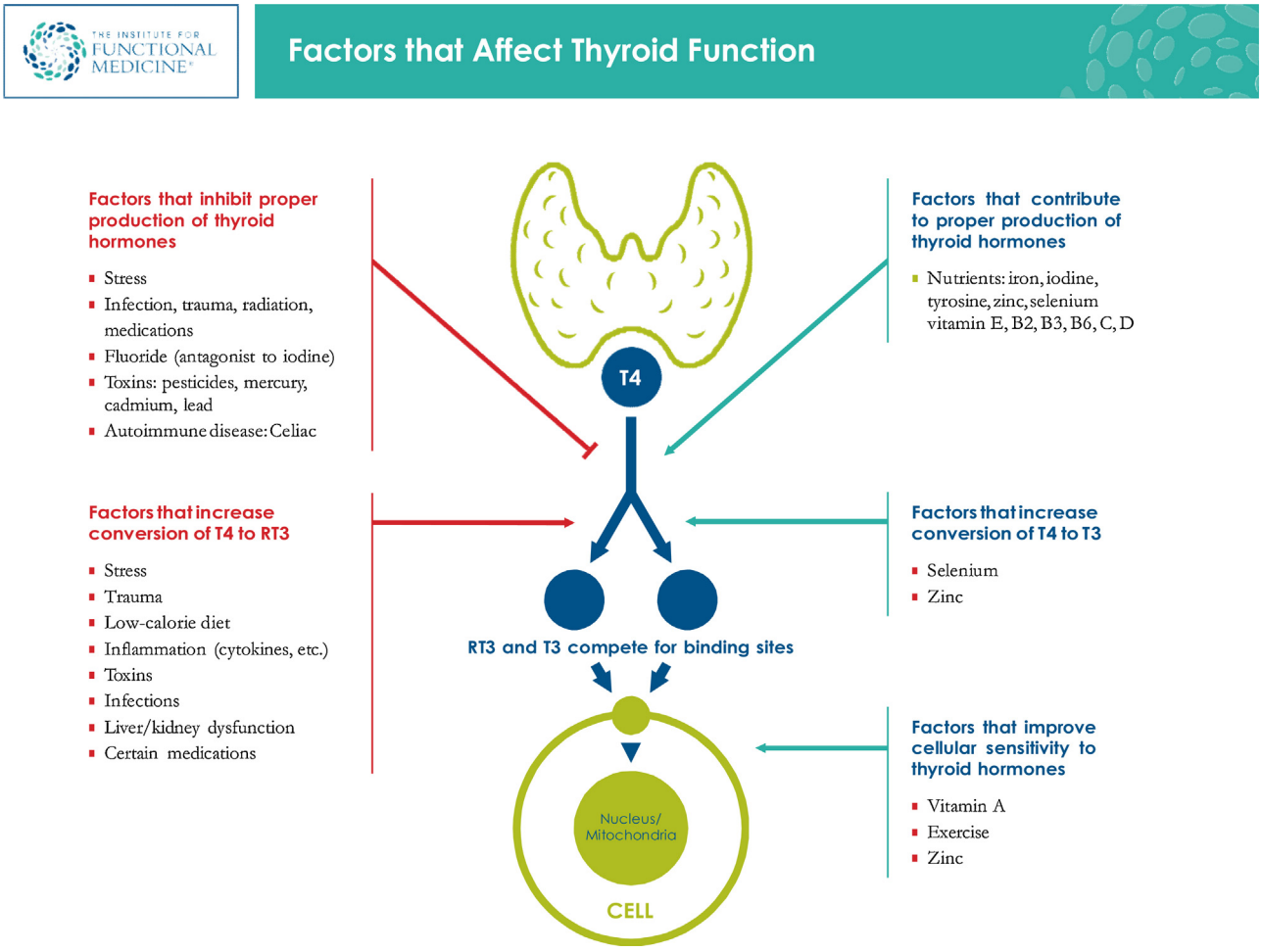

Fig. 2. Diagram showing environmental and nutritional factors affecting thyroid function (both positive and negative) and their sites of action. (Reproduced with permission from the Institute for Functional Medicine).

