RESEARCH ARTICLE

Senay Kocakoglu [1]
Dursun Cadirci [1]
Mehmet Sevki Cadirci [2]
Mehmet Ali Eren [3]

[1] Harran University, Medical Faculty, Department of Family Medicine, Şanlıurfa, Türkiye
[2] Harran University Institute of Health Sciences Haliliye, Şanlıurfa, Türkiye
[3] Harran University Faculty of Medicine Department of Endocrinology, Şanlıurfa, Türkiye

Corresponding Author:
Senay Kocakoglu
mail: senaykocakoglu@yahoo.com

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konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

A Critical Issue for Primary Care Practice: Knowledge and Attitudes of Family Physicians Regarding Levothyroxine Use

ABSTRACT

Objective: Accurate management of hypothyroidism, which is one of the common reasons for referral to primary care, is critically important issue. This study aims to measure the knowledge and attitudes of family physicians (FPs) regarding the use of levothyroxine, which is the main pharmacological agent in the treatment of hypothyroidism.

Methods: This prospective and descriptive study was performed on 102 physicians from family health centers in Şanlıurfa province central districts. The researchers created a questionnaire consisting of eight questions; seven of which were multiple choices and one was open-ended, by scanning the guidelines and literature. Data were obtained by face-to-face interview technique.

Results: Of the participants, 21 (20.6%) were female and 81 (79.4%) male physicians, and the mean age of the participants was 36.9±8.0 (28-66) years. The work duration as a FP was 6.1±3.3 years. Sixteen (15.7%) of the participants reported that they had never prescribed levothyroxine. Two-thirds of them correctly answered the relationship between levothyroxine absorption and food intake, and 36.3% correctly answered that there would be a difference in absorption between different levothyroxine formulations. However, the rate of correct answers to the question of how to start hypothyroidism treatment in patients over 60 years of age or with coronary artery disease was quite low.

Conclusions: The results of this study revealed that FPs in Sanliurfa central districts do not have adequate knowledge about the use of levothyroxine for treatment of hypothyroidism, and they need effective training on this vital issue.

Keywords: Attitude, Hypothyroidism, Knowledge, Levothyroxine.

Birinci Basamak Uygulamaları İçin Kritik Bir Konu: Aile Hekimlerinin Levotiroksin Kullanımına İlişkin Bilgi ve Tutumları

ÖZET

Amaç: Amaç: Birinci basamağa sık başvuru nedenlerinden biri olan hipotiroidinin doğru yönetimi kritik öneme sahip bir konudur. Bu çalışma, aile hekimlerinin hipotiroidi tedavisinde temel farmakolojik ajan olan levotiroksin kullanımına ilişkin bilgi ve tutumlarını ölçmeyi amaçlamaktadır.

Gereç ve Yöntem: Prospektif ve tanımlayıcı tipte olan bu çalışma, Şanlıurfa ili merkez ilçelerdeki aile sağlığı merkezlerinde görev yapan 102 aile hekimi üzerinde yapılmıştır. Araştırmacılar tarafından kılavuzlar ve literatür taranarak yedisi çoktan seçmeli ve biri açık uçlu sekiz sorudan oluşan bir anket oluşturuldu. Veriler yüz yüze görüşme tekniği ile elde edildi.

Bulgular: Katılımcıların 21'i (%20,6) kadın, 81'i (%79,4) erkek hekimdi ve yaş ortalaması 36,9±8,0 (28-66) idi. Aile hekimi olarak çalışma süresi 6,1±3,3 yıldı. Katılımcıların 16'sı (%15,7) hiç levotiroksin reçete etmediğini bildirdi. Üçte ikisi levotiroksin emilimi ile gıda alımı arasındaki ilişkiyi, %36,3'ü ise farklı levotiroksin formülasyonları arasında emilimde bir fark olup olmadığı sorusunu doğru yanıtladı. Ancak 60 yaş üstü veya koroner arter hastalığı olan hastalarda hipotiroidi tedavisine nasıl başlanacağını bilme oranı oldukça düşüktü.

Sonuç: Bu çalışmanın sonuçları, Şanlıurfa merkez ilçelerinde çalışan aile hekimlerinin hipotiroidi tedavisinde levotiroksin kullanımı konusunu yeterince bilmediklerini ve bu hayati konuda eğitime ihtiyaç duyduklarını ortaya koymuştur.

