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Clinical Profile of Patients with Refractory Hypothyroidism

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Abstract

Introduction: *Hypothyroidism is one of the most prevalent endocrine illnesses. Some patients fail to achieve adequate suppression of Thyroid Stimulating Hormone (TSH) despite receiving Levothyroxine (LT4) in doses equal to or higher than 1.9 µg/Kg. This condition is known as refractory hypothyroidism (RH). To understand RH better, we conducted a cross-sectional study, analysing the clinical and laboratory profiles of such patients.*

Methods: *RH patients on LT4 ≥1.9 µg/Kg bodyweight and TSH >5.5 µIU/mL were included in the study. Pregnant and lactating women were excluded. The participants were interviewed about timing of LT4 ingestion, use of any concomitant drugs, symptoms of overt hypothyroidism and symptoms of any GI diseases. Four item Morisky Medication Adherence Scale (MMAS-4) was used to assess the adherence to medication. Investigations included blood tests, DEXA scan, and a GI evaluation in case of GI symptoms.*

Results: *The study included 60 patients, who were predominantly female (96.7%). Weight gain (90%) and fatigue (88.3%) were the most commonly reported symptoms of overt hypothyroidism. Poor adherence to therapy was observed in 68.33% participants based on MMAS-4, and 61.7% were on concomitant proton pump inhibitor (PPI). Upper GI endoscopy was performed on 26 participants, with 13.3% testing positive for Helicobacter pylori (H. pylori) infection. No cases of malabsorptive gastrointestinal diseases were identified.*

Conclusion: *In cases of RH, non-pharmacological causes should be assessed first. Our findings indicate that poor adherence to therapy and concurrent use of PPI are the most frequent contributors to RH. Additionally, H. pylori infection was identified in a subset of patients, highlighting its potential role. Gastrointestinal disorders should also be thoroughly investigated, as they lead to RH.*

Key words: *Refractory hypothyroidism, Thyroid stimulating Hormone, Levothyroxine.*

Introduction

Hypothyroidism is a common clinical condition that is caused by a deficiency of the thyroxine hormone. Hypothyroidism can be classified as primary (due to thyroid hormone deficiency), secondary [due to Thyroid stimulating hormone (TSH) deficiency], tertiary [due to Thyrotropin-releasing hormone (TRH) deficiency], and peripheral (extra-thyroidal). Levothyroxine (LT4) is the treatment of choice. Patients with clinical features of hypothyroidism, and with biochemical confirmation of overt hypothyroidism, are started on 1.5 - 1.8 µg LT4 per Kg of bodyweight[1]. Treatment targets include normalisation of TSH concentration and resolution of symptoms. However, some patients do not achieve adequate suppression of TSH despite receiving LT4 doses equal to or higher than 1.9 µg/kg. This condition is known as refractory hypothyroidism (RH).

Non-compliance to treatment, timing of LT4 ingestion relative to meals, concomitant use of other drugs such as proton-pump inhibitors (PPI), and pregnancy are the most common non-pathological cause of RH. Gastrointestinal (GI) diseases such as *Helicobacter pylori* (*H. pylori*) infection, inflammatory bowel disease (IBD), celiac disease, lactose intolerance, gastroparesis, etc., and poor conversion of tetraiodothyronine (T4) to triiodothyronine (T3) due to less effective deiodinase D2 enzyme, are the main pathological reasons behind RH[2]. We decided to carry out a cross-sectional study of RH patients presenting to a tertiary care hospital and describe the clinical and laboratory parameters of such individuals.

Methodology

This was a single centre, cross-sectional, observational study, carried out at a tertiary care teaching hospital in Western Maharashtra from April 2022 to April 2024. Adults who were on LT4 dose ≥1.9 µg per Kg bodyweight with serum TSH concentrations >5.5 µIU/mL were included. Pregnant and lactating women were excluded.

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The proportion of RH was taken as 10% among all patients with overt hypothyroidism who are on LT4 therapy[3]. Finite correction factor of 100 was applied (based on number of patients of RH likely to visit endocrine and medical OPD during the study period), and a sample size of 60 was calculated, for 95% confidence interval (CI).

