Original Article

The Thyroid Registry: Clinical and Hormonal Characteristics of Adult Indian Patients with Hypothyroidism

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Abstract

Objectives: Appropriate treatment of hypothyroidism requires accurate diagnosis. This registry aimed to study the disease profile and treatment paradigm in hypothyroid patients in India. **Materials and Methods:** We registered 1500 newly diagnosed, treatment-naïve, adult hypothyroid males and nonpregnant females across 33 centers and collected relevant data from medical records. The first analysis report on baseline data is presented here. **Results:** The mean age of the study population was 41.1 ± 14.01 years with a female to male ratio of 7:3. The most frequently reported symptoms and signs were fatigue (60.17%) and weight gain with poor appetite (36.22%). Menstrual abnormalities were reported in all women (n = 730) who had not attained menopause. Grades 1 and 2 goiter (as per the WHO) were observed in 15.41% and 3.27% patients, respectively. Comorbidities were reported in 545 patients (36.36%), type 2 diabetes mellitus being the most prevalent (13.54%) followed by hypertension (11.34%). Total serum thyroxine (T4) and thyroid-stimulating hormone (TSH) levels were assessed in 291 (19.47%) patients only. In majority of patients (81%), treatment was based on serum TSH levels alone. The dose of levothyroxine ranged from 12.5 to 375 mcg. **Conclusions:** Guidelines suggest a diagnosis of hypothyroidism based on TSH and T4 levels. However, most of the patients as observed in this registry received treatment with levothyroxine based on TSH levels alone, thus highlighting the need for awareness and scientific education among clinicians in India. The use of standard doses (100, 75, and 25 mcg) of levothyroxine may point toward empirical management practices.

Keywords: Diagnosis, levothyroxine, subclinical hypothyroidism, thyroid hormone profile

Introduction

Hypothyroidism is a common but underdiagnosed disorder because of its nonspecific clinical presentation.[1,2] Primary hypothyroidism is an abnormality in the thyroid gland itself – it can be subclinical or overt. Disorders affecting either the pituitary gland or the hypothalamus cause secondary or central hypothyroidism. Untreated hypothyroidism may lead to serious cardiovascular and neurological complications.[3,4]

The prevalence of hypothyroidism in developed countries is about 4%–5%, whereas in India, it is reported to be around 10.95%.[5,6] As per the epidemiology study conducted by Unnikrishnan *et al*. in eight cities of India, the prevalence of subclinical hypothyroidism (SCH), a mild thyroid failure, was found to be 8.02%.[7] The prevalence of SCH ranges between 4% and 15% worldwide and is reported to be 11.4% for women and 6.2% for men in India.[7,8]

Patients with hypothyroidism show a greater propensity for comorbidities and complications as compared to the general population. Among the Indian population, patients with asthma, obesity, diabetes, dyslipidemia, and hypertension had the higher prevalence of hypothyroidism.[2] Patients with SCH have a high rate of progression to overt hypothyroidism, 4.3% if thyroperoxidase antibodies are present, and 2.6% per year if they are absent. The rate of progression is also higher in the case of females and the elderly.[9,10]

Early accurate diagnosis and treatment of hypothyroidism is crucial and often challenging in clinical practice because of multiple manifestations; this challenge is even more in SCH. Although the preferred test for diagnosing hypothyroidism is thyroid-stimulating hormone (TSH), in some situations it can be misleading. Guidelines recommend that estimation

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of T4 along with TSH is required for a proper classification of hypothyroid state such as subclinical, overt, or secondary hypothyroidism.[11] Further, based on this classification, a tailored treatment approach for each patient can be adapted.[11]

The aim of this registry was to create a database of Indian patients with newly diagnosed hypothyroidism to determine clinical presentations, hormonal profiles, diagnostic workup, comorbidities, and management practices, being followed in the real-life clinical setting. This first analysis report focuses only on the baseline data of the enrolled population.

Materials and Methods

Study design

This multicenter registry was conducted in compliance with the International Conference on Harmonisation–Good Clinical Practice guidelines. All study documents including protocol, subject information, and patient authorization forms were approved by the Independent Ethics Committee/Institutional Review Board for each site prior to the study conduct. Written informed consent was obtained from each patient prior to enrollment. Newly diagnosed, treatment-naïve, adult hypothyroid males and nonpregnant females visiting a general practitioner or a physician as a part of their clinic visit were included in the study, if eligible and willing. Patients requiring hospital admission at the time of enrolment or who had a malignancy or history of malignancy in the last 5 years were excluded from the study. The patients were scheduled to be followed up as per routine clinical practice.