Anahtar Kelimeler: Levotiroksin, Bilgi, Tutum, Hipotiroidi.

INTRODUCTION

Hypothyroidism can seriously harm many systems and organs, notably the cardiovascular system, if it is not treated properly (1) and so accurate management of hypothyroidism, which is one of the common reasons for referral to primary care is a critically important issue for health of individuals. Today, orally administered levothyroxine (LT4) is accepted as the standard treatment for hypothyroidism and it has become the most commonly prescribed drug worldwide. However, some points should be considered in order to get the maximum benefit from the use of levothyroxine (2, 3).

In recent years, two new formulations of levothyroxine, soft gel and liquid, have been used in addition to the tablet form in some countries (4). It has been reported that the use of these different formulations (brand name or generic) has different effects on serum TSH values (5). The bioavailability of a drug is closely related to how the drug is used by the patient as well as its properties. How it is stored and what the patient eats and drinks affect the absorption of LT4. It is recommended to take it as a single dose in the morning, at least half an hour before breakfast (if possible, one hour before). It should not be exposed to sunlight, and the ambient temperature where it is stored should be between 20-25 °C (6). It is a forgotten point that some agents such as calcium and iron preparations and proton pump inhibitors (PPI), which are frequently prescribed in clinics, inhibit the absorption and bioavailability of LT4 when used simultaneously (7).

In the elderly and people with ischemic heart disease, it is necessary to start with a low dose of LT4 and increase it gradually (5). FPs are expected to have sufficient knowledge and appropriate attitude to advise patients on the necessary rules for patients to get the maximum benefit from LT4 treatment.

Although hypothyroidism is a common and important clinical disorder in primary care practice (8) it is seen that there are not enough studies in the literature evaluating the attitudes and knowledge of primary care physicians regarding levothyroxine administration. Precisely for this reason it is aimed to raise awareness about this critical issue in this study.

MATERIAL AND METHODS

The study was approved by the Harran University Rectorate Clinical Research Ethics Committee on January 13, 2020 with session 01 and decision numbered 05.

The universe of the study is defined as the FPs (total n=621) who were working in family health centers in Şanlıurfa province central districts. Sample size was calculated with G* power 3.1.9.7 program (effect size=0.30, alpha=0.05 and power 0.85) and it was determined as 93. The study was carried out with 10% more of this sample size (n= 102 FP).

In order to determine the knowledge and attitudes of the participants regarding the LT4 application, a questionnaire consisting of eight multiple-choice and one open-ended questions was prepared by the researchers by scanning the guidelines and literature. Additionally, their age, gender, the number of years of practice as a physician, the duration for which they had served as FPs, and the frequency of LT4 administration (per week) prescribed by them were recorded.

All of the participants were explained about the purpose of the study and that their personal data would not be shared and than the consent of the participating physicians were obtained at the beginning and the data were obtained by a face-to-face survey method. 102 (16.9%) FPs out of 621 FPs gave consent to participate in this study.

3 groups were determined according to their working hours as FPs. Group 1 defined the physicians who had a working experience of 1-5 years, Group 2 ; 6-10 years, and Group 3 ; 11 years or more of work experience.

Statistical Analysis: Statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) version 22.0 software. The categorical data were presented as n (%), while other data were presented as mean ±SD (min-max). The categorical data between groups were compared using the Chi-squared test, while continuous data were compared using Student's t-test. All differences between groups were considered to be statistically significant at $p < 0.05$.

RESULTS

The study was conducted with 102 FPs who gave consent to participate. Of the participants, 21 (20.6%) were female, 81 (79.4%) were male, and the mean age was 36.9 ±8.0 (28-66) years.

Participants had been practicing medicine for 10.3 ±7.0 (1-36) years and had been working as FPs for 6.1 ±3.3 (1-15) years. Before working in the family health center, 45 (44.1%) participants worked in other health centers, 46 (45.1%) in emergency services, and 10 (9.8%) worked in private clinics. Sixteen (15.7%) of them never prescribed levothyroxine.

Participants' weekly LT4 prescribing rates were; 18 (17.6%) once a week; 21 (20.6%) twice a week; 31 (30.4%) three-nine per week; 16 (15.7%) 10 or more times per week (Table 1).

