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Original Research

Assessment of Levothyroxine Adherence and Factors Affecting Compliance Among Hypothyroid Patients

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Abstract

Introduction: Although levothyroxine-based hormone replacement therapy is thought to be the best treatment for hypothyroidism, non-adherence is a significant factor in subpar treatment results. The aim of present study is to assess the level of adherence to levothyroxine therapy and identify factors influencing compliance among patients with hypothyroidism. **Material and methods:** 408 hypothyroid patients who had been using LT4 for at least six months participated in a cross-sectional observational study at Government Medical College, Doda. A standardised questionnaire that included the 8-item Morisky Medication Adherence Scale (MMAS-8), clinical features, and sociodemographic information was used to gather data. Adherence levels were divided into three categories: low (<6), medium (6-7), and high (scoring 8). Chi-square and Fisher's exact tests were used in statistical analysis using SPSS v23 to evaluate relationships between adherence and important variables. **Results:** 26% of patients reported high adherence, compared to 37.7% with low adherence and 36.3% with medium adherence. The biggest factors were pill load (39.4%), forgetfulness (62.6%), and difficulties waiting before meals (53.6%). Comorbidities did not substantially correlate with adherence, but education level ($p=0.003$), income ($p<0.001$), suitable LT4 scheduling ($p<0.001$), gender ($p=0.041$), and length of illness ($p=0.049$) did. **Conclusion:** Adherence to levothyroxine in hypothyroid patients is inadequate, influenced by many behavioural and socioeconomic factors that lead to poor compliance. Interventions emphasising patient education, guidance on proper intake techniques, and the resolution of modifiable barriers are crucial for improving adherence and therapeutic efficacy.

Keywords: Endocrinology, Compliance, Levothyroxine, Hypothyroidism, Medication adherence, MMAS-8.

Introduction

Hypothyroidism is a chronic condition in which there is a failure of the thyroid gland to produce sufficient amounts of thyroid hormone to meet the metabolic demands of the body.[1] It is one of the most common endocrine disorders seen worldwide, with a prevalence ranging from 3.05% in Europe to 4.6% and 9.5% in the USA and 11% in India [2-5]. In addition, the prevalence of hypothyroidism, mainly due to autoimmune thyroiditis, increases with increasing age. [6-8]

Levothyroxine (LT4) is a reliable and commonly prescribed drug to treat thyroid disease. The aim of substitution therapy is to resolve symptoms and signs of hypothyroidism and maintain the serum thyrotropin (TSH) concentration within a narrow range, which indicates successful treatment. Even though the management of hypothyroidism is generally considered straightforward, several cross-sectional surveys of patients receiving LT4 have shown that a large percentage of patients (40-48%) are over- or undertreated.[9,10] Moreover, a significant number of patients showed sub-optimal adherence to LT4 therapy, mainly because they had to postpone their breakfast by at least 30 min. [11]

Medication adherence (or compliance) is defined by the World Health Organization as "the degree to which the person's behavior corresponds with the agreed recommendations from a healthcare provider" with respect to timing, dosage, and the frequency of medication-taking during the prescribed length of time.[12] There are five interactive dimensions of non-adherence: (1) healthcare system/team factors, such as access to care and the degree of stress associated with healthcare visits; (2) patient-related factors, especially psychological factors; (3) therapy-related factors, including any unpleasant side-effects of taking the medication; (4) condition-related factors, such as duration of therapy; and (5) socioeconomic factors, including unstable living conditions, lack of family or social support, medication cost, and health insurance. [13,14]

During the past few years, various LT4 formulations (tablets, soft-gel capsules, and liquid solutions) have become available for clinical use.[15] These formulations have been shown to be more efficacious in many cases of refractory hypothyroidism, such as among patients with many gastrointestinal diseases, including *Helicobacter pylori* infection, celiac disease, atrophic body gastritis, but also due to some medications.[16] In addition, in patients with subclinical hypothyroidism and those with central hypothyroidism, LT4 liquid formulations seem to be more effective in restoring euthyroidism than tablets.[17,18] Moreover, recent clinical trials have clearly shown, in particular for liquid forms, that these formulations are able to circumvent the optimal absorption of LT4 arising with concomitant ingestion with food, particularly at breakfast.[19,20] This finding may represent a significant advantage for the liquid LT4 formulation to maximize therapeutic compliance. To date, adherence to LT4 therapy among patients with hypothyroidism is still not well characterized.

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The present study is conducted to assess levothyroxine adherence and factors affecting compliance among hypothyroid patients

Materials and Methods

The present cross sectional observational study was conducted at department of medicine, Government Medical College, Doda among patients of hypothyroidism for a period of 6 months. Ethical clearance was taken from institutional ethics committee of college and hospital before commencement of study. Written informed consent was taken from patients after explaining them about the study. Through consecutive sampling a total of 408 patients diagnosed with hypothyroidism were selected for the study on the basis of inclusion and exclusion criteria.

Inclusion criteria

1. Adult patients (>18years) of both genders.
2. Patients with confirmed diagnoses of hypothyroidism (based on biochemical criteria of thyroid function) .
3. Patients who had been receiving oral levothyroxine therapy for at least 6 months.

