

# Are patients with primary hypothyroidism in India receiving appropriate thyroxine replacement? An observational study

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## ABSTRACT

**Background:** A large proportion of patients worldwide under treatment for hypothyroidism with thyroxine show suboptimal Thyroid Stimulating Hormone (TSH) values. There is a paucity of Indian data on 'out-of-range' TSH values in patients with primary hypothyroidism receiving levothyroxine treatment. **Aim:** To assess the percentage of primary hypothyroid patients with abnormal thyroid function despite being prescribed levothyroxine for at least 2 m. **Materials and Methods:** A cross-sectional, single visit, observational study in adult patients with primary hypothyroidism on treatment with levothyroxine for at least 2m was undertaken across 10 cities in India. Compliance to thyroxine therapy was assessed by interviewing the subjects and their quality of life was assessed by administering the SF-36 questionnaire. A random blood sample (5ml) was drawn from the study subjects during the same visit for assessing serum TSH levels. TSH levels were correlated with the current dose of levothyroxine. **Results:** A total of 1950 subjects (mean age  $41.4 \pm 11.17$  years; female 81.2%, male 18.8%) with primary hypothyroidism were enrolled in the study. Of the 1925 subjects in whom TSH values were available, 808 (41.97%) were under-treated ( $TSH > 4$  mIU/L) and 243 (12.62%) were over-treated ( $TSH < 0.4$  mIU/L). The mean dose of thyroxine in this study was  $1.23 \mu\text{g/kg/day}$  ( $\pm 0.85$ ). Majority of subjects (90.79%) were compliant/moderately compliant to thyroxine therapy. Age and autoimmune hypothyroidism were the factors that had significant impact on serum TSH. Subjects with abnormal TSH had significantly lower scores for role limitation due to emotional problems ( $P = 0.0278$ ) and due to physical health ( $P = 0.0763$ ). **Conclusion:** This study concluded that around half (54%) of known hypothyroid subjects had out-of-range serum TSH despite being treated with levothyroxine for at least 2m. The mean daily dose of thyroxine ( $1.23 \mu\text{g/kg} \pm 0.85$ ) was less than the recommended full replacement dose.

**Key words:** Hypothyroidism, India, levothyroxine, primary hypothyroidism, serum TSH, thyroxine

## INTRODUCTION

Primary hypothyroidism is one of the most common endocrine diseases. Prevalence of hypothyroidism in the general population ranges from 3.8% - 4.6%.<sup>[1]</sup> In a study,

conducted in Delhi from 2007 to 2010 prevalence of overt hypothyroidism was reported to be 4.2%.<sup>[2]</sup> Another epidemiology study in the Indian population suggested the overall prevalence of hypothyroidism to be 10.95%.<sup>[3]</sup> The Wickham twenty year follow up survey to determine the incidence and natural history of thyroid disease in cohort of 2779 adults showed an annual incidence of hypothyroidism of 4.1 per 1000 survivors per year in women and 0.6 per 1000 survivors per year in men.<sup>[4]</sup> It has been estimated that about 42 million people in India suffer from thyroid diseases.<sup>[5]</sup>

Levothyroxine is the treatment of choice for hypothyroidism.<sup>[6]</sup> While treating hypothyroidism, clinicians

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aim to ensure that thyroid stimulating hormone (TSH) levels remain within the normal range. Diagnosis and treatment of hypothyroidism is often considered simple however, studies continue to show problems in the management of this condition. In a survey of thyroid disease prevalence in Colorado, USA, up to 40% of patients taking thyroid medications had TSH levels outside the normal reference range.<sup>[7]</sup> Many factors such as age, etiology of hypothyroidism, concomitant medications and concomitant illness, etc., are known to alter serum TSH, fuelling the need for dosage individualization.<sup>[8]</sup> This concern highlights the need for monitoring thyroxine therapy by regular estimation of serum TSH levels so that they remain within the normal range. Many patients on thyroxine therapy are either over-treated or under-treated.<sup>[9]</sup> TSH values falling outside the normal range could be due to the presence of confounding factors, failure to adjust thyroxine dose as per these confounders or poor compliance on the part of patients.<sup>[7,9-13]</sup> There has been a lack of data on Indian hypothyroid patients with out-of-range TSH values and the reasons for the same.

This study was undertaken to determine the proportion of primary hypothyroid patients in India having out-of-range serum TSH values, despite having been prescribed thyroxine, and to assess the reasons for out-of-range serum values (either non-compliance or failure to adjust dose based on confounding factors). The patients' quality of life parameters (using SF-36 questionnaire) were also assessed and correlated with serum TSH.