Table 1. Distribution of physicians according to the number of prescriptions per week

Number of prescriptions per week	Number of physicians n (%)
0	16 (%15.7)
1	18 (%17.6)
2	21 (%20.6)
3	11 (%10.8)
4	8 (%7.8)
5	10 (%9.8)
7	2 (%2.0)
10	11 (%11.8)
12	1 (%1.0)
15	2 (%2.0)
20	1 (%1.0)
30	1 (%1.0)

When the participants were asked how to start hypothyroidism treatment for someone below 60 years who does not have coronary artery disease, 40 (39.2%) of them answered as “the full planned dose can be started”, and 27 (26.5%) as "I start half of the planned dose and then switch to the full dose after a week".

How is the treatment started for hypothyroidism in someone over 60 or with coronary artery disease were asked and 18 (17.6%) participants replied as, “I start at 12.5/25 mcg and increase by 12.5 mcg once a week”.

When we asked the participants, “What is the best time to use levothyroxine?”, 73 (71.6%) participants answered, "In the morning on an empty stomach".

The relationship between levothyroxine and food intake was asked and 67 (65.7%) of the participants answered as “Absorption decreases with satiety”.

When the participants were asked, “If you think levothyroxine should be used on an empty stomach, how long should the patient fast after taking the drug?”, 69 (67.6%) physicians answered as, "half an hour to an hour".

To the question “What do you think about the formulations of levothyroxine available in the market?", 37 (36.3%) of them gave the answer "Their absorption is different, so it is necessary to continue with the same formulation if possible".

It was asked how the storage conditions of the drug should be. 65 (63.7%) of the participants answered, “below 25 °C and in its box”.

The percentage distributions of multiple-choice questions and their answers are shown in Table 2.

Table 2. Rates of answers given to multiple choice survey questions.

Questions	Answers and rates (%)
How do you start hypothyroidism treatment in someone under 60 years of age who does not have coronary artery disease?	• Planned full dose can be started (39.2%) • I start half of the planned dose, I switch to the full dose a week later (26.5%) • I start at 12.5/25mcg, increase by 12.5mcg once a week (5.9%) • I do not want to answer / I do not know (28.4%)
How do you begin treatment for hypothyroidism in someone over 60 or with coronary artery disease?	• Planned full dose can be started (9.8%) • I start half of the planned dose; I switch to the full dose after a week (30.4%) • I start at 12.5/25mcg, increase by 12.5mcg once a week (17.6%) • I do not want to answer / I do not know (42.2%)
What do you think is the best time to use levothyroxine?	• In the morning on an empty stomach (71.6%) • After meal (12.7%) • Any time during the day (11.8%) • At bedtime (3.9%)
What do you think is the relationship between levothyroxine and food intake?	• Absorption decreases in hunger (14.7%) • Absorption decreases in satiety (65.7%) • Absorption does not change in hunger and satiety (19.6%)
If you think it should be used on an empty stomach, how long should be stay fasted after taking the drug?	• Can be eaten immediately (11.8%) • Half to an hour (67.6%) • At least two hours (20.6%)
What do you think of the oral formulations available in the market?	• Absorption is different, so it is necessary to continue with the same if possible (36.3%) • They all have the same absorption, so whichever is available (33.3%) • No idea (30.4%)
Under what conditions do you think this medicine should be stored?	• In the refrigerator (2%) • On the refrigerator door (10.8%) • Since it is not affected by heat and light, it can be stored under any conditions (23.5%) • Below 25°C and in the box (63.7%)

Finally, the participants were told that some commonly used drugs (eg, cholestyramine) may impair the absorption of levothyroxine and that there should be at least 2-4 hours between the use of two drugs, and they were asked to write what they knew about these drugs. 79 of the participants (77.5%) could not answer this question. The most common response was 'PPI' (21.5%), followed by 'calcium preparations' (5.8%).

The question, "How do you start hypothyroidism treatment in someone under 60 years of age who does not have coronary artery disease?", was answered by a significantly lesser number of physicians in Group 3 26 (76.4%), participants in Group 1, 22 (73.3%), participants in Group 2, and 19 (50.0%) participants in Group 3 (p=0.028).