Exclusion criteria

1. Patients with congenital abnormalities, thyroid cancers, pregnant women, those on lithium or steroid medications.
2. Patients with subclinical hypothyroidism, mental illness or dementia.

A pre-tested and well-structured questionnaire was used for the purposes of data collection. The questionnaire was completed during face-to-face interviews. The questionnaire was divided into three main parts. Part one covered the participants' sociodemographic characteristics, including their age, gender, level of education and degree, marital status, employment status, total monthly income, financial status, smoking status, alcohol consumption, and frequency of physical activity. The second part assessed detailed medical information regarding their hypothyroidism diagnosis and its causes, the presence of comorbidities, and treatment type, duration, dosage, and frequency.

The final section of the questionnaire consisted of the MMAS-8, a pretested, structured, self-reported tool that assesses level of adherence to prescribed medications and related behaviors. Seven of the eight items are yes/no questions designed to evaluate specific medication-taking behaviors, such as forgetfulness, feeling hassled about adhering to the treatment plan, or discontinuing the regimen because the medication makes the patient feel worse, with one point being given to each response of "yes". The remaining item, which assesses the frequency with which the patient has difficulty remembering to take all of their medication, is scored on a 5-point Likert scale from 0 (never/rarely) to 4 (all the time). Total MMAS-8 scores range from 0 to 8, with level of DA categorized into low (scores of <6) medium (scores of 6-7), and high (scores of 8) adherence. [21]

The Statistical Package for the Social Sciences (SPSS), version 23 (IBM Corp., Armonk, New York), was used to analyse the data. The sample's characteristics were described using descriptive statistics. While continuous data were presented using means and standard deviations, categorical variables were reported using frequencies and percentages. As applicable, significance was tested using Fisher's exact test (for low cell frequencies) or Pearson's Chi-squared (χ^2) test, with a p value of 0.05 deemed statistically significant.

Results

Table 1 summarizes the sociodemographic characteristics of the patients. Majority of participants were female (73%), reflecting the known higher prevalence of hypothyroidism in women. Most were aged 31-45 years (38.2%), married (76.5%), and from a moderate socioeconomic background. A substantial proportion (41.2%) had only primary or secondary education, potentially influencing medication comprehension.

Table 1. Sociodemographic Characteristics of the Study Participants

Variable	Category		Percentage (%)
Age (years)	18-30		19.1
	31-45	156	38.2
	46-60		29.7
	>60	53	13.0
Gender	Female		73.0
	Male		27.0
Education level	No formal education		13.2
	Primary/Secondary		41.2
	Graduate		34.1
	Postgraduate	47	11.5
Marital status	Married		76.5
	Unmarried		23.5
Employment	Employed		44.6
	Unemployed/Housewives	226	55.4
Monthly income	<20,000 INR		40.4
	20,000-50,000 INR		43.6
	>50,000 INR		16.0

Table 2 shows the clinical characteristics of patients. Half of the patients had been diagnosed for 1 to 5 years, and autoimmune thyroiditis was the most common cause. More than half needed a dose of 50 to 100 mcg. Most patients took LT4 correctly on an empty stomach, but almost a quarter said they took it at the wrong time, which could have affected absorption.

Table 2 Clinical characteristics of patients

Parameter	Category	n (%)
Duration of hypothyroidism	<1 year	92 (22.5)
	1-5 years	204 (50.0)
	>5 years	112 (27.5)
Etiology	Autoimmune thyroiditis	213 (52.2)
	Post-surgical	41 (10.0)
	Iodine-deficiency/other	154 (37.8)
Comorbidities	Hypertension	148 (36.3)
	Diabetes mellitus	124 (30.4)
	Dyslipidemia	96 (23.5)
	None	163 (39.9)
Levothyroxine dose	<50 mcg	49 (12.0)
	50-100 mcg	228 (55.9)
	>100 mcg	131 (32.1)
Timing of LT4 intake	Fasting morning (correct)	315 (77.2)
	With food / irregular timing	93 (22.8)

Table 3 shows the MMAS-8 Based Adherence Levels among the study patients. Only 26% of participants achieved high adherence, while 37.7% demonstrated poor adherence. Medium adherence accounted for another 36.3%, suggesting that nearly three-fourths of the population had suboptimal compliance.

Table 3 MMAS-8 Based Adherence Levels

	MMAS-8 Score	Frequency (n)	Percentage (%)
High adherence	8	106	26.0
Medium adherence	6-7	148	36.3
Low adherence	<6	154	37.7

Table 4 shows factors affecting non-adherence. The most common contributors to poor adherence were forgetfulness (62.6%), difficulty waiting before breakfast (53.6%), and pill burden. Misconceptions regarding lifelong therapy were also notable.