T4 is the inactive form of the thyroid hormone and needs to be activated to T3. In some patients genetic, environmental toxins, or nutritional deficiencies can lead to inadequate conversion. In these cases, prescribing levothyroxine may lead to poor conversion to T3 and thus not alleviate symptoms. Although it may suppress their TSH so that they look "normal" on testing. Similarly if all the T3 is being rapidly metabolized to reverse T3 (inactive form) the same scenario may be true. In addition, even if there is adequate T3, if the T3 receptor is not functioning appropriately this signal never makes it to the cellular level and so no metabolic changes occur. Fig. 2 (Reproduced with permission from the Institute for Functional Medicine) shows the many nutritional factors that may affect this process.

In hypothyroidism, TSH rises first and abruptly, and the decline of T4 and T3 is slower and later [13].

4. What we think we know

Development of high sensitivity TSH assays have overall facilitated the diagnosis of hyper or hypothyroidism. Hyperthyroidism of any cause, other than excess primary TSH production, results in a lower-than normal TSH level. The sensitive TSH assay is regarded as the single best screening test for thyroid dysfunction in most clinical settings.

The type of algorithm presented in Fig. 3 has been used conventionally in evaluating thyroid function and deciding what additional tests should be ordered.

However, recently published Clinical Practice Guidelines for Hypothyroidism in Adults: AACE and ATA 2012 [14], highlight numerous clinical challenges and pitfalls. By using TSH level alone pitfalls include: the "normal range" widens with age; there are ethnic differences in normal ranges; special challenges occur in pregnancy; lack of correlation to symptoms; challenges of T3 and free T3 assays; role of anti-thyroid peroxidase (TPO) antibodies in diagnosis and treatment; influence of concomitant drugs; lack of steady state levels in some situations (illness and pregnancy); adrenal insufficiency; TSH reference ranges; "routine screening" differences between countries and expert panels; diagnosis of subclinical hypothyroidism; role of thyroid treatment in obesity; hazards of over treating; lack of benefits of "normalizing" TSH; role of L-T3/combination therapy; dosage of L-T4.

Particularly in the elderly, the use of TSH levels in evaluation of thyroid dysfunction may pose unique problems. Epidemiological studies have demonstrated slightly elevated serum TSH concentrations among the elderly population [15]. Of note, in some studies 23.9% of patients over the age of 80 had serum TSH concentrations between 2.5 and 4.5 mIU/L, and 12% had serum TSH concentrations above 4.5 mIU/L. Thus, mild TSH elevations in older individuals may *not* reflect subclinical thyroid dysfunction. There is active debate as to whether elevated TSH levels reflect an increased prevalence of hypothyroidism among the elderly, a normal aspect of healthy aging, or result from other confounding factors such as prescribed medications [16].

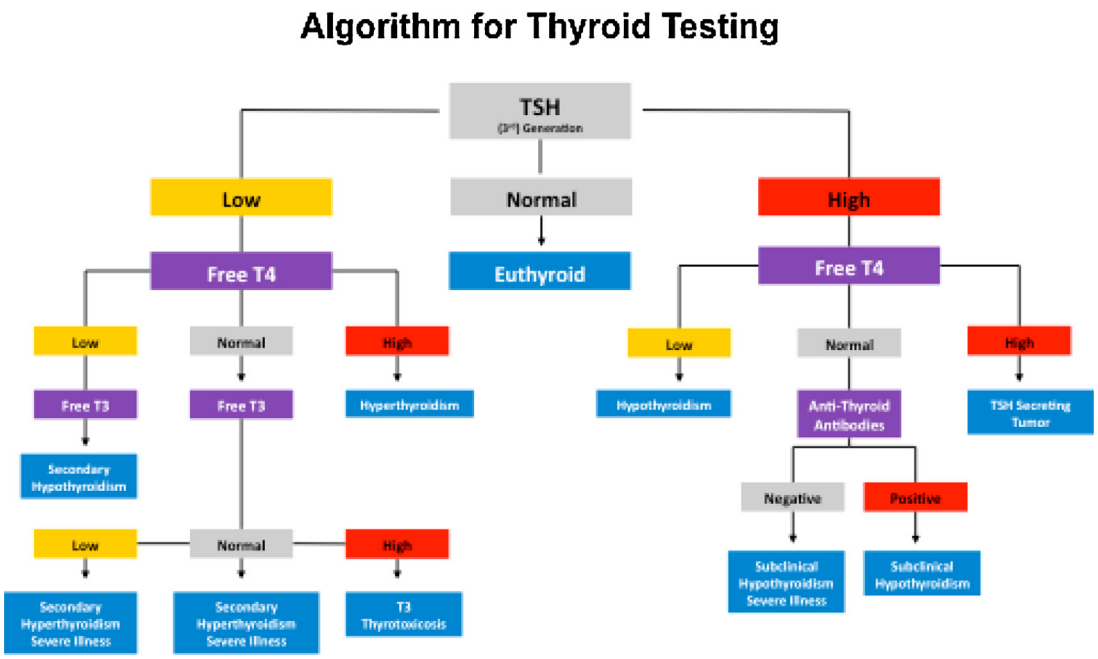

Fig 3. Algorithm for Thyroid testing.

