Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer?

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ABSTRACT
A large number of hypothyroid patients, receiving adequate doses of thyroxine supplementation, continue to complain of dissatisfaction and varied symptoms. This review discusses the concept of tissue hypothyroidism and suggests methods of measuring it, while calling for improvements in the medical management of hypothyroidism.

Key words: Clinical scores, hypothyroidism, tissue hypothyroidism

INTRODUCTION
Advances and improvements in the diagnosis of hypothyroidism have meant that a larger number of patients are being detected with the condition.[1] Economical and easily available therapy, in the form of thyroxine, is available to most patients. Present-day thyroidologists find it easier to titrate doses and plan treatment regimes, based on serum thyroid stimulating hormone (TSH) levels. This is in contrast to the clinical challenges that endocrinologists of the previous generation faced, when they had to titrate desiccated thyroid extract or tri-iodo-thyroxine doses based on clinical symptoms or on unreliable laboratory assays.[2,3]

The improvements in laboratory diagnosis, follow-up, monitoring and treatment, however, have not necessarily improved satisfaction levels of patients. Many patients complain of persistent psychological symptoms after treatment. Others state that they do not feel normal.[4] Some patients report inadequate weight loss or continuous weight gain in spite of normal TSH levels.[5] Many patients also feel that their treating physicians are “unsympathetic and dismissive of their symptoms”.[4]

As many symptoms of hypothyroidism are nonspecific, and are frequently encountered in the general population,[6] in the elderly,[6] and in patients with Vitamin D deficiency,[7] this clinical situation often poses a therapeutic dilemma.

Should we treat patients according to their TSH level, which represents the health of their hypothalamic-pituitary axis, or according to their symptoms, which represent the health of the whole body?

Should we “unsympathetically dismiss” all persistent symptoms such as weight gain or asthenia, or try to find reasons for them?

Can these persistent symptoms be explained by co-morbid conditions such as hyponatremia, or Vitamin D deficiency, or by hypothyroidism alone?

If these symptoms are to be attributed to tissue hypothyroidism, is there a scientific rationale for this explanation?

If tissue hypothyroidism is considered to be a real clinicopathological entity, how do we measure it in the outpatients’ department (OPD)?
In case we are able to measure and quantify tissue hypothyroidism, do we have therapeutic modalities which can benefit our patients?

**Symptoms and Signs of Hypothyroidism**

The clinical symptoms and signs of hypothyroidism are well known. In their classic paper, Billewicz et al., analyzed 21 clinical features of the condition, finally settling on 14 features, which were reasonably sensitive and specific for the condition. With this, the Billewicz score for diagnosis of hypothyroidism was created.\[8\]

This work was revisited three decades later by Zulewski et al., who studied the disease in the light of newer, improved methods of assessing thyroid function. Of the 14 features used by Billewicz, two were discarded as they had low positive and negative predictive values (below 70%). The new clinical score proposed by them contains 12 symptoms and signs.\[6\]

These symptoms [Table 1] however, are not 100% specific or sensitive. Thirty-five percent of controls, for example, were found to have cold intolerance. Older euthyroid women (age ≥ 55 years) present frequently with constipation as compared to younger controls.\[6\]

Because of this, it becomes difficult to rely exclusively on clinical features while diagnosing or monitoring hypothyroidism.

**Thyroxine Dose Titration**

Patients’ wellbeing does not seem to correlate with “biochemical wellbeing”. When assessed by a visual analogue scale of wellbeing, patients reported best results on doses of thyroxine that were 50 mg higher than ‘optimal’ replacement. Highest wellbeing scores were obtained when serum TSH was <0.2 mIU/ml.\[9\] Left to patients, they would prefer clinical assessment, rather than TSH estimation, to titrate thyroxine doses.

Because of concerns regarding adverse effects of the overdosage of thyroxine, however, treatment is geared towards achieving a TSH level within laboratory normal range. A normal TSH implies that the hypothalamo-pituitary axis is in satisfactory control. Because of this, doses of thyroxine have been lowered in many patients, in spite of their wellbeing on earlier, higher, doses.\[10\]

No consensus statement or guideline recommends treating hypothyroid patients for symptomatic relief (though subclinical hypothyroid patients can be treated if symptomatic). Instead in, hypothyroid patients, doses are titrated to normalize serum TSH.

