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Evaluation of the clinical pharmacist's effect on achieving treatment goals in patients with hypothyroidism: a randomized controlled trial

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Abstract

Background and aim Hypothyroidism (HoT) treatment involves lifelong thyroxine replacement therapy and regular monitoring. The objective of this study was to assess the impact of clinical pharmacist (CP) intervention in managing drug-related problems (DRPs) on outcomes among patients with HoT receiving levothyroxine (LT4) therapy.

Method A randomized controlled trial involved patients with HoT attending a university hospital's endocrinology and metabolism outpatient clinic from March 2022 to September 2022. Participants were randomly assigned to control (CG) and intervention groups (IG). CP identified and classified DRPs based on Pharmaceutical Care Network Europe (PCNE) v9.1 criteria. The validated version of the Morisky-Green-Levine (MGL) 4-question scale was used to measure adherence. All patients included in the study were assessed during their first visit and again two months later at their second visit.

Results 43 patients were assigned to the CG ($n=25$) and IG ($n=18$). Diabetes (21.6 vs. 20.5%) and hypertension (16.2% vs. 11.7%) were the most prevalent comorbidities in both the CG and IG, respectively. A total of 118 DRPs belonging to both groups were detected. In the IG group, the total number of DRPs significantly decreased from 66 to 24, and the total potential drug-drug interactions (pDDIs) decreased from 21 to 0 between the first and second visits ($p<0.001$). CG and IG patients had no difference in adherence levels at the first and second visits ($p>0.05$). A statistically significant increase in adherence to the time of taking the medication was observed between the first and second visits in IG (55.5% vs. 94.4%, $p=0.008$).

Conclusion This study highlights the frequent occurrence of DRPs and LT4 therapy adherence problems in patients with HoT. The findings suggest that the intervention of CPs, by increasing adherence to LT4 therapy and decreasing DRPs, could significantly contribute to improving patients' treatment outcomes.

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Trial registration This study protocol has been retrospectively registered at ClinicalTrials.gov (NCT06408909) at 06/05/2024.

Keywords Hypothyroidism, Levothyroxine, Drug-related problem, Clinical pharmacist, Medication adherence

Introduction

Thyroid disorders rank among the most prevalent endocrine conditions worldwide, with hypothyroidism affecting 1–2% of the population in iodine-sufficient regions [1, 2]. Levothyroxine (LT4) replacement therapy is the first-line treatment for hypothyroidism (HoT) [3]. The effectiveness of LT4 replacement therapy depends on adherence, as well as taking the drug at the appropriate time, in the correct dosage, and in the proper manner. Present comorbidities, nutrition, age, and patient weight all influence the benefit obtained from LT4 treatment [4, 5].

LT4, which has a narrow therapeutic index, may cause drug-related problems (DRP) such as non-adherence to treatment, the timing of drug use, inappropriate use of the drug, inadequate therapeutic dose, duration of treatment, inadequate monitoring of treatment and potential drug-drug interactions (pDDIs) [6–8]. In a study conducted in a hospital in India, DRP encountered during treatment with narrow therapeutic index drugs were compared with DRP encountered with other drugs. It was reported that DRPs were associated with pDDIs, adverse effects, dose overdose, dose underdose, untreated indications, inappropriate drug use, unnecessary drug use, and patient-related factors. In the study in which LT4 was also included, the rate of DRPs to narrow therapeutic index was 22%, and the rate of DRPs to other drugs was reported to be 8% [6]. In a study documenting the interventions of pharmacists in hospitals in Germany, the interventions made between 2009 and 2012 were analyzed; LT4 was one of the ten drugs with the highest number of problems, and half of these problems were drug interactions and the inadequate therapeutic dose in patients with organ failure [9].

Aluminum hydroxide, bile acid secretagogues, calcium polystyrene sulphonate, sodium polystyrene sulphonate, calcium salts, iron preparations, multivitamin supplements containing iron, lanthanum carbonate, sevelamer, magnesium salts, orlistat, and raloxifene cause D-level drug interactions (a level requiring therapy change) with LT4 [10]. In the concomitant use of calcium salts with LT4, it is observed that LT4 absorption and, consequently, therapeutic effect decreases [11, 12]. In a systematic review of the concomitant use of LT4 and proton pump inhibitors (PPIs) in patients with HoT with dyspepsia, gastroesophageal reflux, or peptic ulcer, a statistically significant increase in thyroid-stimulating hormone (TSH) levels was observed [13, 14].

Since the therapeutic index of the LT4 drug is narrow, it emphasizes the importance of adherence to the drug in reaching ideal TSH levels. Medication adherence is a dynamic process closely linked to treatment outcomes in patients with chronic diseases. Very few studies exist on LT4 treatment and patient adherence to treatment. In their study, Yavuz et al. emphasized that almost half of patients with HoT had serum TSH values outside the reference range despite receiving LT4 treatment and that adherence with LT4 treatment was one of the most critical determinants in reaching target TSH levels [15].

This study aimed to evaluate the impact of clinical pharmacist (CP) interventions on optimizing the management of DRPs in patients with HoT undergoing LT4 replacement therapy, as well as on the treatment decisions made by physicians.

Materials and methods

Study design and participants

A randomized controlled trial was done on patients with HoT attending the endocrinology and metabolism outpatient clinic of a tertiary university hospital in Istanbul from March 15, 2022 to September 15, 2022. The inclusion criteria for this study included outpatients admitted to the hospital with a confirmed diagnosis of HoT with ICD-10 code E03.9 and who provided informed consent for participation in the study. The study received ethical approval from the Clinical Research Ethics Committee (Decision No: 09.2022.425), and written informed consent was obtained from all participants. All procedures adhered to the ethical standards of the University of Siena and the principles of the 1964 Helsinki Declaration and its later amendments. This study protocol was retrospectively registered at ClinicalTrials.gov (NCT06408909) on 06/05/2024.

