Original Article

Thyroid Symptomatology across the Spectrum of Hypothyroidism and Impact of Levothyroxine Supplementation in Patients with Severe Primary Hypothyroidism

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Abstract

Objective: This study aimed to determine the clinical and biochemical profile of patients with severe primary hypothyroidism (SPH) (TSH ≥40 μIU/ml) as compared to milder forms of hypothyroidism and document improvement in hypothyroidism symptoms in SPH. **Methods:** Thyroid symptomatology and biochemistry were evaluated in SPH, non-severe overt primary hypothyroidism (NSOPH; TSH <40 μIU/ml), subclinical hypothyroidism (ScH) and healthy controls. A total of 598 consecutive patients of hypothyroidism were screened of which 461 patients' data were analyzed (91 SPH, 130 NSOPH and 240 ScH). Thyroid symptomatology was re-evaluated at 12 weeks follow-up in SPH following restoration of euthyroidism with levothyroxine. **Results:** The median (interquartile range) age of patients was 35 (28-42) years with 91.6% female. The commonly noted symptomatology were shortness of breath (93.4%) and fatigueability (91.2%) in SPH, fatigueability (68.46%) and limbs swelling (43.07%) in NSOPH, and fatigueability (56.67%) and shortness of breath (32.92%) in ScH. All symptomatology were significantly higher in SPH. Delayed tendon reflex, carpel tunnel syndrome and meno-metrorrhagia were exclusive in SPH. Occurrence of menstrual irregularities was 73.62%, 28.46% and 16.25% in SPH, NSOPH and ScH, respectively. SPH patients had significantly higher cholesterol and triglycerides. There was significant improvement in symptomatology, reduction in body weight (−2.11 kg), improvement in hemoglobin (+0.64 g/L) with fall in total cholesterol (−18.96%), LDL-cholesterol (−23.46%) and triglycerides (−13.53%) following euthyroidism restoration in subjects with SPH. Common residual symptoms were fatigue (10%), poor memory (8%) and menstrual irregularities (6%). **Conclusion:** Thyroid symptomatology differs significantly across spectrum of hypothyroidism, being significantly worse in SPH. Euthyroidism restoration is associated with reversal of majority of thyroid symptomatology.

Keywords: Hypothyroidism, levothyroxine, subclinical hypothyroidism, symptoms

Introduction

Hypothyroidism is a condition in which the thyroid gland is unable to make adequate amounts of thyroid hormone to meet the requirements of peripheral tissues. Primary hypothyroidism is characterized by failure of the thyroid gland itself; a fall in serum concentration of thyroid hormones causes an increased secretion and elevation of serum thyroid-stimulating hormone (TSH) concentration.[1] It is a common disorder and prevalence of overt hypothyroidism has been reported as 3.5%-4.2%, while subclinical hypothyroidism (ScH) has been reported in 8.02%-19.3% of population in various studies.[2,3]

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The biochemical abnormalities that have been described in context of hypothyroidism are dyslipidemia, hyperprolactinemia, glucose intolerance, increased glycated hemoglobin (HbA_1c) level, anemia, leucopenia, rarely pancytopenia and elevation of serum creatinine.[4-6] Untreated

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primary hypothyroidism may even leads to complications such as mental health problems, peripheral neuropathy, myxedema and infertility.[7] Rare untoward side effects of chronic untreated hypothyroidism include multiple pituitary hormone deficiency, pseudo-precocious puberty.[8,9]

Though there have been many studies that have established the clinical and biochemical effects of hypothyroidism, but there is paucity of data on clinical and biochemical effects of severe primary hypothyroidism (SPH) and response of levothyroxine replacement on them. Hence, we studied clinical and biochemical profile of patients with SPH (TSH ≥40 μIU/ml) as compared to those with milder forms of hypothyroidism. We also evaluated the impact of levothyroxine treatment on thyroid symptomatology and biochemistry after restoration of euthyroidism in patients with SPH.

Materials and Methods

This prospective study was conducted in the outpatient department of Internal medicine and Endocrinology Clinic at two different tertiary care centres in northern India. The study was approved by the institutional ethics committee. Consecutive adult patients (age ≥18 years) with newly detected treatment naïve hypothyroidism were considered for the study. Pregnant/lactating women, those already on levothyroxine replacement therapy, those with current malignancy or history of malignancy in last 5 years, on lipid lowering drugs, patients on glucose lowering medications or any medications that can interfere with thyroid function or any other severe comorbid states were excluded. Only patients who gave informed written consent were included in the study. Study was conducted from April 2016 to September 2017.

