Original Article

Thyroid-Stimulating Hormone in Hypothyroidism – How High is Too High?

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Abstract

Background: The prevalence of hypothyroidism in the developed world is about 4-5% and in India is 10.9%. The goal of treating hypothyroidism is to maintain thyrotropin (TSH) levels within the normal reference range. Studies have shown that even within the normal range of TSH, patients with low normal TSH (LNT) have better outcomes when compared to patients with high normal TSH (HNT). **Aims and Objectives:** Our study aimed to find whether patients treated at a dose of levothyroxine resulting in an LNT had improved clinical outcomes and biochemical parameters, when compared to those on a levothyroxine dose resulting in an HNT. **Materials and Methods:** 180 patients with hypothyroidism on treatment, who had a TSH of 0.27-4.2mIU/L and had been on treatment with a stable dose of at least 50 micrograms of levothyroxine for at least 6 months were administered the Thyroid Symptom Questionnaire. TSH was assayed. Blood pressure and BMI were measured. Serum lipids were measured by spectrophotometry. **Results:** We found that patients with LNT and HNT did not differ with respect to cognitive symptoms , feelings of coldness, lethargy and fatigue. However, patients with LNT had a better lipid profile (mean LDL 132.24 in HNT and 115.39 in LNT p= 0.08) and lower BMI (1.045kg/m 2 lower in LNT compared to HNT) compared to HNT. **Conclusion:** Treating patients with a dose of thyroxine titrated to achieve LNT might decrease the cardiovascular risk by improving the lipid profile and BMI.

Keywords: Hypothyroidism, optimal thyroid-stimulating hormone, symptom relief

Introduction

Hypothyroidism is common around the world and in India. The prevalence of hypothyroidism in India is 10.9%. Yet, hypothyroidism is often underdiagnosed and undertreated.[1] Untreated hypothyroidism is associated with dyslipidemia, obesity, poor cognitive function, and pregnancy loss. It increases the risk of coronary artery disease (CAD).[2] The treatment of hypothyroidism with levothyroxine improves patient well-being. In addition, blood pressure (BP), body mass index (BMI), and biochemical parameters, including the lipid profile normalized.[3]

The therapeutic endpoint for the treatment of hypothyroidism is the thyroid-stimulating hormone (TSH) level, and immunometric assays for TSH are extremely sensitive. Conventionally, 4–5 mIU/L is used as the upper normal limit of TSH. However, within the normal range of TSH itself, there is a difference in clinical outcomes and biochemical parameters.[4] There is a difference of opinion regarding the target TSH in patients are treated for hypothyroidism,[5] and data are lacking as to the clinical and biochemical benefit of achieving low-normal TSH (LNT) values in the treatment of hypothyroidism.

This study was an attempt to find whether patients treated at a dose of levothyroxine resulting in an LNT had improved clinical outcomes in terms of well-being, lower BMI and better biochemical parameters when compared to patients treated to a target of high normal TSH (HNT).

Objectives

1. To correlate TSH with lipid levels, BP, and BMI in hypothyroid patients on treatment
2. To find whether patients with LNT had improved well-being when compared to patients with HNT.

Access this article online

Quick Response Code:

Website: www.actamedicainternational.com

DOI: 10.4103/ami.ami_76_18

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How to cite this article: Senthiappan RP, Bhat S, Krishna S. Thyroid-stimulating hormone in hypothyroidism – How high is too high? Acta Med Int 2019;6:11-6.