The randomization process was performed as simple randomization using an algorithm generated by Research Randomizer® software that assigned patients to the control group (CG) or intervention group (IG) in a 1:1 ratio. In the study, a CP on the team developed a concealed allocation schedule. In this schedule, patients were randomly assigned to groups according to two sequences corresponding to a consecutive series of numbers. Upon enrollment, the CP assigned each participant the following consecutive number, determining the intervention sequence. Participants were then randomly assigned to the CG and IG.

The IG consisted of patients for whom the CP's recommendations regarding DRPs were first communicated

to the physicians. Following physician approval, these interventions were subsequently applied for the patients. Conversely, the CG consisted of patients for whom no such recommendations were made to the physicians by CP concerning DRPs; only observations were conducted. Patients in both groups were evaluated during outpatient clinic visits or by telephone two months after discharge.

The study included patients diagnosed with HoT (ICD-10 code: E03.9) in the endocrinology and metabolic diseases outpatient clinic, aged ≥ 18 years, and who had been continuing LT4 treatment for at least six months. Patients with incomplete data, those enrolled but unreachable during follow-up, those diagnosed with hyperthyroidism and receiving treatment for this condition (e.g., methimazole, propylthiouracil), pregnant or breastfeeding women, as well as patients who had undergone malabsorption or gastric bypass surgery, and those with goiter, were excluded from the study (Fig. 1).

This study has been reported according to recommendation of Consolidated Standards of Reporting Trials (CONSORT) standards [16].

Data collection

In pre-post visits, patients were asked about the time of taking LT4, meal time after taking LT4, simultaneous medication use (PPIs, multivitamins, iron preparations, etc.), taking the pill with water or other liquids (milk, tea, coffee) and daily alternative or were examined in terms of receiving a fixed dose of LT4.

Recommendations were made to the physicians about the instructions for use, dosage, other medications used by the patient, and concurrent dietary habits of the LT4 drug used by patients in IG. DRPs detected by CP in patients were presented to physicians. At the first visit, all participants received a Type III medication review, which involved a detailed review of a patient's medication regimen to identify and resolve DRPs. For context, Type I reviews focus on prescription accuracy, and Type II reviews assess the appropriateness of therapy for individual patients. Patient randomized in the IG, provided patients with education on optimizing LT4 use based on physician-approved recommendations. Regarding the patients in CG, CP did not intervene with the physicians regarding DRPs or provide patient education. Patients in CG were only observed for DRPs.

IG group had structured patient educations sessions led by the CP. Written materials and verbal explanations supported the education provided for patients, and each session lasted approximately 15 min. Standardized educational materials, provided by relevant authorities such as the Ministry of Health and scientific associations focusing on HoT were used. The education covered key

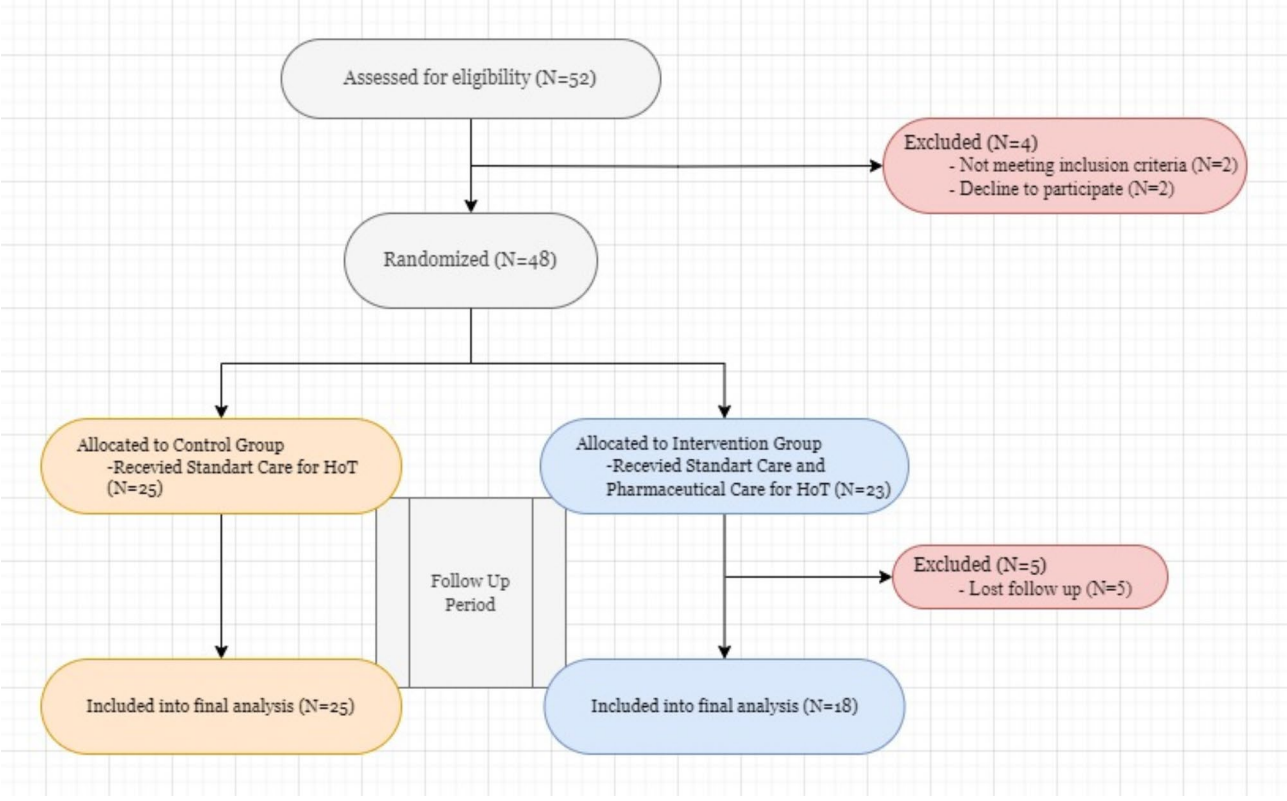

Fig. 1 Study's flowchart

aspects of the disease, including definitions, types, symptoms, complications that could arise from HoT, routine tests that should be conducted, and associated risk factors. The primary objective of these educational sessions was to provide patients with clear and accurate information about their condition and treatment, while also promoting adherence and encouraging the necessary steps to manage the disease effectively.