**Patient Dissatisfaction**

No wonder then, that patients are dissatisfied. Patients report various symptoms, both specific and non-specific, which may or may not be attributed to hypothyroidism.\[4\] A community-based survey found that hypothyroid patients with normal TSH values were more likely to complain of difficulty in remembering things, inability to think of the right word, feeling tired and lethargic, putting on weight, aches and pains all over the body, inability to think clearly, falling over things and, clumsiness, and bumping into things.\[10\]

| Table 1: Symptoms and signs of tissue hypothyroidism |
|-----------------------------------------------------|
| **Symptoms**                                           | **New Score** |
|--------------------------------------------------------|
| **Present**                                            | **Absent**    |
|--------------------------------------------------------|
| **Symptoms**                                           | **Present**    | **Absent**    |
|--------------------------------------------------------|
| Diminished sweating                                    | Sweating in the warm room or a hot summer day         | 1   | 0   |
|--------------------------------------------------------|
| Hoarseness                                             | Speaking voice, singing voice                         | 1   | 0   |
|--------------------------------------------------------|
| Paraesthesia                                           | Subjective sensation                                  | 1   | 0   |
|--------------------------------------------------------|
| Dry Skin                                               | Dryness of skin, noticed spontaneously, requiring treatment | 1   | 0   |
|--------------------------------------------------------|
| Constipation                                           | Bowel habit, use of laxative                          | 1   | 0   |
|--------------------------------------------------------|
| Impairment of hearing                                  | Progressive impairment of hearing                      | 1   | 0   |
|--------------------------------------------------------|
| Weight increase                                        | Recorded weight increase, tightness of clothes        | 1   | 0   |
|--------------------------------------------------------|
| **Physical Signs**                                     | **Present**    | **Absent**    |
|--------------------------------------------------------|
| Slow Movements                                         | Observe patient removing his clothes                   | 1   | 0   |
|--------------------------------------------------------|
| Delayed ankle reflex                                   | Observe the relaxation of the reflex                   | 1   | 0   |
|--------------------------------------------------------|
| Coarse Skin                                            | Examine hands, forearms, elbow for roughness and thickening of skin | 1   | 0   |
|--------------------------------------------------------|
| Periorbital puffiness                                  | This should obscure the curve of the malar bone        | 1   | 0   |
|--------------------------------------------------------|
| Cold skin                                              | Compare temperature of hands with examiner’s          | 1   | 0   |
|--------------------------------------------------------|
| Sum of all symptoms and signs present                  | 12  | 0   |
While these symptoms can be attributed to various other endocrine and medical causes, the community-based nature of this survey, and the less frequent occurrence of these symptoms in controls, points to an etiologic role for hypothyroidism.

“Unsympathetic dismissal” of symptoms is therefore, unwarranted and incorrect.

**Etiology of Symptoms**

Well-controlled hypothyroid patients with persistent symptoms may have co-morbid conditions which can explain some of their clinical features. Vitamin D deficiency, diabetes mellitus, depression, hypertension, heart disease and hyponatremia are more common in the hypothyroid population.[7,10,11] These conditions, as well as the use of certain anti-diabetic, antidepressant and anti-hypertensive medications may explain the occurrence of some of these symptoms. No work has been done, however, to delineate the exact contribution of these medical or pharmacological situations to “hypothyroid symptomatology.

**Tissue or Cellular Hypothyroidism**

The concept of tissue hypothyroidism, or hypothyroidism at the cellular level, has been proposed over two decades ago, to explain the clinical paradox of symptoms, in spite of biochemical euthyroidism with “optimal” thyroxine dosage.[12] The lack of an agreed upon, simple gold standard tool for the measurement of tissue thyroid function[13] has slowed research in this field. However, the large number of patients who complain of symptoms suggestive of “tissue hypothyroidism” warrants a detailed study of this aspect of thyroidology.