The study was registered by the sponsor on a publicly accessible database of the clinical trial registry, India (link: www.ctri.nic.in; CTRI/2015/04/005675).

Study-related information was recorded in the case report forms. The data collected at baseline included demography, medical history, clinical presentations, available laboratory results, thyroid hormone profile, and treatment prescribed. No additional diagnostic or monitoring procedures (other than standard of care) were performed during the study conduct.

Study endpoints

Demographics and clinical profile of patients along with complications and comorbidities associated with hypothyroidism were recorded. The thyroid hormone profile and treatment prescribed by the physician as per the clinical practice were observed.

Statistical methods

All statistical and safety analyses were performed using SAS® version 9.3 (SAS Institute Inc., USA). Continuous variables were summarized with the descriptive statistics and summary of categorical data were summarized using numbers and percentages.

Results

A total of 1500 patients with newly diagnosed hypothyroidism were enrolled in this registry across 33 centers in India between December 2014 and September 2015. Of these, 1499 were included in the full analysis set. One patient was excluded from the analysis due to insufficient data.

Demographic characteristics

Of the 1499 patients, 1061 (70.78%) were women and 438 (29.22%) were men. Most of the study population was urban (86.86%) and the age ranged from 18 to 87 years (mean ± standard deviation of 41.1 ± 14.01 years). A larger number of patients (40.43%) were in the age group of 18–35 years followed by 25.08% in the age group of 36–45 years. A majority of the patients were married (86.32%) and belonged to the upper-middle socioeconomic class (60.71%). The mean BMI was 26.4 ± 4.95 kg/m^2 (range: 13.6–47.4 kg/m^2). Demographic characteristics are mentioned in Table 1.

Clinical presentation

Fatigue (902 [60.17%]) was the most common presenting symptom, followed by weight gain with poor

Table 1: Demographics and baseline characteristics of hypothyroid patients full analysis set

Parameter	Total (*n*=1499)
Gender, *n* (%)	
Female	1061 (70.78)
Male	438 (29.22)
Age (years)	
Mean±SD	41.1±14.01
Minimum-maximum	18.0-87.0
Age by gender (mean±SD)	
Female	39.8±13.53
Male	44.3±14.66
Age groups (years)	
18-35	
n (%)	606 (40.43)
Mean±SD	27.8±4.71
36-45	
n (%)	376 (25.08)
Mean±SD	40.5±2.85
46-54	
n (%)	235 (15.68)
Mean±SD	49.9±2.57
>55	
n (%)	282 18.81
Mean±SD	63.1±6.93
Residential, *n* (%)	
Urban	1302 (86.86)
Rural	197 (13.14)
Socioeconomic class, *n* (%)	
Upper	229 (15.28)
Upper middle	910 (60.71)
Lower middle	222 (14.81)
Upper lower	131 (8.74)
Lower	7 (0.47)
BMI (kg/m^2)	
n (%)	1479 (98.67)
Mean±SD	26.4±4.95
Minimum-maximum	13.6-47.4

n: Number of patients, SD: Standard deviation, BMI: Body mass index

appetite (543 [36.22%]), poor memory and concentration (297 [19.81%]), constipation (272 [18.15%]), shortness of breath (251 [16.74%]), and feeling cold (228 [15.21%]). Most frequently observed signs in the study population included hair loss (463 [30.89%]), swelling of limbs (271 [18.08%]), and dry and coarse skin (255 [17.01%]). Distribution of clinical symptoms and signs is displayed in Table 2.

Menstrual abnormalities were reported in all the women in the study ($n = 730$) who had not attained menopause. Menorrhagia was reported in 727 (99.58%) women, irregular cycle in 155 (21.23%), and intermenstrual bleeding in 40 (5.48%) women. Among the postmenopausal women ($n = 327$), 12 (3.67%) reported postmenopausal bleeding.

Clinical assessment of goiter

On clinical examination, Grade 1 (as per the WHO classification) goiter was observed in 231 (15.41%) patients, while 49 (3.27%) patients had Grade 2 goiter with visible neck swelling [Table 3].