Recommendations were made to the physicians about the instructions for use, dosage, other medications used by the patients in IG. No patient education or recommendations were made to the physicians regarding DRPs in CG patients; only observations were made. All patients included in the study were examined at their first visit to the endocrinology and metabolic diseases outpatient clinic and two months later (second visit) at the outpatient clinic, and their level of treatment adherence, DRPs, and laboratory values of thyroid function tests were analyzed. The patients' level of treatment adherence was assessed using the Morisky-Green-Levine (MGL) adherence scale, a 4-item tool. The effect of patient education by the CP on the changes in TSH, free T4, and free T3 levels of all patients was evaluated compared to patients who did not receive education. For the patients who could not come to the hospital for the control examination, thyroid function tests were completed at an external center, and the results of treatment adherence were obtained by telephone.

The study also delved into DRPs, encompassing their causes, CP recommendations for resolution, and physicians' subsequent acceptance and implementation. The Turkish version of the Pharmaceutical Care Network Europe Association (PCNE) Classification Scheme for Drug-Related Problems v9.1 was employed to identify DRPs. This version, validated by the PCNE working group, features a comprehensive classification system consisting of primary domains for problems, causes, planned interventions, level of acceptance (of interventions), and the status of the problem. On a more detailed level, the scheme comprises grouped sub-domains, providing explanatory granularity for the principal domains. The validated PCNE classification scheme offers a robust framework for systematically categorizing and addressing DRPs in the study context (https://www.pcne.org/upload/files/417_PCNE_ classification _V9-1_ final.pdf).

Laboratory evaluation

Laboratory reference values for thyroid function tests were accepted as TSH = 0.48–4.8 mIU/mL, free T3 = 2.02–4.42 mIU/mL and free T4 = 0.78–1.51 mIU/mL Laboratory tests for routine follow-up of patients were collected from electronic health records or patients. Values below the specified reference ranges are categorized as "low", values above the reference range are categorized as "high", and values within the reference range are categorized as "normal". Before taking LT4, the values obtained from venous blood samples in the morning, after an 8-hour fast, were considered for thyroid function analysis.

Evaluation of drug-related problems and clinical pharmacist interventions

During the outpatient clinic visit of patients presenting with a diagnosis of HoT at the endocrinology and metabolic diseases clinic, the CP played a complementary role in this process by closely monitoring outpatient clinical follow-ups and treatment adjustments for patients and identifying DRPs through a comprehensive assessment of medication information. In the IG, the CP made face-to-face recommendations for DRPs to the attending physician. The CP endeavored to identify and prevent DRPs, thus helping patients admitted to the hospital with a diagnosis of HoT to achieve their treatment goals.

Recommendations included managing pDDIs, drug-nutrient interactions, and adjusting medication use/administration instructions in the patient's treatment. pDDI, drug-food interactions, and information on drug use/administration instructions in the patient's treatment were evaluated based on the patient's statement. The UpToDate® Lexidrug™ (Wolters Kluwer Health Inc.) database analyzed medicines and assessed food-drug interactions and pDDIs. pDDIs are categorized as level A, B, C, D, and X risk rating according to the UpToDate® Lexidrug™ database. Level A is defined as no known interaction; level B indicates an interaction, but no action is required; and level C indicates therapy should be monitored. Level D interactions are defined as interactions that require special patient evaluation to determine whether the benefits of concurrent use outweigh the risks and require dosage modifications or selection of alternative agents to achieve the benefits and/or minimize the harms of concurrent use. Level X interactions are defined as interactions where the combination should be avoided, and the potential harms outweigh the benefits of concurrent use. pDDIs are categorized as fair, good and excellent reliability rating to the UpToDate® Lexidrug™ database [17]. All levels of evidence for pDDIs were considered. Accordingly, as a result of the evaluation of pDDIs, recommendations regarding the instructions for the use of the drugs were presented to the patients with the approval of the physicians.

In the IG, the CP recommendations, approved by the patient's primary physician, were conveyed to the patient through patient education. These recommendations were designed to address pDDIs, drug-food interactions, and inappropriate drug intervals, which were identified as DRPs. The educational sessions aimed to enhance patient understanding and adherence by addressing pDDIs,

drug-food interactions, and inappropriate medication intervals. To facilitate comprehension, visual aids such as medication timing charts and reminders were utilized. These tools clearly represented medication schedules, including appropriate intervals between doses and recommendations for spacing between LT4 and other medications. The education was delivered orally and in writing, ensuring the patient received comprehensive guidance. This included detailed instructions on when to take their medications, managing intervals between different drugs, and coordinating their medication schedule with meals. The 24-hour medication schedule was emphasized as a practical tool to reinforce adherence and minimize DRPs.

Main outcome measure

The study's primary outcomes were to identify and classify DRPs related to LT4 therapy and determine the acceptance rate of CP recommendations. It was also aimed to compare the TSH levels of CG and IG patients in the target range and the changes in the LT4 doses used between the groups. These outcomes were integral to assessing the impact of CP interventions on patient care and treatment outcomes. By systematically evaluating patients with these measurements, this study aims to provide valuable information regarding the effectiveness of CP interventions in optimizing patient care and improving treatment outcomes by systematically assessing patients with these measures.