## MATERIALS AND METHODS

This was an observational cross-sectional single visit out-patient study, that included adult patients with primary hypothyroidism who were on treatment with levothyroxine for at least 3m and on a stable dose of thyroxine for at least 2m prior to enrolment. Approximately 150 physicians were selected from across 10 cities in India. Approximately 13 patients were planned to be recruited from each participating site/physician to reach a total sample size of about 2000. The study was conducted in accordance with the International Conference on Harmonization (ICH-GCP) and regulations and guidelines having their origin in the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation.

### Objectives

The primary objective of the study was to assess the percentage (%) of primary hypothyroid patients with abnormal thyroid function (measured using serum TSH level as surrogate marker of thyroid function), despite being prescribed levothyroxine for at least 2 m prior to enrolment.

### Secondary objectives were

- To assess the reasons for out-of-range serum TSH values and included: (i) Presence of confounding factors (age, etiology of hypothyroidism, concomitant medication and illness etc.) and failure to adjust dose for such confounders, (ii) Poor compliance on part of patients and
- To assess their quality of life.

### Study Procedure

#### Participants

Subjects aged  $\geq 18$  and  $\leq 60$  years diagnosed with primary hypothyroidism were enrolled in the study. They were required to be on treatment with any brand of levothyroxine for at least 3 m and on a stable dose of thyroxine for at least 2 m prior to enrolment. Those receiving tri-iodothyronine (T3) therapy, pregnant women, lactating mothers, mentally retarded patients and those with central hypothyroidism or with transient hypothyroidism were excluded from the study.

#### Measurements

Medical history, physical examination and vital signs were recorded for each subject along with a review of previous medical/laboratory record prior to enrolment.

An attempt was made to document the first (original) TSH level to ensure that study participants suffered from primary hypothyroidism. Data pertaining to demography; etiology of primary hypothyroidism; the dose, duration and brand of thyroxine used; concomitant medications and illness were documented. Compliance to thyroxine therapy and quality of life were assessed by interviewing subjects and administering the SF-36 questionnaire during the visit. A random blood sample of 5 ml was drawn from these subjects during the same visit for assessment of serum TSH and T4 levels.

The reference range for TSH for male/female in the age range of 18-20 years was 0.70 - 6.40 mIU/L while, for 21-60 years was 0.40-5.50mIU/L. Based on the current thyroid function test result, participants were classified using following definitions.

Abnormal TSH value: Patients who had out of range TSH values were classified into over and under treated patients; Over-treated patients with TSH  $< 0.40$  mIU/L and Under-treated patients with TSH value  $> 4$  mIU/L). Adequately treated patients were in the range of  $0.4 \leq \text{TSH} \leq 4$ . Low TSH: Subjects with TSH value less than the minimum reference range. High TSH: Subjects with TSH value greater than the minimum reference range.

### Assessment of compliance

Compliance to thyroxine therapy was assessed by asking the patients the number of doses missed in the last 1m and was categorized as follows:

- Compliant to treatment: Missed <5% dose in the last 1m
- Moderately compliant to treatment: Missed  $\geq 5\%$  but <15% dose in the last 1m
- Non-compliant to treatment: Missed  $\geq 15\%$  dose in the last 1m

### SF-36 Questionnaire

The SF-36 questionnaire contained 36 questions, arranged in 8 items or subscales (physical functioning, role limitation due to physical health and emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health). Each question was scored in a way that a higher score meant a better quality of life.

### Statistical methods

The analysis set considered in this study was Full Analysis Set (FAS), which consisted of all enrolled patients. The demographic characteristics were summarized for age, height, weight and sex. Continuous variables were summarized using descriptive statistics such as 'n' mean, standard deviation, median, Inter-quartile range (IQR), minimum and maximum. Categorical variables were summarized using counts and percentages.

The percentage and counts of subjects who had serum TSH value outside the normal range was calculated along with two-sided 99% CI. Percentage of subjects in various compliance categories was calculated and any implication of poor compliance on serum TSH levels was evaluated using Chi-square test and logistic regression. Descriptive statistics was provided for each of the 8 items of SF-36 questionnaire. Sub group analysis was undertaken in a post-hoc fashion to assess the impact of possible confounding factors (age, etiology of primary hypothyroidism, concomitant medications, concomitant illness, etc.) on serum TSH level and it was assessed whether this subgroup of subjects received an ideal dose of thyroxine, individualized as per their requirement. For such subgroup analysis, serum TSH levels were compared using Analysis of Variance (ANOVA) or Kruskal-Wallis test as applicable. Post-hoc analysis was undertaken for SF-36 subscale scores between subgroups of subjects who had TSH value within the normal range versus those with TSH value outside the normal range.