Patients with hypothyroidism included in this study were classified into three groups, Group-1: Overt SPH, defined as TSH ≥40 μIU/ml with low T4 and T3, a limit of TSH ≥40 μμIU/ml to define SPH was based on a previous study.[6] Patients of hypothyroidism with low T3 and T4 with elevated TSH <40 μIU/ml were defined to have non-severe overt primary hypothyroidism (NSOPH; Group-2). The remaining patients with normal T3 and T4 with elevated TSH were defined to have ScH (Group-3). Group-4 consisted of the healthy controls, who were recruited from the nursing staff, healthcare professionals of the hospitals who were apparently healthy, not on any medications, who gave informed written consent and had a normal thyroid profile on biochemical evaluation.

The included patients were called on a separate day after 12 hours fast for clinical, biochemical, and anthropometric assessment. Clinical profile of the patients evaluated in this study was collected using a predesigned study proforma. Information was collected regarding the age, sex, demographic parameters and all symptoms of hypothyroidism [Table 1]. All patients underwent detailed clinical examination. Data were collected on height, weight, pulse rate, blood pressure, specific signs of hypothyroidism like delayed tendon reflex relaxation, carpel tunnel syndrome, peri-orbital and limb edema. Blood samples were collected; serum separated and stored at −80°C for estimation of free tetraiodothyronine (fT4), TSH, total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides, fasting blood glucose (FBG), hemoglobin and serum creatinine.

Patients were subsequently treated with levothyroxine in doses as per standard clinical practice.[1] Patients with SPH (Group-1) were followed up in the endocrine clinic 6 weekly for the study duration to evaluate the impact of restoring euthyroidism on thyroid symptomatology. The patients were enquired about drug compliance, side effects underwent examination, and empty levothyroxine bottles were collected, and fresh set of drugs issued. Patients were contacted telephonically/messaging services weekly to ensure compliance. Serum TSH was evaluated at 6 weeks of follow-up and the dose of levothyroxine was accordingly adjusted based on TSH level. Patient had final visit after 12 weeks of levothyroxine replacement. History and examination pertaining to all symptoms and signs initially collected was repeated for theses participants at this visit. Blood samples were again collected for biochemical evaluation at the end of the study.

Statistical analysis

Normality of the distribution of variables was checked using the Kolmogrov–Smirnov test. Normally distributed variables were expressed as a mean ± standard deviation, and non-normally distributed variables were expressed as median [inter-quartile range/25th–75th percentile]. $P < 0.05$ was considered as statistically significant. Chi-squared tests were used for categorical variables. Pearson's or Spearman's correlation coefficient was calculated for normally and non-normally distributed variables, respectively. Statistical Package for the Social Sciences (SPSS) version 20 (Chicago, IL, USA) was used for statistical analysis.

Results

A total of 598 consecutive patients of hypothyroidism were screened (310 from Center-A and 288 from Center-B) of which 497 patients were found to fulfill the inclusion criteria. Twenty-five patients were excluded, as they did not fulfill the exclusion criteria (7 patients were on anti-tuberculosis therapy, 7 patients had chronic kidney disease, 3 patient with chronic liver disease and 8 patients with other associated severe co-morbid states). In all, 472 patients were eligible for inclusion in the study, out of which 11 patients did not consent for this study. Hence, data from 461 patients (91 patients with SPH, 130 with NSOPH and 240 patients with ScH) who fulfilled all inclusion and exclusion criteria and gave informed written consent were analyzed. Twenty-five healthy controls recruited from the hospital staff were also evaluated.

The median (interquartile range) age of study subjects was 35 (28-42) years with 91.6% of them being female.The clinical and biochemical profile of the patients evaluated in this study has been elaborated in Table 1. Age and body

Table 1: Clinical, biochemical and thyroid symptomatology profile of patients with spectrum of thyroid dysfunction