Adherence to LT4 therapy

The validated version of the MGL 4-question scale was used to measure adherence [18]. Four questions were asked of the patients to measure their adherence with LT4 treatment. Their "yes" answers to these questions were evaluated as 1 point. The second question was scored in reverse because it had a positive meaning. If the patient's total adherence score is 0–1, it is considered "high"; if it is 2–3, it is considered "moderate", and if it is 4, it is considered "low" adherence level.

Sample size

Based on data obtained from the literature, the sample size calculation was performed with $\alpha = 0.05$ and $\beta = 0.95$ [19]. This analysis determined that a total of 24 patients were required to achieve sufficient statistical power. Considering a potential 15% loss to follow-up, it was decided to include 14 patients in the CG and 14 patients in the IG.

Statistical analysis

The study used descriptive statistics to present the central tendency and variability of continuous variables, including mean, median, standard deviation, interquartile range (IQR), or count and percentages, as appropriate. For categorical variables, frequency and percentages were provided. Normality of continuous variables was evaluated using the Kolmogorov-Smirnov test and was found to have a non-parametric distribution. Mann-Whitney U tests were utilized for continuous variables to examine differences among groups, while Chi-square tests were employed to investigate relationships between categorical variables. Statistical significance was set at a 95% confidence interval and p-value < 0.05. Missing data were excluded from the analysis, and the entire dataset was processed using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, New York: IBM Corp.).

Results

Fifty-two patients were assessed for eligibility, with two patients excluded for not meeting the inclusion criteria and another two declining to participate, leaving them out of the randomization process. Following randomization, 25 patients were assigned to the CG, and 23 to the IG. During the follow-up period, five patients from the IG group were lost to follow-up, resulting in 18 patients in the IG group and 25 in the CG group being included in the final analyses (Fig. 1). Regarding gender distribution, there were 19 (44%) female patients in CG and 14 (32.6%) female patients in IG. The mean (± SD) age of the patients was 45.32 (13.99) years in CG and 53.83 (15.79) years in IG. In both groups, 88.3% of the patients had at least one comorbidity other than HoT. The median (IQR) number of comorbidities 1 (1–3) in CG and 1 (1–2) in IG respectively. Diabetes mellitus (21.12%) and hypertension (14.08%) were the most common comorbidities in both groups. The groups had no significant differences in sociodemographic parameters ($p > 0.05$). Additional sociodemographic information is shown in Table 1.

When the patients were evaluated regarding LT4 treatment, all of the patients were administered the drug in the morning and fasting. Patients in CG and IG were administered LT4 approximately 60 min before a meal (59.96 ± 65.84 vs. 63.44 ± 64.08, respectively, $p = 0.864$). CG and IG patients' LT4 doses and thyroid function tests were analyzed at the first and second visits. There were no statistically significant differences in the analyzed values between the visits ($p > 0.05$) (Table 2). In addition, when the changes in thyroid function tests and LT4 doses in CG and IG patients were analyzed, there were no statistically significant differences between the first and second visits ($p > 0.05$). When TSH levels were examined categorically (low, normal, high) in the first - second visit periods in CG and IG patients, no statistically significant differences were obtained ($p > 0.05$) (Table 2).

In the evaluations made to examine the adherence levels of the patients, it was understood from the scores that the patients generally adhered to the treatment.

Table 1 Demographic characteristics of patients

Variable	Total ($n=43$)	Control group ($n=25$)	Intervention group ($n=18$)	p
Age (mean ± SD)	48.88 ± 15.19	45.32 ± 13.99	53.83 ± 15.79	0.076
Sex (*n.* %)				
Female	33, 77	19, 44	14, 32.6	0.892
Male	10, 23	6, 14	4, 9.3	
Body Mass Index (mean ± SD)	29.28 ± 5.53	28.96 ± 4.78	29.76 ± 6.6	0.674
Occupation (*n.* %)				0.463
Housewife	25, 58.1	14, 32.6	11, 25.6	
Student	5, 11.6	4, 9.3	1, 2.3	
Retired	5, 11.6	2, 4.7	3, 7.0	
Not working	1, 2.3	0, 0	1, 2.3	
Other	7,16.3	5, 11.6	2, 4.7	
Education level (*n.* %)				0.185
Illiterate	4, 9.5	0, 0	4, 9.5	
Primary school	15, 35.7	9, 21.4	6, 14.3	
Middle school	5, 11.9	3, 7.1	2, 4.8	
High school	13, 31.0	9. 21.4	4, 9.5	
University	5, 11.9	3. 7.1	2, 4.8	
Comorbidities (*n.* %)				
Diabetes mellitus	15, 21.12	-	-	
Hypertension	10, 14.08			
Acromegaly	3, 4.22			
Hepatitis B	3, 4.22			
Thyroid cancer	4. 5.63			
Hyperlipidemia	4, 5.63			
Osteoporosis	3, 4.22			
Migraine	2, 2.81			
Others	27, 38.02			
Comorbidity number (mean ± SD)	1.71 ± 1.37	1.83 ± 1.46	1.56 ± 1.25	0.512
Charlson Comorbidity Index	1.79 ± 1.71	1.44 ± 1.47	2.28 ± 1.93	0.133
Hypothyroid disease duration (year) (mean ± SD)	10.71 ± 7.8	9.88 ± 6.73	11.83 ± 6.42	0.407
Total mediacation number (mean ± SD)	5.09 ± 3.15	4.76 ± 3.5	5.56 ± 2.59	0.397