The study participants were interviewed about timing of LT4 ingestion, use of any concomitant drugs, symptoms of overt hypothyroidism and symptoms of any GI diseases. Four item Morisky Medication Adherence Scale (MMAS-4) was used to assess the adherence to medication in the study participants[4]. A score of 0 or 1 was taken as poor adherence.

All study participants underwent the following investigations: complete blood count, liver function test, lipid profile, blood sugar fating, blood sugar post-prandial, and DEXA scan for whole body fat percentage. Patients with symptoms suggestive of GI diseases were subjected to an upper GI endoscopy along with Rapid Urease Test (RUT) and D2 biopsy if indicated. Written informed consent was taken from each participant. Ethical approval was obtained from institutional ethics committee.

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Data had been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests were used for a difference in mean involving independent samples or unpaired samples.

Results

In our study, total 60 patients were enrolled, out of which 58 (96.7%) were female and 2 (3.3%) were male. The clinical and biochemical characteristics of the study population is shown in Table I.

54 out of 60 participants reported the symptom of weight gain and 53 out of 60 participants reported the symptom of fatigue. Fig. 1 shows the various symptoms of overt hypothyroidism reported by the study participants.

Table I: Clinical and biochemical characteristics of the study population.

Parameter	Mean	Standard Deviation
Age (years)	40.7	± 12.2
Height (cm)	156	± 5.28
Weight (Kg)	74.62	± 7.19
BMI[$] (Kg/m^2)	30.91	± 3.20
TSH[#] (µIU/mL)	9.38	± 3.16
Thyroxine Dose (µg)	161.03	± 24.05
Thyroxine Dose (µg/ Kg bodyweight)	2.15	± 0.29
Duration of Treatment (years)	8.23	± 3.42
Haemoglobin (g/dL)	11.77	± 1.62
Total Bilirubin (mg/dL)	0.62	± 0.25
AST[€] (U/L)	34.18	± 8.68
ALT[¥] (U/L)	39.61	± 7.91
Fasting Blood Sugar (mg/dL)	123.7	± 30.34
Post-prandial Blood Sugar (mg/dL)	175.37	± 53.71
Total Cholesterol (mg/dL)	179.25	± 44.41
Triglycerides (mg/dL)	144.08	± 28.07
LDL[¶] (mg/dL)	92.85	± 34.90
HDL[£] (mg/dL)	52	± 7.45
Total Body Fat Percentage (%)	37.82	± 3.02

[$]BMI: Body Mass Index, [#]TSH: Thyroid Stimulating Hormone, [€]AST: Aspartate Aminotransferase [¥]ALT: Alanine Aminotransferase [¶]LDL: Low Density Lipoprotein [£]HDL: High Density Lipoprotein.

68.33% (n = 41) participants were found to have poor adherence to therapy based on MMAS-4. 61.7% (n = 37) participants were on concomitant PPI therapy. 5% (n = 3) patients gave history of ingesting food within 60 minutes of taking LT4.

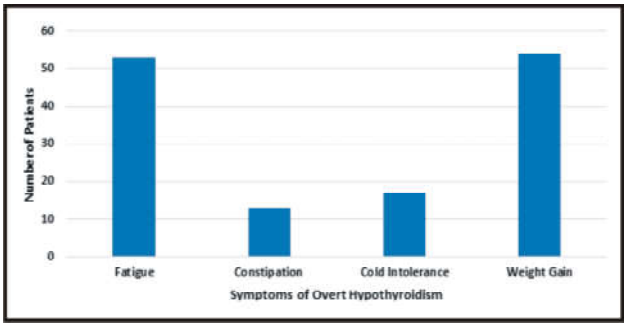

Fig. 1: *Symptoms of overt hypothyroidism in the study population.*

26 out of 60 study participants underwent upper GI endoscopy. 13.3% (n = 8) were found to have *H. pylori* infection by Rapid Urease Test (RUT). No patients were found to have any malabsorptive GI diseases.