## RESULTS

A total of 1950 subjects were enrolled in the study across 10 cities in India and all subjects completed the study.

Out of the 1950 subjects, 1584 (81.2%) were female and 366 (18.8%) were male subjects [Table 1]. Mean age of subjects was 41.1 years. Two major causes underlying the etiology of primary hypothyroidism were autoimmune diseases (50.3%) and iodine deficiency (12.8%) [Table 2]. Benign thyroid nodules were observed in 6 (0.31%) subjects with duration of nodule ranging from 0 to 5 years while 2 (0.1%) subjects had history of thyroid surgery. All the subjects enrolled in the study were taking some brand of levothyroxine. The average daily dose of levothyroxine was found to be 1.23 $\mu$ g/kg/day. There was no evidence that the daily thyroxine dose affected TSH levels in the under and over-treated groups.

### Primary hypothyroid subjects with abnormal TSH values

Of the 1950 study subjects, 25 had missing values for TSH. Of the 1925 subjects for whom the TSH values were available, a total of 1051 (54.6%) subjects were found to have abnormal thyroid function (99% CI - 51.7, 57.5), of which 808 (41.97%) subjects were under-treated and 243 (12.62%) subjects were over-treated.

**Table 1: Demographic characteristics of the study population**

	n=1950
Gender, n* (%)	
Female	1584 (81.20)
Male	366 (18.80)
Age (years)	
Mean $\pm$ SD**	41.40 $\pm$ 11.17
Min-max (years)	18-60
Weight (Kg)	
Mean $\pm$ SD	66.53 (13.62)
Min-max (Kg)	33-164
Height (cm)	
Mean $\pm$ SD	157.39 (7.75)
Min-max (cm)	89-185

\*n: Number of subjects, \*\*SD: Standard deviation

**Table 2: Etiology of primary hypothyroidism of the study population**

Primary diagnosis	Categories	N=1950* n** (%)
Autoimmune	Hashimoto's thyroiditis	884 (45.3)
	Atrophic thyroiditis	97 (5.0)
Congenital hypothyroidism	Dyshormonogenesis	1 (0.1)
	TSH-r mutation	1 (0.1)
Drugs	Iodine excess (including iodine-containing contrast media and amiodarone)	1 (0.1)
	Lithium	1 (0.1)
	Antithyroid drugs	1 (0.1)
	Interferon and other cytokines	1 (0.1)
	I <sup>131</sup> treatment	3 (0.2)
Iatrogenic	Subtotal or total thyroidectomy	1 (0.1)
	Other	345 (17.7)

\*etiology for hypothyroidism was unknown for 614 patients, \*\*n: Number of subjects. TSH-r: Thyroid stimulating hormone receptor

### Analysis of subjects with abnormal TSH values in compliant and non-compliant group

Among the subjects who were compliant to the treatment ( $n = 1754$ ), 760 (43.33%) subjects had abnormal TSH values (99% CI - 40.28, 46.38) and the remaining 994 had normal TSH value. Though these subjects were compliant to treatment, a significant number ( $P < 0.0001$ ) had an abnormal TSH value as compared to those having normal TSH value. Out of 760 subjects who were compliant to treatment and had abnormal TSH values, 69.47% subjects ( $n = 528$ ) were found to have abnormal high TSH values and 30.35% ( $n = 232$ ) subjects had abnormal low TSH values.

Among the 171 subjects who were non-compliant to the treatment, 68 (39.77%) subjects had abnormal TSH value (99% CI - 30.13, 49.41) and remaining 103 (60.23%) had normal TSH value. Significant difference ( $P < 0.0001$ ) was observed between subjects who had abnormal TSH value as compared to those having normal TSH value in the non-compliant to treatment group. Out of 68 subjects who were not compliant to treatment and had abnormal TSH values, 79.41% subjects ( $n = 54$ ) were found to have abnormal high TSH values and 20.59% ( $n = 14$ ) subjects had abnormal low TSH values.

### Association between compliance and TSH values

No association was observed between compliance (compliant/non compliant) and the TSH values (normal/abnormal) with  $P = 0.3690$ .

### Secondary variables

#### Subgroup analysis by the following confounding factors

##### Age

It was observed that age categories had a significant ( $P < 0.0494$ ) impact on the TSH levels. Subjects  $\geq 41$  years had significantly lower serum TSH than subjects  $< 41$  years [Table 3].