SD: Standard deviation

Table 2 Comparison of Levothyroxine treatment and laboratory values

Variable	Pre (First visit)			Post (Second visit)		
	Control Group	Intervention Group	p	Control Group	Intervention Group	p
Levothyroxine dosage (mcg/kg/day), mean ± SD	1.16 ± 0.47	1.31 ± 0.42	0.749	1.16 ± 0.48	1.22 ± 0.43	0.549
TSH level, mean ± SD	3.2 ± 3.01	2.73 ± 2.84	0.612	3.21 ± 2.17	2.4 ± 2.36	0.316
TSH level (%)						
Low	16.6	23.5	0.843	20	28.5	0.843
Normal	66.6	58.8		55	50	
High	16.6	17.6		25	21.4	
FT3 level, mean ± SD	2.56 ± 0.64	2.5 ± 0.7	0.843	2.72 ± 0.46	2.58 ± 0.53	0.544
FT4 level, mean ± SD	1.96 ± 3.39	1.29 ± 0.25	0.422	1.28 ± 0.24	1.35 ± 0.21	0.344

FT3: Free triiodothyronine, FT4: Free thyroxine, SD: Standard deviation, TSH: Thyroid Stimulating Hormone

CG and IG patients had no difference in adherence levels at the first and second visits ($p>0.05$). A statistically significant increase was observed in paying attention to the time of taking the medication between the first and second examination in IG (55.5% and 94.4%, respectively, $p=0.008$). Likewise, an increase in adherence with taking the medication on time was observed in CG (56% and 84%, respectively, $p=0.02$). Similarly, in the CG, the rate of forgetting to take the medication decreased from 64 to 20% ($p=0.002$), while in the IG, it decreased from 77.8 to 16.6% ($p<0.001$). In the CG group, the total adherence score decreased from 1.20 ± 1.0 to 0.44 ± 0.82, while in the IG group, it decreased from 1.27 ± 0.75 to 0.27 ± 0.45. Moreover, statistically significant reductions in total adherence scores were observed between the first and second visits in both groups (CG: $p=0.013$; IG: $p=0.002$) (Fig. 2). There is no statistically significant difference in the adherence rates in other questions (Table 3).

118 DRPs were detected in the first visit, and 76 DRPs were detected in the second visit. When DRPs were

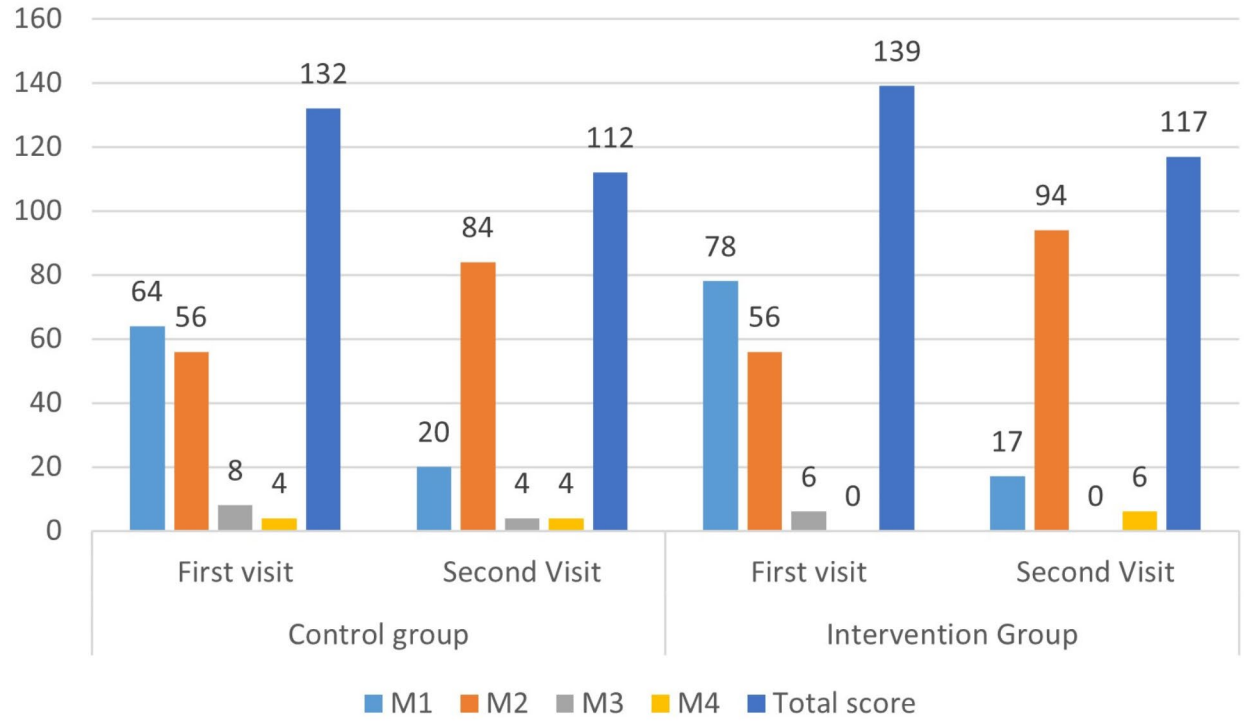

Fig. 2 Comparison of adherence score averages in first-second visits of control and inervention groups (Scores are expressed by multiplying by 100 for visualization. The meanings of the "M" expressions are shown in Table 3)

Table 3 Comparison of patients' adherence with Levothyroxine treatment

	Pre (first visit)			Post (second visit)		
	CG (%)	IG (%)	*p*	CG (%)	IG (%)	*p*
Variable						
M1. Do you ever forget to take your medications? / Yes	64	77.8	0.503	20	16.6	1.000
M2. Do you pay attention to the time when taking your medications? / Yes	56	55.5	1.000	84	94.4	0.380
M3. When you feel better, do you sometimes stop taking your medications? / Yes	8	5.5	1.000	4	0	1.000
M4. If you sometimes feel worse when you take your medications, do you stop taking them? / Yes	4	0	1.000	4	5.5	1.000
Adherence level						
High	60	50	0.628	88	94.4	0.424
Moderate	40	50		12	5.6	
Total score (mean ± SD)	1.20 ± 1.0	1.27 ± 0.75	0.628	0.44 ± 0.82	0.27 ± 0.45	0.424

CG: Control Group, IG: Intervention Group, M: Morisky, SD: Standard deviation

categorized, they frequently developed in the pre-post period due to reasons arising from the patients. Total DRP numbers were compared in the first-second visit. Accordingly, the total number of DRPs was significantly higher in IG than in CG in the first visit ($p < 0.001$). DRPs caused by pDDIs (C1.3) and inappropriate timing of medication (C7.7) in the first visit were statistically significantly reduced in the second visit in IG ($p = 0.016$). In CG, DRPs remained the same, as no recommendations were made for DRPs. In the IG, there was a significant reduction in the total number of DRPs (from 66 to 24) and the total number of pDDIs (from 21 to 0) (respectively, $p < 0.001$ and $p < 0.001$) in the first-second visits with CP recommendations (Fig. 3).