Table 2: Clinical presentation of hypothyroidism at baseline

	Overall ($n=1499$), *n* (%)
Symptoms#	
Fatigue	902 (60.17)
Weight gain with poor appetite	543 (36.22)
Poor memory and concentration	297 (19.81)
Constipation	272 (18.15)
Shortness of breath	251 (16.74)
Feeling cold	228 (15.21)
Periorbital edema/puffiness below eyes	172 (11.47)
Irregular menstruation	156 (10.41)
Hoarseness of voice	131 (8.74)
Signs*	
Hair loss	463 (30.89)
Swelling of limbs	271 (18.08)
Dry, coarse skin	255 (17.01)
Other	156 (10.41)
Delayed relaxation of tendon reflexes	112 (7.47)
Cool extremities	66 (4.4)
Slow pulse rate	48 (3.20)
Carpel tunnel syndrome	19 (1.27)

#Symptoms: Information provided by the patient, *Signs: Observations made by the doctor

Table 3: Clinical assessment of goiter at baseline

Goiter grade	Baseline and enrollment visit ($n=1499$), *n* (%)
0	1219 (81.32)
1	231 (15.41)
2	49 (3.27)

Grade 0: Absence of goiter, Grade 1: Presence of goiter with neck thickening for enlarged, palpable thyroid. Neck thickening however is missing in normal position of the neck. Also includes nodular goiter if thyroid enlargement remains invisible, Grade 2: Presence of goiter with neck swelling when the neck is in normal position corresponding to enlarged thyroid found in palpation

Comorbidities

Comorbidities were reported in 545 patients (36.36%). The most commonly reported comorbidities were type 2 diabetes mellitus (203 [13.54%]), hypertension (170 [11.34%]), hypovitaminosis (89 [5.94%]), dyslipidemia (64 [4.27%]), hypocalcemia (43 [2.87%]), vitamin D deficiency (26 [1.73%]), and anemia and obesity (19 [1.27%] each) [Table 4].

Thyroid hormone profile and treatment

Levothyroxine replacement therapy as a treatment of hypothyroidism was based on TSH levels in 1494 patients, while five patients were treated based on thyroid autoantibody values. Of the 1494 patients, 1203 (80. 52%) patients were treated solely based on TSH values, while 291 (19.48%) patients had both TSH and total serum T4 levels available. Among the patients who had both values, 177 patients (11.8%) could be categorized as SCH, 97 patients (6.47%) had overt hypothyroidism, and 10 patients had inappropriate TSH secretion. The TSH values were considered low if the TSH level was <0.5 mU/L and high if the TSH level was >4.7 mU/L. Similarly, T4 was considered low if the T4 level was <58 nmol/L and high if the T4 level was >140 nmol/L. Classification of hypothyroidism used for this study is depicted in Figure 1.

A large majority of patients (81%) were treated based on serum TSH alone by the physicians. The dose of levothyroxine ranged from 12.5 mcg to 375 mcg. The most frequently prescribed dose of levothyroxine was 50 mcg (479 [31.95%]) with a mean TSH level of 21.1 ± 44.4 mIU/L. The mean TSH levels for other frequently prescribed doses of 100 mcg (374 [24.95%]), 25 mcg (347 [23.15%]), and 75 mcg (154 [10.27%]) were 64.3 ± 72.7, 14.2 ± 46.6, and 30.8 ± 59.0 mIU/L, respectively, in the overall population. The mean free T3 and T4 levels are presented in Table 5.

Table 4: Prevalence of comorbidities associated in hypothyroid patient population at baseline

Comorbid conditions	Overall ($n=1499$), *n* (%)
Type 2 diabetes mellitus	203 (13.54)
Hypertension	170 (11.34)
Hypovitaminosis	89 (5.94)
Dyslipidemia	64 (4.27)
Hypocalcemia	43 (2.87)
Vitamin D deficiency	26 (1.73)
Anemia	19 (1.27)
Obesity	19 (1.27)
Lethargy	16 (1.07)
Mineral deficiency	13 (0.87)
Iron deficiency	12 (0.80)
Basedow's disease	8 (0.53)
Neuralgia	8 (0.53)
Vitamin B12 deficiency	8 (0.53)

Total number of comorbidities reported: 912

Table 5: Serum thyroid-stimulating hormone, triiodothyronine, and thyroxine levels and prescribed doses of levothyroxine at baseline