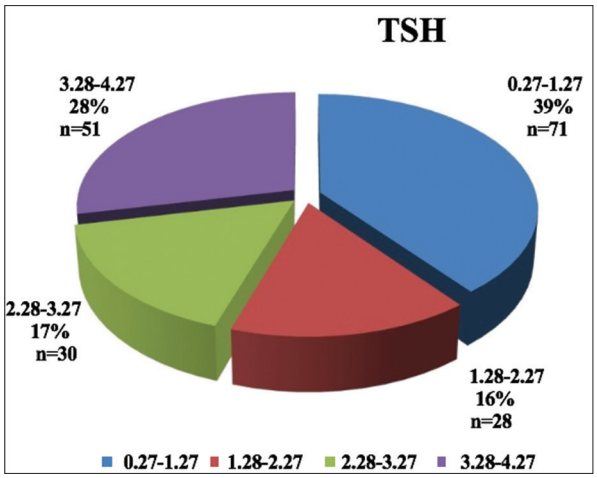

Figure 1: Patients with varying ranges of thyroid-stimulating hormone

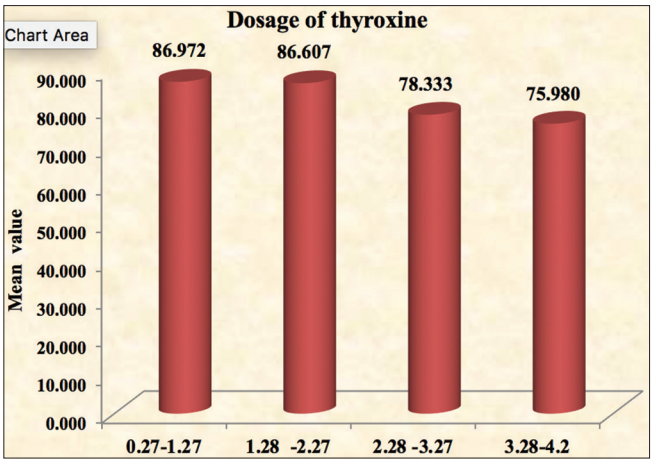

Figure 2: Thyroid-stimulating hormone versus mean dose of thyroxine

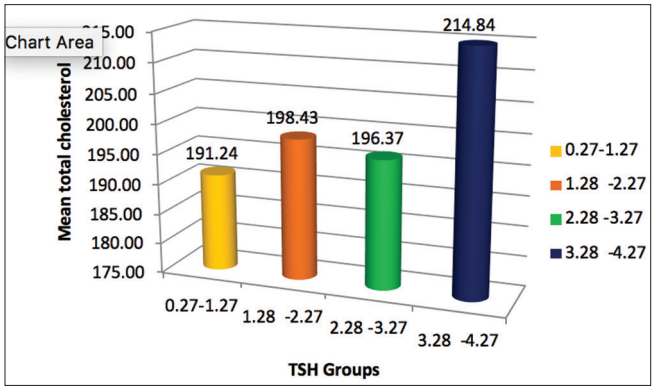

Figure 3: Thyroid-stimulating hormone versus total cholesterol

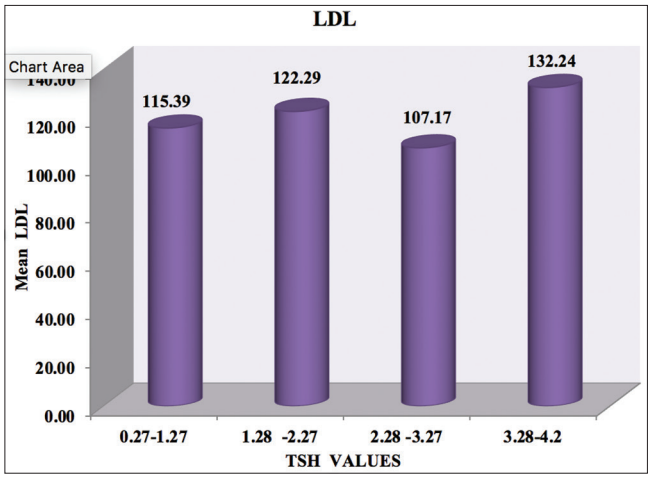

Figure 4: Thyroid-stimulating hormone versus low-density lipoprotein cholesterol

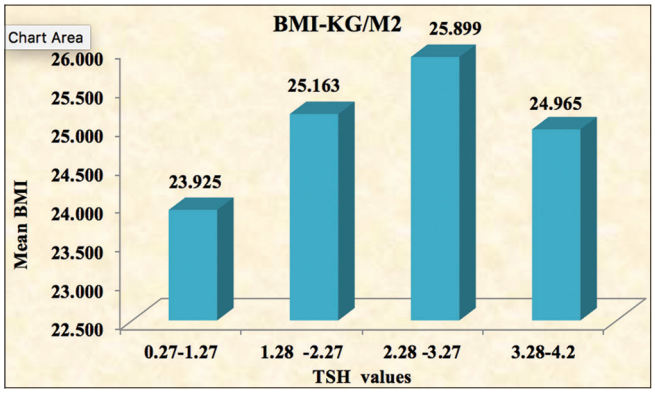

Figure 5: Thyroid-stimulating hormone versus body mass index

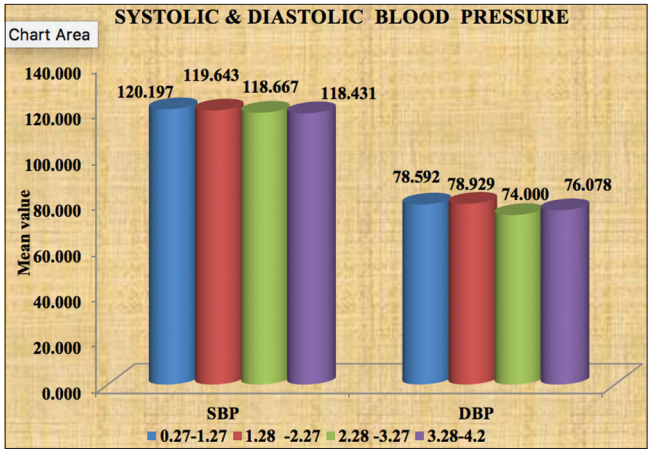

Figure 6: Thyroid-stimulating hormone versus blood pressure

Materials and Methods

The study was conducted on hypothyroid patients availing the out-patient and in-patient services of a medical college hospital in Mangalore, a city on the West coast of South India.

During the study period of 18 months, 180 consecutive adult patients with hypothyroidism on treatment, who fulfilled the inclusion criteria, were recruited for the study. Written informed consent was obtained. Patients who included in the study had a TSH of 0.27–4.2 mIU/L and had been on treatment with a stable dose of at least 50 µg of levothyroxine for at least 6 months. TSH was assayed by electro-chemiluminescence immunoassay that has a sensitivity of 0.005–100 µIU/ml. We excluded the patients who were on treatment for psychiatric illness, as also conditions which affected the lipid profile,