A total of 29 pDDIs were detected by CP in both groups at the first visit. The physicians accepted and implemented all of the recommendations (100%) for 21 pDDIs of the patients in IG. All of the recommendations for food-drug interactions were accepted but have yet to be implemented by the patients. All of the CP's recommendations for DRPs were at the level of changing the instructions for the use of the medication after the physician's approval.

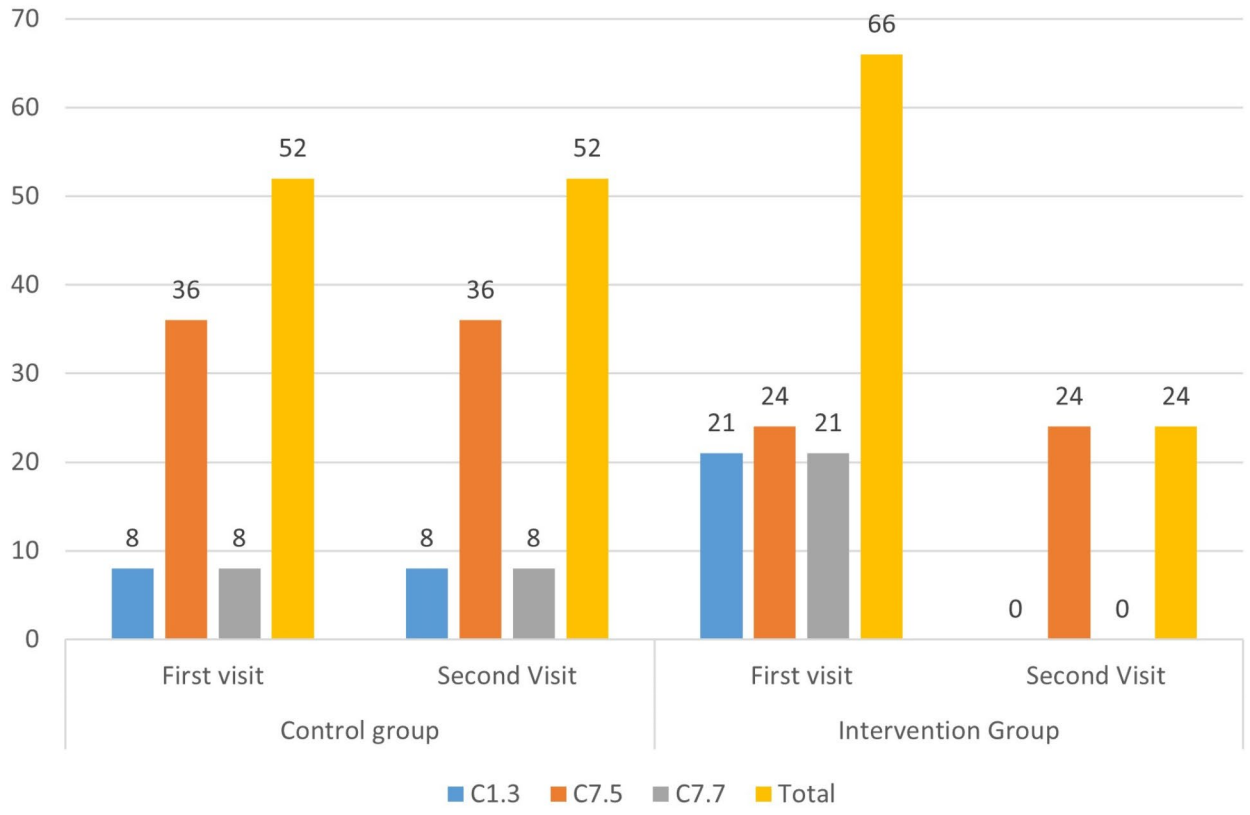

Fig. 3 Comparison of the number of drug related problems in the first-second visits for both groups (The meanings of the "C" expressions are shown in Table 4.)

Table 4 Classification of causes of drug-related problems with Levothyroxine

Classification Divisions	Pre (First visit)			Post (Second visit)		
	CG, *n* (%)	IG, *n* (%)	*p*	CG, *n* (%)	IG, *n* (%)	*p*
The Causes (including possible causes for potential problems)						
1. Drug selection	**8 (15.3)**	**21 (31.8)**		**8 (15.3)**	**0 (0)**	
C1.3 Inappropriate combination of drugs or drugs and herbal medications	8 (15.3)	21 (31.8)	< 0.001	8 (15.3)	0 (0)	**0.016**
7. Patient related	**44 (84.6)**	**45 (68.1)**		**44 (84.6)**	**24 (100)**	
C7.5 Patient takes food that interacts	36 (69.3)	**24 (36.3)**	0.740	36 (69.3)	**24** (100)	0.740
C7.7 Inappropriate timing or dosing intervals	8 (15.3)	**21** (31.8)	< 0.001	8 (15.3)	0 (0)	0.016
Total DRP (*n* = 118)	**52 (100)**	**66 (100)**	**< 0.001**	**52 (100)**	**24 (100)**	**0.053**

C: Cause, CG: Control group, IG: Intervention group

Among all pDDIs, calcium carbonate (41.37%) and pantoprazole (27.58%) were the most common drug-drug interactions with LT4. 51.72% of pDDIs were level D, and 48.28% were level B. The reliability rating distribution of pDDIs was mostly (55.17%) "fair". CP did not make any recommendations regarding pDDIs in CG, and pDDIs could not be found in patients in IG on the second visit. For this reason, only the pDDIs of the patients at the first visit are shown in Table 5.