Importantly in this era of polypharmacy, it is known that certain medications may interfere with TSH levels both in vitro and in vivo. [17,18]. A number of drugs cause *hypothyroxinemia* in euthyroid patients by decreasing TBG concentrations (androgens, niacin), decreasing T4 binding to TBG (high dose salicylates, phenytoin, carbamazepine), and/or increasing T4 metabolism (carbamazepine, phenobarbital and phenytoin). Others cause *hyperthyroxinemia* in euthyroid patients by increasing TBG concentrations (clofibrate, estrogen, 5 fluorouracil, heroin/methadone) or may raise circulating T4 levels by inhibiting the conversion of T4 to T3 (amiodarone, iopanoic acid and high-dose propranolol and nadolol) [18].

5. Hypothyroidism controversies

5.1. Does treatment affect outcomes?

Normal ranges are exactly that, ranges. There will be 5% of the population who are normal but are above or below the "normal" range, yet are symptom free. Over-treating thyroid disease especially in the elderly can be associated with multiple co-morbidities as we can see from Case 1. In addition it can cause tachycardia and cardiac stress that can affect exercise tolerance and may precipitate a cardiac event. A recent metaanalysis looking at heart failure risk in subclinical hypothyroidism [19] highlighted the challenge of "normal" ranges and concluded that "until randomized controlled trials are performed, the data favours treating younger patients and higher TSH values (>10)."

Another study critically reviewed the data on the prevalence and progression of subclinical hypothyroidism, its tissue effects, and its prognostic implications, as well as the issue of treating slight thyroid hormone deficiency or excess in relation to the patient's age [20]. The relative benefit was apparent in those under 70 years of age. However, beyond 85 years the risks clearly outweighed the benefits of treating subclinical hypothyroidism.

In addition, symptomatic hypothyroid patients treated into the low-normal, or high-normal TSH levels showed no difference in metabolic markers [21].

5.2. Does over-treatment matter?

The Baltimore Longitudinal Study of Aging [10], a long-term study of aging begun in 1958 that recruits healthy volunteers over age 20, living independently in the community, evaluated 1450 subjects from 2003 to 2014 and showed iatrogenic thyrotoxicosis accounted for approximately half of both prevalent and incident low TSH events in this community-based cohort. Highest rates were among older women, who are vulnerable to atrial fibrillation and osteoporosis. They concluded that physicians should be particularly cautious in treating subclinical hypothyroidism in elderly women in light of recent studies demonstrating no increased risk of cardiovascular morbidity or death for individuals with elevated TSH levels less than 10 mIU/L.

Of note, iatrogenic hyperthyroidism has been reported in patients taking over-the-counter nutritional supplements for "thyroid health" or weight loss. A recent study evaluated ten commercially available products in the United States, and found the majority contained T3 or T4, often at doses higher than those prescribed for hypothyroid patients [22].

Low TSH levels (<0.3 mIU/L) have been associated with an increased risk for osteoporotic fractures in men and women, especially hip fracture [23]. Other authors [24] suggest that patients with either a high or very low (suppressed) TSH also have an increased risk of cardiovascular disease, dysrhythmias, and fractures. In contrast, patients with a low but unsuppressed TSH did not. In this study the cut-off level for very low was 0.04 mIU/L or less. With regard to subclinical hyperthyroidism (TSH < 0.1 mIU/L), treatment may decrease the risk of atrial fibrillation and the risk of low bone density in postmenopausal women [23].