Dose groups (mcg)	Study population, *n* (%)	Mean TSH level (number of patients with T3 values)	Mean total T3 level (number of patients with T3 values)	Mean total T4 level (number of patients with T4 values)
25	347 (23.15)	14.2±46.57 (*n*=346)	1.0±0.85 (*n*=138)	101.9±31.53 (*n*=146)
50	479 (31.95)	21.1±44 (*n*=470)	0.9±0.82 (*n*=163)	94.2±40.56 (*n*=176)
75	154 (10.27)	30.8±59 (*n*=151)	0.9±0.88 (*n*=51)	107.1±146.98 (*n*=59)
100	374 (24.95)	64.3±72.71 (*n*=362)	0.4±0.62 (*n*=119)	59.1±47.56 (*n*=133)

TSH level is measured in mIU/L, T3 level is measured in nmol/L, T4 level is measured in nmol/L. T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid-stimulating hormone

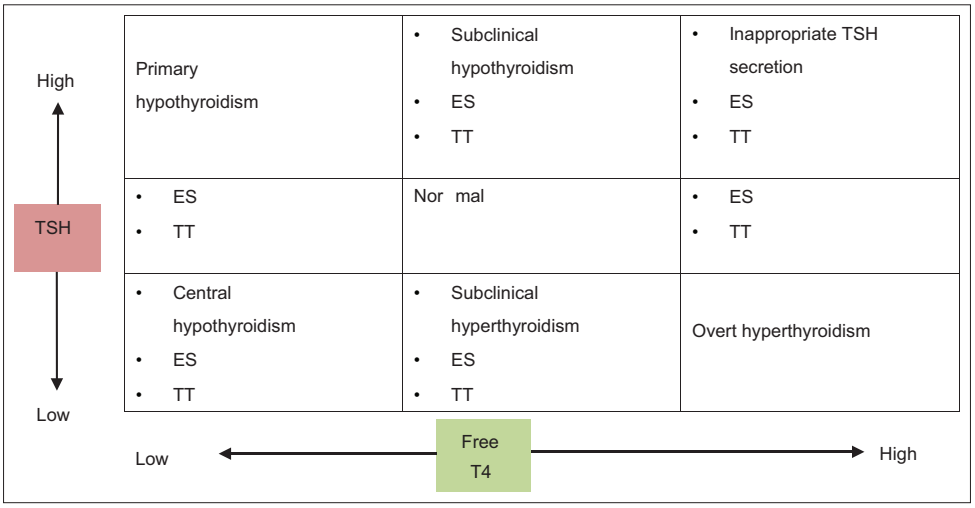

Figure 1: Classification of hypothyroidism. ES: Euthyroid sick, TT: Thyroid in transition (adapted from: SR Joshi. JAPI. Jan-2011; Vol-59; 14-20.)

Discussion

This hypothyroid registry is among one of the largest databases of Indian patients with newly diagnosed hypothyroidism across various geographical locations in India. This study has helped delineate the constellation of various clinical presentations, thyroid hormonal profile, diagnostic workups, comorbidities, and management practices being followed in the routine clinical practice.

In our study, we observed that hypothyroidism was more prevalent in women than men (7:3 ratio), which is consistent with worldwide epidemiological findings.[1,4,7,10] Two-thirds (65.5%) of the patients were in the age group of 18–45 years. A recent study from the Central India had also reported a higher prevalence rate of hypothyroidism (45%–55%) in the age group of 19–45 years.[12]

Frequency of fatigue, which emerged to be the most common clinical symptom, and other symptoms such as weight gain and cold intolerance have been consistent with the study findings by Delemer *et al*.[13] The most important symptoms of hypothyroidism such as fatigue, weight gain, lethargy, and amenorrhea often overlap with other common diseases. This makes it difficult to ascertain whether the symptoms that patients complained of at presentation are due to thyroid disorders or not. Hence, clinicians should maintain a high level of suspicion, else diagnosis of hypothyroidism may get delayed. In addition, the nonspecific nature of these symptoms may not always warrant thyroid profiling of the patient.