Parameter	Severe Primary Hypothyroidism (Group-1) (n=91)	Non-severe Overt Primary Hypothyroidism (Group-2) (n=130)	Subclinical Hypothyroidism (Group-3) (n=240)	Healthy controls (Group-4) (n=25)	*P*
Age (years)	37.84±13.24	35.60±8.99	35.65±12.08	33.88±12.12	0.321
Sex (Male: Female)	20:71	11:119	10:230	2:25	<0.001
BMI (kg/m^2)	26.21±5.15	27.67±5.72	27.58±6.29	28.43±6.36	0.182
TSH (mU/L)*	105 [74-171]	17.06 [12.15-21.93]	7.19 [6.30-8.60]	2.4 [1.8-3.55]	<0.001
Hemoglobin (g/L)	11.18±1.76	10.6±1.47	10.53±1.73	10.47±1.53	0.013
Fasting blood glucose (mg/dl)	98.4±18.53	98.96±17.46	101.79±26.58	94.36±14.65	0.283
Total cholesterol (mg/dl)*	195 [170-227]	192 [162-243]	161 [128-210]	202 [140-270]	0.138
LDL-C (mg/dl)*	120 [100-151]	112 [85.72-137]	92.5 [82-112.97]	80 [76-115]	0.409
Triglycerides (mg/dl)*	138 [101-185]	119 [6-179]	115 [91.32-162]	140 [106-286]	<0.001
HDL-C (mg/dl)*	45 [36-49]	36.7 [31.2-48.4]	38 [32-42]	30 [22-35]	<0.001
Feeling cold	63 (69.23%)	24 (18.46%)	32 (13.33%)	6 (24%)	<0.001
Fatigue	83 (91.20%)	89 (68.46%)	136 (56.67%)	12 (48%)	<0.001
Poor memory and concentration	72 (79.12%)	33 (25.38%)	53 (22.08%)	8 (32%)	<0.001
Weight gain	44 (48.35%)	52 (40%)	77 (32.08%)	12 (48%)	<0.001
Shortness of breath	85 (93.40%)	53 (40.76%)	79 (32.92%)	21 (84%)	<0.001
Hoarseness of voice	63 (69.23%)	22 (16.92%)	13 (5.41%)	0	<0.001
Menstrual irregularities	67 (73.62%)	37 (28.46%)	39 (16.25%)	6 (24%)	<0.001
Types of menstrual irregularities					
Amenorrhea	13 (14.29%)	-	-	-	-
Oligomenorrhea	25 (27.47%)	37 (28.46%)	39 (16.25%)	6 (24%)	<0.001
Meno-metrorrhagia	9 (9.89%)	-	-	-	-
Menorrhagia	20 (21.97%)	-	-	-	-
Dry coarse skin	66 (72.52%)	4 (3.07%)	17 (7.08%)	0	<0.001
Cool extremities	63 (69.23%)	17 (13.07%)	4 (1.67%)	0	<0.001
Hair loss	70 (76.92%)	35 (26.92%)	77 (32.08%)	8	<0.001
Swelling of limbs	74 (81.31%)	56 (43.07%)	68 (28.33%)	12 (48%)	<0.001
Peri-orbital edema	82 90.10%)	34 (26.15%)	44 (18.33%)	12 (48%)	<0.001
Delayed tendon reflex	63 (69.23%)	0	0	0	-
Carpel tunnel syndrome	12 (13.18%)	0	0	0	-

Normality of the distribution of variables was checked using the Kolmogrov-Smirnov test. Normally distributed variables were expressed as a mean±standard deviation, and non-normally distributed variables were expressed as median [inter-quartile range/25th-75th percentile]. P<0.05 was considered as statistically significant; *: Non-normally distributed; BMI: Body mass index; TSH: Thyroid stimulating hormone; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol

mass index (BMI) were comparable across the spectrum of thyroid dysfunction and healthy controls. The four most common clinical features reported by patients with SPH in this study were shortness of breath (93.4%), fatigueability (91.2%), peri-orbital edema (90.1%) and swelling of limbs (81.3%) [Table 1]. The corresponding four most common clinical features in patients with NSOPH were fatigueability (68.46%), swelling of limbs (43.07%), shortness of breath (40.76%) and weight gain (40%) [Table 1]. The four most common clinical features in patients with ScH were fatigueability (56.67%), shortness of breath (32.92%), hair loss (32.08%) and weight gain (32.08%) [Table 1]. All the symptoms associated with hypothyroidism were significantly higher in patients with SPH (Group-1). Specifically symptoms attributed to hypothyroidism such as feeling cold, fatigue, poor memory and concentration, weight gain, shortness of breath, hoarseness of voice, menstrual irregularities, dry coarse skin, cool extremities, hair loss, swelling of limbs and peri-orbital edema were highest in patients with SPH, followed by NSOPH and ScH, which was statistically significant [Table 1]. Delayed tendon reflex, carpel tunnel syndrome and meno-metrorrhagia were exclusively seen in patients with SPH [Table 1]. Menstrual irregularities were very common in women with SPH (73.62%). Occurrence of menstrual irregularities were lower in patients with NSOPH (28.46%) and ScH (16.25%) [Table 1]. Patients with SPH had significantly higher serum cholesterol and triglycerides as compared to those with NSOPH and ScH [Table 1].