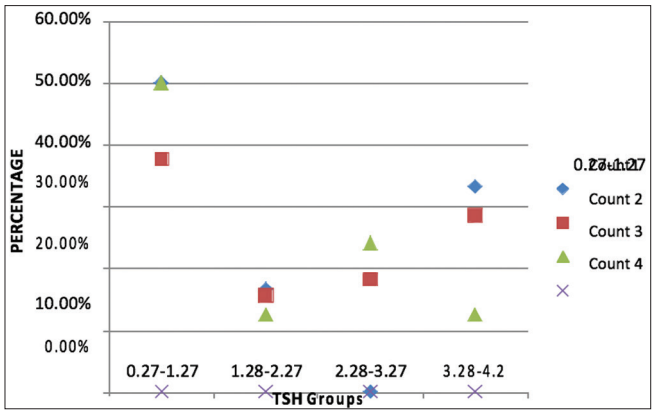

Figure 7: Thyroid Symptom Questionnaire clumsiness

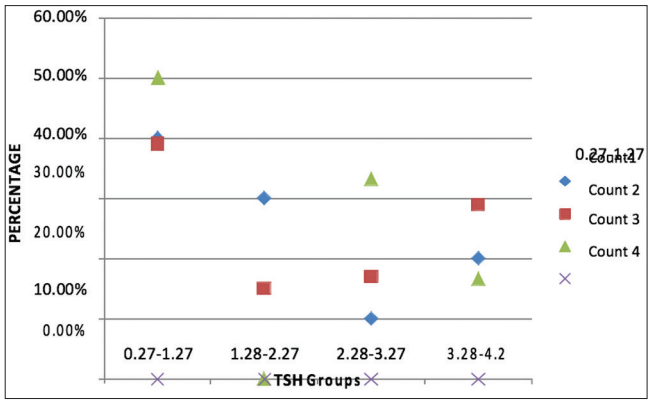

Figure 8: Thyroid Symptom Questionnaire making mistakes

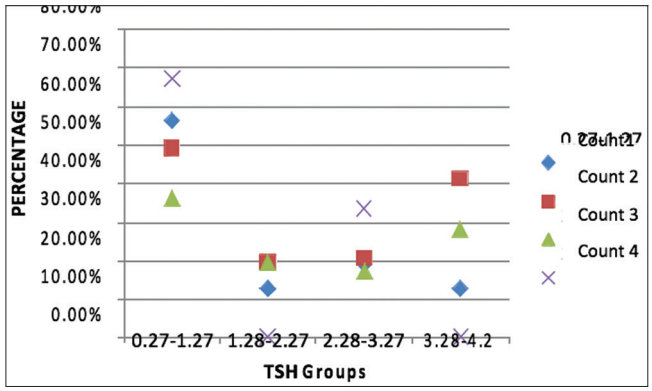

Figure 9: Thyroid Symptom Questionnaire inability to remember

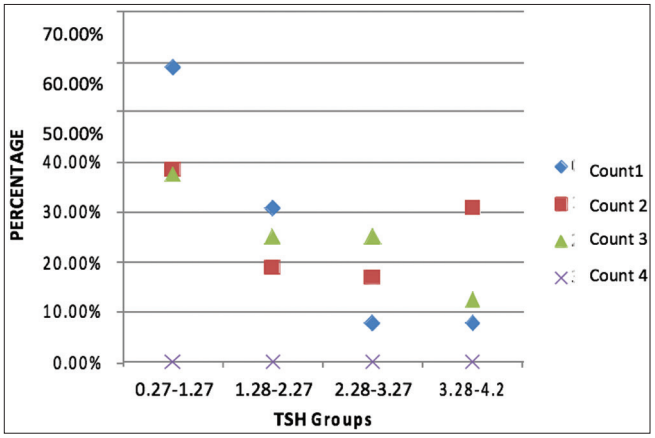

Figure 10: Thyroid Symptom Questionnaire difficulty in finding the right word

i.e., chronic kidney disease. Patients who were already on treatment for dyslipidemia were excluded from the study.

Recruited patients were administered the Thyroid Symptom Questionnaire (TSQ). BP and BMI were measured. Serum lipids were measured by the spectrophotometry.

Results

Of the 180 participants in the study, 96.1% were female and 3.9% were male. The majority of patients (71) were in the LNT range, i.e., 0.27 mIU/L to 1.27 mIU/L. Sixteen patients had TSH levels between 1.28 mIU/L and 2.27 mIU/L, 17 patients had TSH between 2.28 mIU/L and 3.27 mIU/L, and 51 patients had HNT, i.e., between 3.28 mIU/L and 4.27 mIU/L [Figure 1].

The mean average dose of thyroxine was the highest in LNT at 86.9 μg/day [Figure 2].

Patients with HNT had higher total cholesterol and low-density lipoprotein-cholesterol (LDL-C) values but no significant difference in high-density lipoprotein (HDL) or very low-density lipoprotein values [Figures 3 and 4].

Patients in the LNT group had higher diastolic BP and higher BMI [Figures 5 and 6].

We found that patients with irregular cycles and infertility were more frequent in the HNT group, while menorrhagia was a more common complaint in the LNT group. A higher number of patients in the LNT complained of headache.

There was no difference between groups in the cognitive parameters assessed by the TSQ, i.e., clumsiness, making careless mistakes, inability to remember things, or to find the right word [Figures 7-10].

Discussion