No significant differences were found between the data when TSH levels, LT4 doses, and adherence levels were compared according to the presence of pDDI ($p > 0.05$) (Table 6). The duration of HoT disease and adherence categories (high and others) of patients at the first visit were analyzed. Accordingly, it was observed that patients with a shorter disease history (9.40 ± 8.10 years) had better adherence to LT4 treatment compared to those with a more extended disease history (13.06 ± 6.71 years) ($p = 0.039$).

Discussion

In this study, we evaluated the effect of CP recommendations on medication adherence and thyroid function tests in patients admitted to the endocrinology and

Table 5 Frequency of possible drug-drug interactions with Levothyroxine in patients at the first visit

	CG, *n* (%)	IG, *n* (%)	Risk Rating*	Reliability Rating*
Esomeprazole	1 (12.5)	2 (9.5)	B	Fair
Lansoprazole	0 (0)	3 (14.2)	B	Fair
Pantoprazole	4 (50)	4 (19.0)	B	Fair
Iron (II) sulfate	1 (12.5)	0 (0)	D	Good
Hydrotalcite	0 (0)	1 (4.7)	B	Fair
Calcium carbonate	2 (25)	10 (47.6)	D	Good
Magnesium oxide	0 (0)	1 (4.7)	D	Fair
Total	8 (100)	21 (100)		

CG: Control group, IG: Intervention group

*Risk rating and reliability rating information of potential drug-drug interactions are expressed according to the UpToDate® Lexidrug™ database [17]

Table 6 Statistical analysis of patient data in the first visit according to potential drug-drug interaction situations

Variables	Potential drug-drug interactions		*p*
	Yes	No	
TSH levels (first visit), (*n*, %)			
Low	4, 19	4, 20	0.942
Normal	13, 62	13, 65	
High	4, 19	3, 15	
TSH levels (first visit), (mean ± SD)	2.8 ± 2.6	3.1 ± 3.2	0.990
Levothyroxine dosage (first visit) (mcg/day), mean ± SD	83.6 ± 26.9	96.5 ± 38.6	0.224
Total adherence score (first visit), (mean ± SD)	1.3 ± 0.7	38.2	0.604

SD: Standard deviation

metabolism outpatient clinic. We examined the contribution of CP to the treatment by comparing specific parameters at the patients' first and second visits.

TSH levels of the patients included in the study in CG and IG at the first-second visits were out-of-reference in approximately half of the patients. These rates are similar to the adherence study conducted by Yavuz et al. in a multicenter study in Turkey. Yavuz et al. emphasized that patients with a high out-of-reference rate have a low adherence rate [15]. In this study, although the patients' adherence rates to LT4 therapy were at a high-moderate level in both periods, the number of patients with TSH levels within the normal range was relatively low. This suggests that patients have factors influencing their decisions other than treatment adherence. Factors such as age, the etiology of HoT, concomitant medications, and other underlying illnesses are also recognized to affect serum TSH levels, highlighting the necessity for individualized dosage adjustments. A study evaluating elderly patients with HoT showed that more than 40% of patients had low TSH levels, and 16% had high TSH levels. This study associated this situation with low weight [20]. The patients in this study were relatively younger and had a higher mean body mass index than those reported by Somwaru et al. [20]. However, less than 30% of the patients had low TSH levels in both groups and periods. This leads us to other reasons why TSH levels in patients are outside the reference range.

TSH values outside the normal range may be due to confounding factors such as failure to adjust the LT4 dose or poor adherence of the patients [21]. One of the most common reasons for non-compliance is avoiding or forgetting to take the medication [20]. In this study, the patients had many comorbidities, and as a result, polypharmacy emerged (total number of drugs = 5.09 ± 3.15). However, drug adherence rates in the patients were at a high-moderated level in total. However, there were similar problems with adherence in this study, especially about forgetting the medication and being careful to take it on time. Many studies have highlighted the positive impact of CP patient counseling on medication adherence and quality of life [22–25]. Notably, in this study, patients began to take care to take their medications on time after CP interventions. In this study, patients with a long-term history of disease had a lower rate of adherence to treatment than patients diagnosed with shorter-term HoT. Al-Noumani et al. also stated that drug adherence decreases as the duration of the disease increases and the frequency of daily drug treatment increases [26]. In this case, the CP and the physicians plan to provide education on using medications at regular intervals, which will contribute to increasing the patients' adherence.

In studies investigating DRPs conducted by CPs, LT4 is infrequently identified as one of the drugs contributing to DRPs [7, 9, 27–29]. In this study, we focused only on LT4-derived DRPs. Looking at other DRP studies, pDDIs are among the most common causes of DRP [28, 30–33]. In this study, one of the leading causes of LT4-related DRPs was pDDIs. In IG, pDDIs were significantly reduced between the first and second visits with CP

recommendations. This benefit is one of the main contributions of CP to patients receiving LT4 therapy.

One of the factors affecting LT4 absorption is stated as pDDIs [34]. However, although half of the pDDIs were D-level drug interactions, no changes in TSH levels were observed between periods in IG. Considering that all pDDIs mostly have a "fair" level of evidence in this study, the effects of drug interactions on the patient's thyroid function tests and LT4 absorption should be examined separately [17]. In addition, the treatment duration, doses, and administration methods of the drugs used simultaneously with LT4 should also be examined [14].

