Review Article

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

Sanjay Kalra, Sachin Kumar Khandelwal[1]

Department of Endocrinology, Bharti Hospital, [1]BRIDE, Kunjpura Road, Karnal, Haryana, India

ABSTRACT

A large number of hypothyroid patients, receiving adequate doses of thyroxine supplementation, continue to complain of dissatisfaction and varied symptoms. This review discuses 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)?

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.83333

Corresponding Author: : Dr. Sanjay Kalra, BRIDE, Kunjpura Road, Karnal, Haryana, India. E-mail: brideknl@gmail.com

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 seems 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 mμ/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

		New Score	
		Present	Absent
Symptoms			
Diminished sweating	Sweating in the warm room or a hot summer day	1	0
Hoarseness	Speaking voice, singing voice	1	0
Paraestheisa	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			
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
Peritorbital 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.[5]

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.[6]

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[20] others advise a combination of TSH measurement and clinical assessment for the same.[21] 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.[14]

Studies have reported benefit with a combination of thyroxine and T3 replacement in improving psychological symptoms, while maintaining a normal TSH.[22] 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.

References

1. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. Indian J Endocrinol Metab 2011;15:S78-81.
2. Macgregor AG. Why does anybody use thyroid BP? Lancet 1961;1:329-32.
3. O'Reilly DS. Thyroid function tests-time for a reassessment. BMJ 2000;320:1332-4.
4. Robert ND. Psychological problems in thyroid disease. Br Thyroid Found Newsl 1996;18:3.
5. Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA. Weight gain following treatment of hyperthyroidism. Clin Endocrinol (Oxford) 2001;55:233-9.
6. Zulewski H, Muller B, Excer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 1997;82:771-6.
7. Kalra S, Kalra B, Khandelwal SK. Vitamin D deficiency in hypothyroid patients in Haryana, India. Thyroid Research and Practice 2011 [In Press].
8. Billewicz WZ, Chapman RS, Crooks J, Day ME, Gossage J, Wayne E, *et al*. Statistical methods applied to the diagnosis of hypothyroidism. Q J Med 1969;38:255-66.
9. Card D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: Comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormone and clinical assessment. Clin Endocrinol (Oxf) 1988;28:325-33.
10. Saravaven P, Cahu WF, Roberts N, Vedhara K, Greenwood R, Dayon CM. Psyshological well-being in patients on 'adequate' doses of L-thyroxine: Results of a large, controlled community- based questionnaire study. Clin Endocrinol (Oxf) 2002;57:577-85.
11. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, *et al*. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1997;7:481-93.
12. Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, *et al*. The spectrum of subclinical and overt hypothyroidism effect on TSH prolactin, thyroid reserve and metabolic impact on target issues. Am J Med 1992;92:631-42.
13. Leslie PJ, Toft AD. The replacement therapy problem in hypothyroidism. Baillieres Clin Endocrinol Metab 1988;2:653-69.
14. Andersen S, Pedersen KM, Brunn NH, Lauberg P. Narrow individual variations in serum T4 and T3 in normal subjects: A clue to understanding subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068-72.
15. Sturgess I, Thomas SH, Pennell DJ, Mitshell D, Croft DN. Diurnal variation in TSH and free thyroid hormones in patients on thyroxine replacement. Acta Endocrinol (Copenh) 1989;121:674-6.
16. Larsen PR, Sliva JE, Kaplan MM. Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. Endocr Rev 1981;2:87-102.
17. Larsen PR. Thyroid-pituitary interaction: Feedback regulation of thyrotropm secretion by thyroid hormones. N Engl J Med 1982;306:23-32.
18. Maritinez L, Nascimento AS, Nunes FM, Phillips K, Aparicio R, Dias SM, *et al*. Gaining ligand selectivity in thyroid hormone receptors via entropy. Proc Natl Acad Sci USA 2009;106:20717-22.
19. Abraham AS, Atkinson M, Roscoe B. Value of Ankle-jerk Timing in the Assessment of Thyroid Function. Br Med J 1966;1:830-3.
20. Skinner GR, Thomas R, Taylor M, Sellarajah M, Bolt S, Krett S, *et al*. Thyroxine should be tried in clinically hypothyroid but bio-chemically enthyroid patients. BMJ 1997;314:1764.
21. Lazarus JH. Investigation and treatment of hypothyroidism. Clin Endocrinol (Oxf) 1996;44:129-31.
22. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triodothyroxine in patients with hypothyroidism. N Engl J Med 1999;340:424-9.

Cite this article as: Kalra S, Khandelwal SK. Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer?. Indian J Endocr Metab 2011;15:S95-8.

Source of Support: Nil, **Conflict of Interest:** None declared.