### Etiology of hypothyroidism

Autoimmune hypothyroidism had a significant ( $P = 0.0013$ ) impact on TSH levels. Subjects with autoimmune hypothyroidism had significantly ( $P = 0.0013$ ) higher serum TSH than those without this etiology (8.63 vs. 8.08 mIU/L) [Table 4].

### Concomitant medication and concomitant illness

Hypertension (14.4%) and Diabetes mellitus (9.38%) were the most common concomitant diseases observed in the study population and consequently the most common concomitant medications taken were antihypertensives and antidiabetics. The Wilcoxon two sample test showed that concomitant medication and presence or absence of a concomitant illness as confounding factors did not have

a significant ( $P = 0.9528$  and  $P = 0.8852$ , respectively) impact on serum TSH.

### Analysis of SF-36 Questionnaire

Analysis of role limitation due to emotional problems showed that there was significant ( $P = 0.0278$ ) difference between subjects with normal TSH and those with abnormal TSH. The mean scores for subjects with normal TSH was higher ( $70.9 \pm 37.5$ ) as compared to subjects with abnormal TSH ( $67 \pm 38.84$ ) indicating that people with normal TSH had a significantly better quality of life. Similarly, scores for role limitation due to physical health was significantly ( $P = 0.0763$ ) different between subjects with normal TSH (mean score:  $69.6 \pm 37.16$ ) and those with abnormal TSH (mean score:  $66.6 \pm 37.48$ ), indicating that people with normal TSH had a significantly better quality of life [Table 5].

Scores for general health, physical functioning, social functioning, pain and energy/fatigue as derived from the SF- 36 questionnaire were not significantly different for subjects with normal TSH and those with abnormal TSH values.

## DISCUSSION

In the present study, we assessed the proportion of primary hypothyroid patients in India who had abnormal thyroid function values despite taking levothyronine, and the reasons for the out-of range TSH value. We found that despite receiving stable doses of levothyroxine, 54.6% hypothyroid subjects ( $n = 1051$ ) were found to have out of range TSH values. These subjects were either under-treated (41.97%) with TSH value  $> 4$  mIU/L, or over-treated (12.62%) with TSH  $< 0.40$  mIU/L.

**Table 3: Analysis of serum TSH levels based on age**

Summary statistics	Age categories		
	$< 41$ years	$\geq 41$ years	P value (Wilcoxon two sample test)
Serum TSH levels			
$n^*$	928	994	0.0190
Mean score $\pm$ SD**	9.60 $\pm$ 27.29	7.20 $\pm$ 22.09	

\*n: Number of subjects, \*\*SD: Standard deviation

**Table 4: Analysis of serum TSH levels based on autoimmune hypothyroidism**

Summary Statistics	Auto immune hypothyroidism		P value (Wilcoxon Two sample test)
	Yes	No	
Serum TSH levels			
$n^*$	973	952	0.0013
Mean score $\pm$ SD**	8.63 $\pm$ 21.52	8.08 $\pm$ 27.66	

\*n: Number of subjects, \*\*SD: standard deviation



**Table 5: Summary of Role Limitation Due to Emotional and Physical Health of SF-36 Questionnaire**

	Categories	Normal TSH	Abnormal TSH	P value by T-Test
Quality of life in Role limitation due to emotional health - SF36	<i>n</i> *	1097	828	0.0278
	Mean±SD	70.9±37.5	67±38.84	
Quality of life in Role limitation due to physical health - SF36	<i>n</i> **	1097	828	0.0763
	Mean±SD	69.6±37.16	66.6±37.48	

\**n*: Number of subjects, \*\*SD: Standard deviation

Various other studies have shown similar findings, a thyroxine treatment study in the UK revealed that serum TSH was outside the reference range in almost half of the cases (47%), with approximately one quarter (27%) having results above normal and one-fifth below normal.<sup>[9]</sup> In the National Health and Nutritional Examinations Survey (NHANES III), abnormal thyroid function tests were detected in a third of patients who self-reported thyroid disease or use of thyroid medications.<sup>[11]</sup> While a raised TSH level might have adverse consequences in terms of an increased risk of ischemic heart disease and dyslipidemia,<sup>[14-16]</sup> the suppression of TSH levels might have an impact on bone mineral density predisposing to osteoporosis and also an increased risk of cardiac arrhythmias and a hyperthyroid state.<sup>[17,18]</sup>

The reasons for inadequate thyroid hormone replacement are many fold and include factors such as inappropriate dosage, poor patient compliance or concurrent use of medicines.<sup>[19]</sup> Primary hypothyroidism can be treated satisfactorily with levothyroxine at an average daily dose of about 1.6 µg/kg ideal body weight.<sup>[20]</sup> The mean dose of thyroxine in this study was found to be 1.23 µg/kg/day (±0.85).