Hypothyroidism can present with multiple symptoms which impair the quality of life.[6] Hypothyroidism is diagnosed and therapy monitored by assessing the level of TSH. Symptoms tend to correlate with TSH level with patients with higher TSH are more symptomatic.[7] At present, the third-generation chemiluminometric assays are available, and the detection limit is 0.01. The optimal normal range of TSH remains controversial. The upper limit of TSH in most labs is considered to be 4–4.5 mIU/L. However, a large study showed that most euthyroid individuals had TSH <2.5 mIU/L.[8] Another study showed that most euthyroid participants had a TSH ranging between 0.3 and 3.63 mIU/L.[9] It is worth noting that TSH levels do not remain constant throughout life but tend to increase with age.[10]

Even when treated, not all the symptoms remit, and not all patients are satisfied with the management of their disease.[11]

It is possible that this dissatisfaction is due to an inadequate dose of thyroxine replacement. It has been found that patients feel relatively healthier when they are slightly hyperthyroid.[12] In fact, some studies have assessed whether supplementing thyroxine in patients who are clinically hypothyroid, but biochemically euthyroid has any benefit.[13] These studies have shown conflicting results with some studies showing benefit[14] while others do not.[13,15] Thus, controversy prevails about the reference range of normal TSH.

In view of this lack of clarity regarding a target TSH level, we wanted to find whether, while treating hypothyroidism titrating to a lower range of TSH resulted in better outcomes.

We assessed well-being and cognition with the TSQ. The TSQ was designed by Saravanan *et al*. It uses 12 questions to assess the symptoms in patients who are being treated for hypothyroidism.[16] It has been used to assess well-being and cognition in various studies, including ones to assess the impact of treating hypothyroidism with a combination of levothyroxine and liothyronine.

In this cross-sectional study of patients with treated hypothyroidism and normal levels of TSH, the majority of patients 71 (39%) had a LNT, and 58 (28%) patients had HNT. The remaining had TSH between 1.28 and 3.27 mIU/L. Those treated with a higher dose of thyroxine had an LNT. They were found to have lower LDL-C, higher diastolic BP, and an increased incidence of headache. Patients treated to an HNT had a higher chance of being infertile or having irregular menstrual cycles.