Table 4 Factors Affecting Non-Adherence (Low + Medium Adherence Groups Only)

Factor	Yes (n, %)	No (n, %)
Forgetfulness	189 (62.6)	113 (37.4)
Difficulty taking medication on empty stomach	162 (53.6)	140 (46.4)
Feeling better → stopped medication intermittently	104 (34.4)	198 (65.6)
Side effects (palpitations, anxiety)	57 (18.9)	245 (81.1)
Misconceptions about lifelong therapy	88 (29.1)	214 (70.9)
Pill burden / multiple drugs	119 (39.4)	183 (60.6)

Table 5 association between adherence and sociodemographic/clinical variables shows higher education, higher income, correct medication timing, female gender, and longer disease duration showed significant positive association with high adherence ($p < 0.05$). Comorbidities did not significantly influence adherence.

Table 5 Association Between Adherence and Sociodemographic/Clinical Variables

Variable	High adherence (%)	Low/Medium adherence (%)	p-value
Gender	Female: 28.5	Male: 20.0	0.041*
Education level	Graduate/Postgraduate: 39.1	Below graduate: 23.4	0.003*
Income	>50,000 INR: 41.5	<20,000 INR: 18.8	<0.001*
Correct LT4 timing	34.6	12.9	<0.001*
Presence of comorbidities	22.3	28.4	0.128
Duration of illness (>5 yrs)	33.9	24.1	0.049*

Discussion

LT4 treatment is one of the most frequent therapies worldwide. It is generally considered straightforward even though many surveys on hypothyroidism show that 40-50% of patients are either over- or undertreated. Many factors can explain this “failed” treatment, such as interference with intestinal absorption of LT4 from food, drugs, and disease, but also poor medication adherence.[21] This last point is important not only because it represents the main cause of low therapeutic efficacy but also affects health care costs.[22] Patient questionnaires are widely used to measure adherence to therapies in the clinical setting due to their simplicity and low cost. The MMAS is one of the most frequently used patient questionnaires for the assessment of medication adherence.[23]

In our study only 26% of participants achieved high adherence, while 37.7% demonstrated poor adherence. Medium adherence accounted for another 36.3%, suggesting that nearly three-fourths of the population had suboptimal compliance. Few data are available on therapeutic adherence in patients with hypothyroidism with heterogeneous results. Briesacher et al.[24] using health care claims data, reported therapeutic adherence of 36.8%, whereas Crilly and Esmail [25] reported 78% adherence. This result was also observed by Vezzani et al. [26] who reported medium-high adherence in 76.1% of patients with hypothyroidism. Moreover, these percentages were confirmed among pregnant women with hypothyroidism.[27]

In our study it was found that higher education, higher income, correct medication timing, female gender, and longer disease duration showed significant positive association with high adherence ($p < 0.05$). Comorbidities did not significantly influence adherence. Kumar et al reported that levothyroxine adherence was linked with gender among Pakistani patients, with significantly higher rates of DA observed among men compared to women ($p = 0.0002$).[28] Although research shows that women appear to be less compliant than men when it comes to taking medications in general, it is important to note that there are many variables which may influence this relationship, including gender disparities in drug utilization, prescription, and monitoring.[29,30] El Helou et al did not find gender to be related to DA among Lebanese patients ($p = 0.187$).[31] Higher mean DA scores were observed among retired patients compared to unemployed or employed patients ($p = 0.008$) as well as among patients with no comorbidities ($p = 0.002$). Moreover, the researchers found a significant, inverse correlation between mean DA scores and age, with increasing age associated with decreasing adherence ($p = 0.004$). Patients with higher monthly incomes generally demonstrate better DA; this is to be expected, as such patients are more likely to be able to afford to pay for medications.[31] According to a retrospective analysis of insurance claims data in the USA, the overall rate of DA fell by 11.6% between 6 and 12 months of drug administration.[28,29] In contrast, Kumar et al. found that DA was higher among patients who had been taking levothyroxine for >5 years compared to those who had been taking the drug for 1-5 years. [28]

Various strategies could be implemented in order to improve compliance rate. These may include encouraging physicians and pharmacists to become more involved in patient educational initiatives, promoting self-monitoring or self-management interventions, or prescribing less complex dosing regimens as well as more preferable pharmaceutical formulations. Literature confirmed that the bioequivalence of levothyroxine is maintained regardless of choice of formulation; as such, it may be beneficial for healthcare practitioners to suggest that patients with a history of non-compliance to oral levothyroxine tablets switch to soft-gel capsules or liquid solutions. In addition, there is a need for further research to determine psychosocial and cultural factors affecting non-adherence to medication.

Conclusion

The current study underscores that compliance with levothyroxine therapy in hypothyroid patients is inadequate, as merely one-fourth of participants exhibited high adherence. A substantial percentage indicated missed doses, inconsistent intake timing, and challenges in adhering to fasting requirements, all of which adversely affect therapeutic outcomes. Sociodemographic factors, including education and income, in conjunction with appropriate medication timing, were significantly correlated with improved adherence, highlighting the multifactorial nature of compliance. These results show that we need to focus on patient education, make dosing instructions easier to understand, and come up with better counselling methods to help people stick with their treatment over the long term. Increasing awareness and addressing modifiable barriers may ultimately enhance biochemical control, alleviate symptoms, and improve the overall quality of life in patients undergoing levothyroxine therapy.

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