5.3. Persistent "hypothyroid" symptoms

While overtreatment can cause clinical concerns, many clinicians have patients whose "hypothyroid" symptoms do not improve when treated with a standard approach: standard blood work is within the normal range, but symptoms continue to persist. How should this euthyroid patient be approached? From a hormone replacement standpoint, the debate that has gained con-

siderable clinical and research support is the use of liothyronine (T3 thyroid hormone) in combination with levothyroxine [25]. Liothyronine can be given as a synthetic hormone, or as a thyroid porcine glandular extract. For instance, it has been shown that impaired psychological well-being and depression or anxiety remains in some hypothyroid patients on monotherapy (levothyroxine) despite normal TSH levels [26]. A review of the literature in 2014 [27] reported that 7 of 11 studies showed that patients treated 'adequately on T4', in other words their TSH levels were in the normal range, had increased symptoms of depression and/or anxiety compared to controls. From a biochemical perspective, persistent symptoms might be explained by the inability of levothyroxine to restore T3 levels in serum and all target tissues [27]. There is also increasing support for the use of standardized porcine glandular products, as some research suggests that hypothyroid patients may have equal or greater improvements with this prescription [28]. Additionally, some reports [28] suggest a preference of patients for levothyroxine plus liothyronine combination therapy over levothyroxine monotherapy.

6. The role of nutrition

This is an often forgotten part of the traditional management of thyroid disease. Fig. 2 illustrates the key nutrients involved in ensuring adequately cellular response to the thyroid hormones. Ten dietary nutrients are required to facilitate this process. Treating only with thyroid hormones may mask underlying nutritional deficiencies. Iodine is the most well known nutrient in thyroid health [29], but increasing research has focused also on the key roles of selenium and iron. A recent review summarises the evidence for the role of selenium in thyroid health [30].

7. The role of the gastrointestinal (GI) tract

Problems with the GI tract are well documented in hypothyroidism as well as hyperthyroidism, and include constipation, diarrhoea, dysphagia, dyspepsia, etc. [31]. These symptoms usually improve with treatment of the thyroid dysfunction. A bidirectional relationship also occurs between the thyroid and the liver that is important for health, and is disrupted with disease [32]. This includes conditions such as non-alcoholic fatty liver disease (NAFLD), which has also been shown to improve with normalization of thyroid function [33]. In addition, in hypothyroidism small intestinal bacterial overgrowth (SIBO) has been described, and in one study was found in 54% of cases versus 5% of controls [34]. These authors recommend testing for SIBO in those patients who are euthyroid but have persistent GI symptoms. Similarly symptoms of irritable bowel syndrome should prompt investigation of thyroid function [35]. The autoimmune basis of some cases of thyroid disease (AITD) is well established, yet associated autoimmune diseases may be missed. For example, in AITD a prevalence of 2–5% of co-existing coeliac disease has been reported [36] with the majority being asymptomatic from a GI perspective. But because coeliac disease is associated with an increased risk for malignancy and mortality, it is important it is not missed. Once non-compliance is excluded, coeliac disease and other malabsorptive and maldigestive disorders are reported as the commonest causes of treatment refractory hypothyroidism [36]. In known cases of coeliac disease, the prevalence of AITD is 6–21%. This has prompted recommendations for routine thyroid testing in known coeliac disease [37]. Inflammatory bowel disease and primary biliary cirrhosis are also known to be associated with AITD [38,39].

8. Where does that leave us now?

Symptoms of hypothyroidism are vague and can be mistaken for other conditions, especially in the elderly. The symptoms need to be taken into account along with a full laboratory evaluation of the thyroid status (including TPO, T4, T3 and rT3 in certain cases). If symptoms do not resolve, it is important to look at other factors, especially GI function and nutritional status, to assess if there are undiagnosed nutritional deficiencies. The presence of thyroid antibodies confirms an autoimmune basis for thyroid disease, and behoves the clinician to look for other markers of autoimmunity and address other conditions that may be contributing to this. The most likely source of the inflammation is the GI tract with possible undiagnosed GI disease, food allergies or intolerances.

There is currently general agreement that patients with serum TSH values $\geq$ 10 mU/L should be treated with levothyroxine, to prevent adverse effects on serum lipids and to decrease the risk of progression to overt hypothyroidism [18,19]. There is less agreement about whether to treat those with milder degrees of subclinical hypothyroidism (TSH < 10 mU/L), but it seems reasonable to consider therapy with levothyroxine in patients: with symptoms that could be attributed to hypothyroidism; in those with hyperlipidaemia; and, in patients with elevated serum TPO antibody levels, who are most likely to progress to overt hypothyroidism [18]. If a patient with subclinical hypothyroidism is not treated, close follow-up is warranted, given the high rate of progression to overt disease [40].