The question, "What do you think of the oral formulations that are commercially available?", was answered by a significantly lesser number of physicians in Group 3. The rate of the answers were as 15 (44.1%) participants in Group 1, 11 (36.7%) in Group 2, and 11 (28.9%) participants in Group 3 (p = 0.016). No significant difference was found for the other answers in the three groups (Table 3).

Table 3. Distribution of the rate of correct answers given to the questions according to the groups.

Questions and correct answers	Group 1 (n=34)	Group 2 (n=30)	Group 3 (n=38)	p
Question How do you start hypothyroidism treatment in someone under the age of 60 who does not have coronary artery disease?" **Answer** "The planned full dose can be started" or "I start half the planned dose; I switch to the full dose after a week"	26 (%76.4)	22 (%73.3)	19 (%50.0)	0.028
Question "How do you start treatment for hypothyroidism in someone over 60 or with coronary artery disease?" **Answer** "I start at 12.5/25mcg, increase by 12.5 mcg once a week"	4 (%11.7)	6 (%20.0)	8 (%21.1)	0.328
Question What do you think is the best time to use levothyroxine?" **Answer** "Morning on an empty stomach"	26 (%76.4)	29 (%96.6)	27 (%71.1)	0.732
Question "What do you think is the relationship between levothyroxine and food intake?" **Answer** "Absorption decreases in satiety"	23 (%67.6)	20 (%66.7)	24 (%63.2)	0.051
Question "If you think it should be used on an empty stomach, how long should you fast after taking the drug?" **Answer** "Half to an hour"	21 (%61.7)	25 (%83.3)	23 (%60.5)	0.186
Question "What do you think of the oral formulations that are commercially available?" **Answer** "Their absorptions are different, so it is necessary to continue with the same if possible"	15 (%44.1)	11 (%36.7)	11 (%28.9)	0.016
Question "In what condition do you think this drug should be stored?" **Answer** "Under 25ºC and in the box"	17 (%50.0)	24 (%80.0)	24 (%63.2)	0.301

** Group 1; 1-5 years, Group 2; 6-10 years and Group 3; 11 years work experience.*

DISCUSSION

Hypothyroidism is an important disease that is a frequent reason for referral to primary care physicians. Several studies have investigated the management and treatment of hypothyroidism in patients (9-14). Studies on the knowledge and attitudes of physicians, who play an important role in the follow-up and treatment of patients, are frequently conducted on pregnant women (15, 16) In this study, the knowledge and attitudes of FPs regarding the use of levothyroxine were emphasized and the training needs on this subject were revealed.

In the study of Negro et al., on the management of thyroid diseases by General Practitioners (GP), 122 of 622 physicians participated in the study with a rate of 19.6% (17). In this study, 102 out of 621 physicians participated (participation rate was 16.4%), and the participation rate was slightly lower than that in the abovementioned study.

In a study by Askari et al. on the level of knowledge of physicians regarding thyroid disorders in pregnant women, 41.4% of the participants were male (16). In our study, 79.4% of the participants were male.

In a study by Hussien and Eldin on the knowledge and attitudes of primary care physicians regarding thyroid disorders, the mean age of the physicians was 34 ±7.8 years, and the mean working duration was 6.8 ±5 years (18). In a quantitative study conducted by Dew et al. on the knowledge of healthcare professionals regarding hypothyroidism, the age of the participants ranged from 25 to 60 years, which was similar to the age range in this study (19). In the study by Askari et al., the mean age of the physicians was 37.8 ±7.6 years (16) smilar to this study (36.9±8.0 years). Work experience as a FPs was found to be 6.1±3.3 years.

About 62-82% of levothyroxine is absorbed within 3 h, mainly from the duodenum and jejunum (7, 20). Maximum absorption occurs on an empty stomach. Levothyroxine intake with food can disrupt thyroid hormone regulation (5, 20). Thus, T4 preparations are recommended to be administered as a single dose, preferably with a glass of water, on an empty stomach (6) In this study, the participants were asked the best time to take levothyroxine, and most of the participants correctly answered as "In the morning on an empty stomach". When they were asked about the relationship between levothyroxine and food, two-thirds of the participants gave the correct answer which should be Absorption decreases with satiety". The participants were also asked about the duration of fasting after taking the drug. For optimal absorption, patients are recommended to take levothyroxine at least 0.5 to 1 h before breakfast (6, 20). Most of the participants answered this question correctly.