Levothyroxine requirements decrease with age. The present study included adult patients >18 to ≤60 years of age. The median age of the study population was 41 years. It was found that age (< or ≥ than 41 years) as a confounding factor had a significant impact on TSH values. Subjects who were ≥41 years of age had lower TSH levels than those who were below 41 years. This indicates that it is essential to adjust the dose of levothyroxine based on age of the patient to achieve a euthyroid state, and failure to do so may result in out-of-range TSH values.

The commonest cause of hypothyroidism in developed countries is autoimmune thyroiditis which may be associated with Hashimoto's thyroiditis or thyroid atrophy. In some parts of the world iodine deficiency remains highly prevalent. It was observed in this study that 50.3% had autoimmune disease (Hashimoto's thyroiditis and Atrophic thyroiditis) and 12.8% had Iodine deficiency as the primary diagnosis. Statistical analysis of the study data showed that the presence of autoimmune disease

(as a confounding factor) had a significant impact on TSH values. Patients with autoimmune hypothyroidism had significantly higher serum TSH than those without this etiology indicating a need for higher average doses of levothyroxine. Iodine deficiency which was the second major cause of hypothyroidism (12.8%) in the study population did not have any impact on the TSH values. The most common concomitant illnesses observed in the study population were Diabetes mellitus (9.38%) and Hypertension (14.41%), and the presence of either of these illnesses did not have a significant impact on TSH levels. Concomitant medication was not found to have a significant impact on TSH levels. However; it should be noted that, of the 1950 patients in the study, 125 were taking metformin (5.64%) or its combinations (0.8%). It is reported that the use of metformin is associated with a significant reduction in the serum TSH levels in diabetic patients with primary hypothyroidism, both with and without levothyroxine replacement therapy.<sup>[21]</sup> As a result, levothyroxine therapy may show inadequate treatment outcomes in the presence of Metformin as a concomitant medication.

The commonest cause of inadequate response to treatment (as indicated by out-of-range TSH value in this case) is poor compliance, which is not unusual with any chronic therapy. In this study, the majority of patients (90.82%) were found to be compliant/moderately compliant to thyroxine therapy. Our study did not find a co-relation between compliance and TSH values. However logistic regression analysis of serum TSH based on the broad category of compliance was performed for the subgroup of patients having autoimmune hypothyroidism. In this subgroup, the chance of a compliant patient showing abnormal TSH was significantly low. Likewise in the patients who did not have autoimmune hypothyroidism the chance of compliant patient showing abnormal TSH was significantly high. This finding suggests compliance could play an important role especially in autoimmune hypothyroidism. Apart from poor patient compliance, inadequate dosage/dosing adjustment resulting in under- and over-treatment of thyroid diseases is also a major cause of a poor therapy outcome. As per the Indian guidelines,<sup>[22]</sup> for patients below the age of 60 years with no history of cardiac or respiratory disease, the full replacement dose of levothyroxine ranges from

1.6-1.8 µg/kg body weight. The mean dose of thyroxine in this study was found to be 1.23 µg/kg which is less than the full replacement dose. This could be the reason for under-treatment seen in the population studied. The final objective of the study was to evaluate the effect of out-of-range TSH values on the quality of the patient's life. In this study, the scores for role limitation due to emotional problems was significantly ( $P = 0.0278$ ) different between patients with normal TSH (having higher mean score) and those with abnormal TSH (lower mean score). Similarly, scores for role limitation due to physical health was significantly ( $P = 0.0763$ ) different between patients with normal TSH (higher mean score) and those with abnormal TSH (lower mean score), indicating that subjects with normal TSH values showed a better quality of life. General health, physical functioning, social functioning, pain and vitality scores were not significantly different between patients with normal and abnormal TSH values.

## CONCLUSION

This study concluded that around half (54%) of known Indian hypothyroid patients had out-of-range serum TSH values despite being treated with levothyroxine for at least 2 m. The prevalence of hypothyroidism was more common in females than in males. The mean daily dose of thyroxine (1.23 µg/kg  $\pm$  0.85) was less than the recommended full replacement dose. Though the majority of patients were compliant to treatment, no association was found between compliance and serum TSH. Age and autoimmune hypothyroidism were the factors that had significant impact on serum TSH. Patients with abnormal TSH experienced role limitation due to emotional problems and physical health.

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