9. Case follow up

9.1. Case 1

Of her own accord, she discontinued her levothyroxine. Her sleep returned to normal and she was able discontinue the clonazepam, at which time her balance and cognition returned to her baseline normal levels.

9.2. Case 2

With the addition of liothyronine (T3), she was able to reduce her dose of levothyroxine (T4), however her symptoms remained unchanged. Her TSH level recovered to 2.5 mU/L. Dietary history suggested features of "irritable bowel syndrome". It was recommended she go on a trial of a gluten, dairy and egg free diet for a minimum of four weeks, before re-introducing the eliminated foods one at a time over several weeks. During the four week diet, her GI symptoms settled completely, and her energy level and "brain-fog" both improved substantially. She was found to have a gluten related enteropathy, and so she remains gluten-free with no further GI symptoms. For the first time since her diagnosis, her hypothyroid symptoms have continued to improve with her current thyroid supplements, a gluten free diet, and a focus on adequate protein and micronutrients in her diet.

10. Practice points

- Lessons from the cases: listen to the patient in context with the blood work, and do not feel that blood test "normalization" is the only goal.
- Interpret TSH levels in the clinical and concomitant medication context.
- The evidence for screening and treating subclinical thyroid dysfunction is limited.

- Special caution is required in diagnosing and treating thyroid dysfunction in women who are taking oral estrogens or selective estrogen receptor modulators [23].
- Caution in treating subclinical **hypo**thyroidism in elderly women in light of recent studies demonstrating no increased risk of cardiovascular morbidity or death for individuals with elevated TSH less than 10 mU/L.
- Subclinical **hyper**thyroidism is associated with an increased risk of hip and other fractures, particularly among those with TSH levels of less than 0.10 mIU/L and those with endogenous subclinical hyperthyroidism [12].
- Treating subclinical **hyper**thyroidism remains controversial, but current guidelines recommend considering treatment when serum TSH values are persistently < 0.1 mIU/L [29].
- Iatrogenic thyrotoxicosis is highest among older women, who are vulnerable to atrial fibrillation and osteoporosis [10].
- Patients should be counselled about the potential side effects of over-the-counter "thyroid support" or "weight loss" products since they may contain iodine, levothyroxine and/or liothyronine and may induce hyperthyroidism [10,22].
- Ensure compliance: levothyroxine should be taken with water consistently 30–60 min before breakfast or at bedtime 4 h after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption.
- In cases of persistent symptoms, (where compliance is ensured) it is important to consider: 1. Diet: adequate protein and micronutients are key, and in cases where the diet seems adequate, but symptoms persist; 2. Undiagnosed malabsorption or maldigestion such as coeliac disease, gluten sensitivity, SIBO, etc., should be considered.

11. Further research

Further study is needed: to determine whether treating subclinical hyperthyroidism can prevent fractures; and to understand the extent to which patient preferences may be driving physician practices with respect to over-treatment.

Larger randomized trials, with a longer follow-up, are needed to clarify the ideal TSH reference range during treatment of primary hypothyroidism. Given the high prevalence of subclinical hypothyroidism and heart failure in the elderly, levothyroxine replacement should be investigated with appropriately powered randomized controlled trials, with clinical heart failure included as an outcome.

12. Conclusion

Einstein defined Insanity as "doing the same thing over and over again and expecting a different result."

With the rising prevalence of thyroid disease, it is time for a new, more holistic and individualised approach to managing thyroid disease.

Contributors

Dr Juby: I declare that I participated in the above manuscript by: responding to the request for an article on thyroid disease management from Dr Rees; by formatting, preparing and editing the manuscript; by contacting two colleagues for specific areas of collaboration; by collating the paper and preparing the final manuscript; by submitting the article.

Dr Hanly: I declare that I participated in the above entitled manuscript with the section on physiology and laboaratory testing/interpretation and pitfalls.

Dr Lukaczer: I declare that I participated in the above manuscript with the paragraph on persistent hypothyroid symptoms and the role of liothyronine therapy. In my role with the Institute for Functional Medicine I also gave permission for the use of Fig. 2 in the manuscript.

Conflict of interest

All authors declare no conflicts of interest in relation to this publication.

Funding

The authors have received no funding for this article.

Provenance and peer review

Commissioned; externally peer reviewed.

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