It has been postulated that symptomatic individuals with a high-normal TSH may earlier have had a low-normal set point for TSH, prior to developing hypothyroidism, and are therefore used to higher circulating levels of thyroxine.[14]

Another explanation is that the diurnal variation in TSH secretion, which is maintained on non-suppressive doses of thyroxine, may cause false overestimation of thyroid status. This can happen if TSH levels are measured during early afternoon, when they are at their lowest.[15]

Exogenous thyroxine replacement cannot mimic the natural circadian rhythm of thyroxine secretion, which occurs with an intact hypothalamo-pituitary axis. This too, may lead to suboptimal symptom relief.

The pituitary gland is thought to be more sensitive to T4 than the liver and kidney, as it derives its intracellular T3 directly from T4[16] it also expresses Type II deiodinase, which maintains higher levels of T3, due to its inability to degrade sulphated T3, and inability to generate inactive reverse T3.[17] Because of this differential sensitivity, the pituitary may respond to “higher” levels of TSH than the rest of the body, thus showing a euthyroid TSH response to thyroxine while other tissues remain hypothyroid at the cellular level.

Recent work has been carried out on selective entropy of the thyroid hormone receptors TR1 and TR2, but the clinical significance is uncertain.[18]

It is also thought that unsatisfactory weight loss, or unwanted weight gain during the course of therapy may impact psychological wellbeing and cause psychological symptoms.[9]

**Measurement of Tissue Hypothyroidism**

The clinical relevance of tissue hypothyroidism has been debated without clear-cut results because of the lack of an easy, convenient, gold standard for measurement of the condition[13] so far. Various clinical, biochemical and other laboratory parameters have been proposed, however, which can be used in a clinical setting to assess tissue thyroid status.

The clinical score proposed by Zulewski et al., has been shown to be useful for the clinical diagnosis, or exclusion, of hypothyroidism. A score of >5 points to a diagnosis of hypothyroidism with a positive predictive value of 94.2% while a score of ≤2 excludes hypothyroidism with a negative predictive value of 94.2%. This score can be used to assess the degree of tissue hypothyroidism, to aid management of patients with conflicting laboratory results, to decide whether or not to treat subclinical hypothyroidism, and to monitor patient response to therapy.[9]

Biochemical parameters such as total cholesterol and serum creatine kinase may be elevated in tissue hypothyroidism. Other etiological factors for elevated values should be ruled out before ascribing these abnormalities to tissue hypothyroidism. Both serum cholesterol and creatine kinase demonstrate excellent correlation with the symptoms of hypothyroidism.[6] They should be measured routinely in all hypothyroid patients.

The ankle reflex relaxation time (ART), which can be measured using an achillometer[6] or kinemometer,[19] also correlates well with the severity of tissue hypothyroidism. This symptom also, rightly, receives maximum weightage
in the Billewicz score for hypothyroidism.[8] Unfortunately, this simple clinical tool is underutilized in clinical practice.

**Management of Tissue Hypothyroidism**

The mainstay of management of hypothyroidism is thyroxine. The endpoint for optimal thyroxine replacement, however, is debatable. While some advocate using the clinical status of patients to titrate thyroxine dosage,[9] others advise a combination of TSH measurement and clinical assessment for the same.[10] One may also choose to maintain serum TSH at low-normal, rather than at high-normal levels, in order to provide maximal clinical benefit to patients.[11]

Studies have reported benefit with a combination of thyroxine and T3 replacement in improving psychological symptoms, while maintaining a normal TSH.[12] However, no large studies have been carried out in recent years to confirm this.

Patients with euthyroid TSH levels, on thyroxine replacement, who complain of persistent symptoms, should be assessed for features of tissue hypothyroidism, such as hyperlipidemia and myalgia.

All secondary causes, such as diabetes, nephropathy and Vitamin D deficiency should be excluded or corrected. Appropriate therapy for dyslipidemia is indicated if the lipid profile does not normalize in spite of achieving euthyroidism.

**Conclusion**

As we manage our patients with hypothyroidism, we not only have to maintain normal TSH levels, but also achieve symptomatic relief and satisfaction. We have to avoid being unsympathetic and dismissive of their complaints.

The concept of tissue hypothyroidism may explain many of the clinical features that biochemically euthyroid patients present with. Using simple clinical and laboratory tools to measure, and correct, tissue thyroid function, will provide immense clinical benefit to patients of hypothyroidism.

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