In patients with SPH (Group-1), follow-up data following restoration of biochemical euthyroidism was available from 50 out of the initially evaluated 91 patients (54.95%). There was a significant reduction in BMI, improvement in hemoglobin levels with fall in total cholesterol and LDL-C levels following restoration of euthyroidism in patients with SPH [Table 2]. Body weight before and after resolution of hypothyroidism in patients with SPH was 71.01 ± 13.21 kg and 68.9 ± 12.34 kg, respectively (Δ weight − 2.11 kg; P < 0.001).

Table 2: Changes in thyroid symptomatology, clinical and biochemical parameters after attaining euthyroidism in patients with severe primary hypothyroidism

Parameter	Severe Primary Hypothyroidism (*n*=91)	Post-treatment Euthyroid state (*n*=50)	*P*
Age (years)	37.84±13.24	41.22±13.93	0.102
Sex (Male: Female)	20:71	14:36	0.423
BMI (kg/m^2)	26.21±5.15	25.8±4.85	<0.001
TSH (mU/L)*	105 [74-171]	1.92 [0.66-3.62]	<0.001
Hemoglobin (g/L)	11.63±1.89	12.27±1.67	<0.001
Fasting blood glucose (mg/dl)	98.4±18.53	97.21±18.3	0.479
Total cholesterol (mg/dl)*	195 [170-227]	178 [58-197]	<0.001
LDL-C (mg/dl)*	120 [100-151]	107 [90-120]	<0.001
Triglycerides (mg/dl)*	138 [101-185]	127.5 [93.75-163.75]	0.096
HDL-C (mg/dl)*	45 [36-49]	46 [42-52.5]	0.692
Creatinine (mg/dl)	0.90±0.26	0.86±0.26	<0.001
Feeling cold	63 (69.23%)	2 (4%)	<0.001
Fatigue	83 (91.20%)	5 (10%)	<0.001
Poor memory and concentration	72 (79.12%)	4 (8%)	<0.001
Weight gain	44 (48.35%)	2 (4%)	<0.001
Shortness of breath	85 (93.40%)	2 (4%)	<0.001
Hoarseness of voice	63 (69.23%)	0	-
Menstrual irregularities	67 (73.62%)	3 (6%)	<0.001
Types of menstrual irregularities			
Amenorrhea	13 (14.29%)	0	-
Oligomenorrhea	25 (27.47%)	3 (6%)	-
Meno-metrorrhagia	9 (9.89%)	0	-
Menorrhagia	20 (21.97%)	0	-
Dry coarse skin	66 (72.52%)	1 (2%)	<0.001
Cool extremities	63 (69.23%)	2 (4%)	<0.001
Hair loss	70 (76.92%)	2 (4%)	<0.001
Swelling of limbs	74 (81.31%)	1 (2%)	<0.001
Peri-orbital edema	82 90.10%)	1 (2%)	<0.001
Delayed tendon reflex	63 (69.23%)	0	-
Carpel tunnel syndrome	12 (13.18%)	0	-

Normality of the distribution of variables was checked using the Kolmogrov-Smirnov test. Normally distributed variables were expressed as a mean±standard deviation, and non-normally distributed variables were expressed as median [inter-quartile range/25th-75th percentile]. *P*<0.05 was considered as statistically significant; *: Non-normally distributed; BMI: Body mass index; TSH: Thyroid stimulating hormone; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol

The mean decrease in serum total cholesterol, LDL-C and triglycerides after restoration of euthyroidism in patients with SPH was 39.5 mg/dl (−18.19%), 32.41 mg/dl (−23.46%) and 22.47 mg/dl (−13.53%), respectively ($P < 0.001$; Table 2). There was a non-significant elevation in serum HDL-C following restoration of euthyroidism (0.74 mg/dl; +1.62%). There was a significant improvement in thyroid symptomatology following restoration of biochemical euthyroidism in this cohort of patients [Table 2]. The occurrence of anemia significantly reduced after restoration of euthyroidism (41.75% [38/91] vs. 34% [17/50]; $P < 0.001$). The mean rise in hemoglobin levels following restoration of euthyroidism in patients with SPH was 0.64 g/L. There was a significant reduction in serum creatinine following resolution of hypothyroidism in patients with SPH (Δ creatinine −0.04 mg/dl; $P < 0.001$; Table 2). The most common residual symptoms noted were fatigue (10%), followed by poor memory and concentration (8%) and menstrual irregularities (6%) [Table 2].