This study contrasts with work done by a Reh *et al*. which did not find a higher rate of infertility or miscarriage in patients treated to an HNT.[17] Even within the normal range, our patients with a higher TSH tended to have a higher body weight. Thyroid function variation even within the normal range might be one of the factors determining the body weight, with a significant association found with a BMI >30 and serum TSH levels.[18]

Hypothyroidism results in cognitive and emotional dysfunction. The depression and fatigue are both due to the thyroid disease itself and the effect of thyroxine deficiency on the brain tissue. When hypothyroidism is treated, the recovery of emotional and cognitive dysfunction is inconsistent.[19] We found no significant benefit in terms of less tiredness or improved cognitive function in patients treated to an LNT. Previous studies have also shown that psychological well-being is not one of the parameters which improve with the treatment of hypothyroidism.[16] This is in contrast to studies which show that treating autoimmune hypothyroidism[20] and subclinical hypothyroidism[21] results in some improvement in fatigue. Interestingly, it has been found that amelioration of fatigue when hypothyroidism is treated does not depend on the absolute value of TSH so much as the fall in TSH values with treatment.[22] Another factor which might have influenced persistence of fatigue even after the treatment is the fact that the majority of our patients were female, and females were more likely to complain of persistent fatigue even after the treatment.[22]

Participants with LNT had lower total and LDL-C levels. Even within the normal range of TSH, increasing TSH correlates with increasing LDL-C and decreasing HDL cholesterol levels.[23] Thyroxine induces HMG co-A-reductase, and T3 upregulates LDL receptors.[24] In addition, thyroid hormones increase the activity of cholesteryl ester transfer protein. Hypothyroidism is associated with dyslipidemia, hypertension, and elevated levels of homocysteine.[25] In addition, endothelial dysfunction has been noted in hypothyroidism.[26] Thus, the implication of hypothyroidism in CAD is multifactorial. Subclinical hypothyroidism has also been shown to increase the risk of coronary heart disease.[27] Whether treating patients with mild hypothyroidism decreased the incidence of CAD has been studied. It was found that though treating hypothyroidism improved the lipid profile,[28] this did not translate into an overall mortality benefit.[29]

Patients with LNT did not fare better in terms of well-being and quality of life.

The literature shows that various symptoms of hypothyroidism respond differently to treatment with levothyroxine and not all are ameliorated even with normal TSH.[7]

In this study, infertility and menorrhagia were more common with HNT. We found that patients with HNT had a higher rate of infertility and irregular menstrual cycles. Subclinical hypothyroidism impacts reproductive health and results in increased risks of abruptio placentae and preterm delivery.[30]

In patients being treated for hypothyroidism, inadequate replacement with levothyroxine results in abortion and premature delivery.[31] Normal TSH levels seem to be a prerequisite for normal conception and delivery, as even HNT may result in infertility.[32]

It has been found that even subclinical or minimal hypothyroidism during pregnancy is associated with a greater risk of miscarriage, and may also have far-reaching adverse consequences on later cognitive development of the infant.[33] Therefore, patients with menstrual disturbances and expectant mothers might benefit from titration to LNT.

There were some interesting findings which could not be explained by chance alone. We found that headache was one of the symptoms that worsened when hypothyroidism was treated to LNT. This has been seen in other studies, including a large cross-sectional study where the prevalence of headache was greater in individuals with an LNT. It was speculated that LNT reflected high adrenergic activity.[34] The role of the sympathetic nervous system in the pathogenesis of migraine has been suggested by various researchers.[35,36]

In a large population-based study in Norway, it was found that women with higher TSH values had a lower headache prevalence.[15] However, hypothyroidism is itself known

to cause headaches and must be ruled out while treating headache.[37] The influence of thyroxine on headache is not clear yet and requires further work.

Another interesting finding was the increased diastolic blood pressure in patients with LNT. One study showed that, within the normal range of TSH, different levels of TSH had no relation with the BP. [38] However, there is contradictory evidence regarding the effect of TSH within the normal range on BP – a study on the elderly Chinese women showed that HNT was an independent risk factor for the development of hypertension. Whether the effect of the thyroid on BP is influenced by ethnicity is a question that remains to be answered.

This study had certain limitations. First, the TSQ was initially not developed for the use of Indian patients, and the responses when translated into the local language may have reflected symptoms and the state of well-being less accurately. It depends on responses by the patient and hence suffers from the inherent limitation of a subjective instrument. The study was not blinded.

Conclusion

In spite of these limitations, an important take-home message from this study is that treating hypothyroid patients with a dose of thyroxine titrated to maintain LNT resulted in lower BMI and lower total and LDL-C. This might decrease cardiovascular risk. Randomized controlled trials with more objective measures of well-being will help to elucidate ideal target levels of TSH.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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