All women in the reproductive age group (not attained menopause) experienced menstrual abnormalities (irregular cycle, menorrhagia, or intermenstrual bleeding) in this study. The prevalence of menstrual irregularities (mainly oligomenorrhea) as reported by Krassas *et al*. was 23% against 8% in the control population.[14] Symptoms such as hair loss and dryness, coarse skin can affect general well-being and patients' quality of life.[15-17] Considering the clinical presentation and female preponderance, it becomes very important to screen patients, especially younger females, for hypothyroidism who present with this symptomatology.[18]

Studies have suggested a decline in the prevalence of goiter in India post the universal salt iodization program in 1983.[19] In our study, we found the prevalence of Grades 1 and 2 goiter in about 15.4% and 3.3% patients, a noteworthy finding. A similar trend was observed in a study from South India. Patients with hypothyroidism and goiter had higher levels of iodine than those found in the control population.[20] Intake of iodine above the recommended daily threshold is generally well tolerated. However, in certain cases, it is known to increase the risk of iodine-induced thyroid dysfunction.[21]

The percentage of patients with SCH (11.8%) (*n* = 291) among those in whom T4 levels were assessed, was

consistent with various epidemiological studies conducted in India (9.4% to 11.3%).[8,22] Percentage of patients with overt hypothyroidism (6.4%) was, however, higher than those reported by Deshmukh *et al*. (1.6%).[22]

Patients with SCH have a high rate of progression to overt hypothyroidism.[10] However, the true prevalence of SCH could not be determined as T4 values were not a part of the clinical assessment in majority of patients (n = 1208); this could be higher in our population. Many studies have recommended the analysis of T4 levels in addition to performing a TSH assay to establish the diagnosis of hypothyroidism.[23-25] In our study, TSH and T4 levels were available for only 291 patients at baseline. This highlights the fact that common clinical practice is focused only on screening patients for TSH levels and does not include T4 estimation. In addition, for patients with TSH level at borderline or <10 mIU/L, it is recommended that the decision to treat should be based on T4 levels. Vigilant screening, early diagnosis, and effective treatment are necessary to prevent the progression to more severe thyroid hormone deficiency that can eventually develop into overt hypothyroidism.[26] In addition, most authors advise individualizing management based on clinical judgment. In this registry, majority of patients were treated with levothyroxine based on serum TSH levels alone. Need for treatment could have been better evaluated if a proper assessment based on TSH and T4 levels was practiced. However, there is a paucity of evidence and complete study results from this registry may provide insights into clinical benefit of thyroxine replacement in patients with SCH as this would shed light on patient response to thyroxine, frequency of dose titration, and tolerability of thyroxine.

During the last few decades, there has been a plethora of reviews on clinical benefit and relevance of managing SCH; treatment is recommended, especially if TPO (thyroid peroxidase) is positive or other risk factors/comorbid conditions are present. SCH should be treated in pregnant women and women who are planning for a pregnancy. It is recommended that all patients with SCH having thyrotropin levels above >10 mIU/L and those with overt hypothyroidism be treated with levothyroxine.[4,27] A recent report[28] provided some preliminary evidence of benefit in favor of normalizing the serum TSH in patients aged 40–70 years. In this report, thyroxine replacement had shown to reduce the risk of cardiac events in patients with SCH.

Levothyroxine treatment can be affected by comorbid conditions such as inflammatory bowel disease, *Helicobacter pylori* infection, gastroesophageal reflux disease, lactose intolerance, and gastroparesis, and their treatments.[29,30] Dose adjustment is required in such cases. Gastrointestinal comorbidities were not noted among patients in our study that would affect levothyroxine treatment giving unperturbed interpretation and understanding of the treatment pattern and dosing.

This manuscript discusses the baseline data of hypothyroid patients in India. The thyroid hormone profile, levothyroxine dose, and resolution of symptoms, if any, were being recorded for subsequent follow-up visits. However, this study brings out an important deficit in the clinical practice and management of hypothyroidism in India, warranting the need for educating our medical fraternity. Appropriate assessment with both T4 and TSH levels and when required, assessment of T3 level and thyroid peroxidase antibodies are essential and should be practiced in routine clinical setup.

Conclusions

Guidelines suggest a diagnosis of hypothyroidism based on TSH and T4 levels. However, most of the patients from this registry study were advised treatment with levothyroxine based on TSH levels alone, thus highlighting the need for awareness and scientific education among clinicians in India. Levothyroxine replacement is the standard of treatment for hypothyroidism and is tailored. The use of standard doses (100, 75, and 25 mcg) of levothyroxine may point toward empirical management practices. However, this needs to be further evaluated.

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Conflicts of interest

Dr. Upal Vyas is an employee of Abbott India Ltd., and was involved in all aspects of the study design and implementation. Dr. Bipin Sethi, Dr. Sumitav Barua, Dr. M.S. Raghvendra, Dr. Jagdish Gotur, and Dr. Deepak Khandelwal have received research funding from Abbott India Ltd.

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