Discussion

The highlight of this study is that for the first time the clinical symptomatology and metabolic profile was evaluated across the spectrum of thyroid dysfunction ranging from ScH at one end to SPH at the other end of the spectrum. This study highlighted that symptoms associated with hypothyroidism are diverse and can be non-specific.[10] Fatigue was the most common noted symptom among patients with hypothyroidism, across the spectrum of hypothyroidism. In another multicentric thyroid registry, fatigue was the most commonly noted symptom.[11] In that study although 1500 patients were evaluated, biochemical status of hypothyroidism (serum TSH) was available only from 291 patients.[11] There was a drastic increase in the occurrence of menstrual irregularities with increase in severity of hypothyroidism in our study (73.62% in SPH vs. 16.25% in ScH). The occurrence of menstrual irregularities in the Indian thyroid registry study and similar other studies have been 16%, similar to the rates observed

in patients with ScH in our study.[11,12] Evaluation of milder forms of hypothyroidism in previously reported studies explains the lower occurrence of menstrual irregularities in them. Studies among the Caucasian population have reported occurrence of menstrual irregularities of 20%-20% in patients with hypothyroidism.[13,14] Our study showed the profile as well as the degree of thyroid symptomatology was different across the spectrum of hypothyroidism. This is in contrast to the Colorado study (25,862 patients evaluated in a cross-sectional study), which concluded that euthyroid subjects and patients with overt primary hypothyroidism or ScH all had similar constellations of symptoms.[15] Our study highlights that even in patients with most severe form of hypothyroidism, the mean weight loss after restoration of euthyroidism was only 2.11 kg. This is concrete data against the common social misconception of hypothyroidism being a cause of weight gain and obesity.[16,17] It must be highlighted that the presenting features of hypothyroidism in children and adolescents is starkly different from that of adults. Short stature, goiter and weight gain have been reported to be the three most common symptoms associated with hypothyroidism at initial presentation in adolescents.[18]

A significant improvement in hemoglobin levels (0.64 g/L) was noted with resolution of hypothyroidism in patients with SPH. Previous studies have documented the prevalence of anemia in patients with hypothyroidism ranging from 40% to 60%.[19,20] A recent study suggested that the resolution of the symptoms and signs associated with hypothyroidism might be more marked in patients with overt hypothyroidism as compared to ScH.[12] A 12% reduction in LDL-C was documented following restoration of hypothyroidism in the Rotterdam study.[21] A greater severity of hypothyroidism at baseline was associated with larger beneficial effects of levothyroxine therapy on dyslipidemia (lowering of total cholesterol and LDL-C).[22,23] In our study, there was a 23.46%, 18.19% and 13.53% reduction in LDL-C, total cholesterol and triglycerides following restoration of euthyroidism. A more severe hypothyroidism in our patients with SPH may explain this greater reduction in lipid parameters. The relationship between hypothyroidism and HDL-C has been more conflicting with a few reports suggesting increase in HDL-C and others showing decrease in HDL-C in patients with hypothyroidism.[24] In our study, there was a statistically non-significant mild increase in HDL-C levels following restoration of euthyroidism. Consistent and reversible elevation of serum creatinine in hypothyroidism has been reported previously, and our results are in accordance.[10]

Strength of this study is the large number of patients undergoing both clinical and biochemical evaluation. Also follow-up data on impact of restoring euthyroidism in patients with SPH on thyroid symptomatology has been elaborated; a cohort that has been least studied. Most of the symptoms associated with hypothyroidism resolved following restoration of euthyroidism in patients with SPH. Lack of availability of follow-up data on thyroid symptomatology resolution in patients with milder forms of hypothyroidism is a limitation of this study.

To summarize, this study provided objective data on the spectrum of thyroid symptomatology across the spectrum of hypothyroidism. Thyroid symptomatology, as expected was worst in patients with SPH (TSH >40 μIU/ml) followed by those in NSOPH and ScH. Certain classical symptoms associated with hypothyroidism such as delayed deep tendon reflexes, carpel tunnel syndrome were noted only in the patients with most severe form of hypothyroidism. Similarly, certain non-specific symptoms associated with hypothyroidism like fatigue and poor memory persisted even after restoration of euthyroidism in a small number of patients. Restoring euthyroidism was associated with marked improvement in lipid, renal, hemoglobin and other diverse biochemical parameters.

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Conflicts of interest

There are no conflicts of interest.

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