Discussion

This cross-sectional observational study was carried out at a tertiary care teaching hospital in Western Maharashtra. The mean age of the study population was 40.7 ± 12.2 years and 96.7% of study participants were female. The commonest symptom of overt hypothyroidism reported by the participants, were weight gain (90%) and fatigue (88.3%). Symptoms of hypothyroidism are often non-

specific and show large variations. These may include fatigue, lethargy, cold intolerance, weight gain, constipation, and dry skin[5]. In a population based case-control study commonly reported symptoms by hypothyroid patients included tiredness (81%), and dry skin (63%)[6].

Mean LT4 dose among the study population was 161.03 ± 24.05 µg or 2.15 ± 0.29 µg/Kg bodyweight. A retrospective cohort study of 5749 hypothyroid patients showed a mean daily thyroxine dose of 1.14 µg/Kg bodyweight[7]. In patients with RH, TSH continues to be high despite a relatively higher dose of LT4. Monteiro *et al* evaluated ten female patients for RH and found that the baseline LT4 dosage ranged from 2.5 to 5.3 µg/Kg/day[8].

The mean BMI of the study population was 30.91 ± 3.20 Kg/m^2 and the mean total body fat percentage was 37.82 ± 3.02%. Hypothyroidism decreases the basal metabolic rate and causes decreased thermogenesis. It has also been shown to correlate with a higher BMI and a higher prevalence of obesity[9]. On the other hand obese individuals are also found to have high TSH and low free T4 levels. The underlying cause of these alterations in thyroid functions are not known; however, some scientists suggest an increased deiodinase activity leading to a high conversion rate of T4 to T3. This could be a defence mechanism in obese individuals for counteracting the accumulation of fat by increasing energy expenditure[10].

Poor adherence to LT4 therapy was very high among the study population (68.33%). Poor adherence is influenced by a complex interplay of factors, and despite extensive research into nearly 200 variables, including patient demographics, disease characteristics, and treatment regimens, no single factor reliably explains non-compliance. Communication breakdowns, especially in elderly patients with memory issues, unresolved concerns about side-effects or disbelief in the diagnosis are the common culprits[11]. Patients increasingly seek autonomy in decision-making, and healthcare providers must shift from persuasion to partnership, supporting informed choices rather than enforcing prescriptions. A cross sectional study of 337 patients on LT4 therapy in Lebanon, showed that 54.9% had low adherence to medication[12]. Using the 8-item Morisky Medication Adherence Scale (MMAS-8), Al Kindi *et al*, showed that among 400 hypothyroid patients; 157 (39.2%), 139 (34.8%), and 104 (26.0%) had low, medium, and high drug adherence, respectively[13].

Drugs like iron, calcium, statins and PPI can decrease the effectiveness of LT4 therapy and cause an increase in the patients' TSH concentration[14]. As patients are advised to take both LT4 and PPI before breakfast, they invariably end up taking both these medications concomitantly. A systematic review showed that concomitant use of LT4 and PPI causes a significant increase in TSH concentration[15]. In our study, we found that 61.7% participants were on concomitant PPI therapy along with LT4.

13.3% of the study participants were found to have *H. pylori* infection by RUT. Bugdaci *et al*, reported that in patients with hypothyroidism, chronic *H. pylori* gastritis may be responsible for an inadequate response to treatment[16]. However, routine testing for *H. pylori* is not recommended in patients with RH, until unless they are symptomatic.

Our study is a single centre study with a small sample size. This is a major limitation of the study. We did not conduct a Levothyroxine absorption test as there is no gold standard protocol for the same.

Conclusion

To conclude, we found that RH patients have very high BMI, with commonest presenting symptoms being weight gain and fatigue. Poor adherence and concomitant use of PPI were the most prevalent cause for ineffective therapy among these patients. A subset of patients was also found to have *H. pylori* infection. The physician should review the medications and compliance history in patients presenting with RH. Once non-pharmacological causes have been ruled, a history of GI diseases should be taken and patient should be evaluated for *H. pylori* infection, IBD, Celiac disease and other digestive tract disorders.

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