LT4 should be taken with food at certain intervals. Otherwise, LT4 absorption may decrease [34, 35]. In this study, it was determined that the patients' habits did not change in terms of drug-food interactions that cause DRPs. In this case, patients must comply with comprehensive and continuous education that includes medication, nutrition, and drug administration times. Otherwise, it can be predicted that interventions based only on medications will be insufficient to ensure the patient's outcomes. In this context, "interventions based only on medications" refers to approaches that focus solely on adjusting the type, dosage, or timing of medications prescribed to the patient, without addressing other contributing factors such as the patient's dietary habits, timing of food intake, or their understanding of how to take the medication correctly. In this case, it should be emphasized that while medication adjustments are important, they need to be supported by patient education and lifestyle modifications to achieve the best outcomes.

A pDDI study involving LT4 users (7.5% of the population) demonstrated a significant increase in TSH levels during initial exposure to pDDI, which decreased over time [36]. Irving et al. stated that iron, calcium, PPIs, and estrogen increased serum TSH concentration to a clinically significant level in patients receiving LT4 therapy [14]. In this study, PPIs (esomeprazole, lansoprazole and pantoprazole) appear as the drug group that frequently causes pDDIs. There are studies indicating the existence of drug interaction between PPIs and LT4 and increased TSH levels [37–39]. However, contrary to these studies, there are also studies stating that this interaction does not affect TSH levels [40, 41]. PPIs may affect thyroxine absorption by increasing the pH of the stomach, but there is currently insufficient conclusive evidence to confirm this theory. Studies on the mechanism of interactions of PPIs with LT4 require further evaluation as suboptimal dosage may worsen patient symptoms and quality of life and lead to poor management of HoT. It was concluded that the interaction would be clinically significant for the 5–6% of patients receiving LT4 and PPIs concomitantly. Therefore, it is important to highlight that prescribing LT4 alongside potentially interacting drugs may decrease LT4 absorption, potentially necessitating an increase in its therapeutic dose [14]. Clinicians should carefully consider adjusting levothyroxine therapy in the presence of concomitant medications, such as PPIs, that may reduce the bioavailability of LT4.

In DRP studies carried out by CPs, the physicians acceptance rates of CP recommendations are quite high. Especially in studies conducted on internal medicine ward patients, a department close to patients in the endocrinology clinic, a high rate of CP recommendations were accepted and implemented [27, 28]. Accepted CP recommendations were presented to all patients by the CP through education. During the second visit, patients reported that they had followed the clinical pharmacist's recommendations regarding potential drug-drug interactions (pDDIs) when taking their medications. While this effect of CP in adjusting the intervals of patients' medications reduces DRPs, it does not affect the results of thyroid function tests. This requires more comprehensive and continuous follow-up of patients.

Strengths and limitations

To the best of our knowledge, this is among the first randomized controlled studies focusing comprehensively on DRPs and medication adherence, specifically in patients with HoT using LT4. While other studies may address similar topics, we have yet to encounter any in the literature that investigates these aspects with this specific focus on LT4 therapy. One of the critical limitations of the study is that it was conducted in a single center with a small number of patients. Other limitations include solely reliance on patient reports, about medication adherence, drug-food interactions, and pDDIs. Since CP's recommendations are only for LT4 and related DRPs, its effect on patients' thyroid function tests may have yet to be fully revealed. In future studies, a comprehensive evaluation of patients managed by clinical pharmacists integrated into the healthcare team, supported by planned and continuous education programs, is recommended to enhance the achievement of desired clinical outcomes.

Conclusion

It has been observed that TSH levels are out of reference in approximately half of HoT patients. In patients with HoT, DRPs are concentrated in drug-drug and drug-food interactions. The physicians accepted all of the CP's recommendations. Significant reductions in the rate of pDDIs were achieved in patients in IG at the first and second visits. Adherence levels of patients with HoT to LT4 therapy were determined to be moderate and above. With CP interventions, improvements in adherence were achieved by taking medications on time and being careful when using them simultaneously with other medications.

There was no improvement in the patients' nutritional habits to prevent drug-food interactions. Despite all these educations and interventions, no improvement was achieved in the patients' TSH levels. In conclusion, this study points to the importance of reassessing target TSH levels to prevent potential over- or undertreatment and LT4-related problems in patients with HoT, CPs' interventions have positive outcomes, such as identifying and resolving DRP and improving medication adherence.

Abbreviations

CG	Control Group
CONSORT	Consolidated Standards of Reporting Trials
CP	Clinical Pharmacist
DRP	Drug–related Problem
HoT	Hypothyroidism
IBM SPSS	International Business Machines Statistical Package for the Social Sciences
ICD-10	International Classification of Diseases, 10th Revision
IG	Intervention Group
IQR	Interquartile Range
LT4	Levothyroxine
MGL	Morisky–Green–Levine
PCNE	Pharmaceutical Care Network Europe
pDDI	Potential Drug–Drug Interaction
PPIs	Proton Pump Inhibitors
SD	Standard Deviation
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid–Stimulating Hormone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01914-3.

Supplementary Material 1

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None.

Author contributions
Author contributions is as follows YEA: Conceptualization. Methodology. Formal analysis and investigation. Data collection, Writing - original draft preparation. Writing - review and editing. MYB: Conceptualization. Methodology. Data collection. Resources. MS: Formal analysis and investigation. Writing - review and editing. Resources. DGY: Resources. Supervision. MS: Conceptualization. Methodology. Writing - review and editing. Resources. Supervision.

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Data availability
The data will be made available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study received ethical approval from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (Decision No: 09.2022.425), and written informed consent was obtained from all participants. All procedures adhered to the ethical standards of the University of Siena and the principles of the 1964 Helsinki Declaration and its later amendments. This study protocol has been retrospectively registered at ClinicalTrials.gov (NCT06408909) at 06/05/2024.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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