Levothyroxine should be stored at 25 °C in a box, away from light and moisture (20). More than half of the physicians answered the question about the storage conditions of levothyroxine correctly.

Levothyroxine is available in tablet, capsule, intravenous, and liquid forms (5, 21). Two different companies in Turkey have formulations in tablet form. Although the contents are the same, the absorption of different oral formulations might be different (2). The participants were asked for their opinion on the tablet forms available in the market. Approximately one-third of the participants correctly answered that the absorption of different formulations is different, and therefore, it is necessary to continue with the same one if possible. This question was answered by a few of Group 3 physicians, which included those with a work experience of 11 years or more. Physicians need to follow the developments in the field of medicine to administer the best treatment possible to the patient. We argue that these results reflect the need to continue education after graduating on the subject to be updated regarding the latest advancements and trends in the field.

In the study by Dew et al., healthcare professionals stated that hypothyroidism is easy to manage, but GPs and nurses generally have insufficient knowledge about drug interactions and levothyroxine pharmacokinetics (19). It has been reported that the absorption of thyroid hormones may be affected by some agents such as calcium, cholestyramine, sucralfate, and ferrous sulfate. Some antacids containing aluminum hydroxide also have effects on absorption (7, 22). In this study, the participants answered that drugs, such as PPI and calcium preparations, could impair levothyroxine absorption. Since most of the physicians did not give answer this question, it can be assumed that they do not have sufficient knowledge about drug interactions.

In a study by Serin et al., patients were asked about the foods and drugs that interact with levothyroxine, and 86% stated that they were unaware. The researchers also found that approximately 30% of iron and PPI were used along with levothyroxine (23). In the study by Dew et al., healthcare professionals stated that the incorrect administration of levothyroxine was the main reason for inadequate treatment (19). The knowledge of primary care physicians regarding drug interactions is very important in informing and educating patients for treating diseases effectively.

In the study by Dew et al., doctors and nurses were aware of the cardiac complications associated with rapid administration of levothyroxine to the patient (19). In the study by Askari et al., the lowest scores were related to iodine requirements and complications of thyroid disorders, while the highest scores were related to the questions about the diagnosis (16). Gibbons et al. evaluated the knowledge of physicians for diagnosing and managing subclinical hypothyroidism in a qualitative study involving GPs. They reported that there is considerable variation in how GPs perceive subclinical hypothyroidism and their knowledge of the disease. They stated that this variation was due to the uncertainty in the symptoms and prognosis of subclinical hypothyroidism and the variation in recommendations regarding treatment (24). In this study, 39.2% of the participants correctly answered the question on how to start hypothyroidism treatment in individuals below 60 years without coronary artery disease, and 17.6% correctly answered the question on how to start hypothyroidism treatment in individuals over 60 years or with coronary artery disease. When the answers were evaluated according to the groups, the lowest rate of the correct answer was given by the participants in Group 3, who had the longest work experience (11 or more years).

A study that evaluated the level of knowledge regarding thyroid disorders in primary care found that pre-training information was insufficient in GPs and FPs. The knowledge level of internists was found to be higher than that in GPs and FPs. The answers given to the information questions after being educated changed significantly and educating doctors to detect and manage thyroid disorders in primary care is necessary (18). Askari et al. reported that doctors in Iran have insufficient knowledge about the management of thyroid disorders in pregnant women [16]. In a study conducted in Turkey, physicians were found to have insufficient and/or incorrect information on thyroid disorders in pregnant women. While endocrinologists had the highest scores in each department, FPs had higher scores than obstetricians (15). Negro et al. reported that, most of the GPs (72.1%) performed preliminary examinations before referring the patient with suspected thyroid dysfunction to a specialist, and the level of knowledge of the physician determined their attitude toward patient management (17). In this study, however, a comparison could not be made because of the limited number of specialist physicians.

It can be said that adequate control could not be achieved in patients with hypothyroidism using levothyroxine according to some studies on this issue (25, 26)

A study on the management of primary care physicians' use of levotroxine also revealed that participants had a proactive attitude in therapy and that they deviated from the recommendations in the guidelines for various reasons (27).

CONCLUSION

We believe that the results of this study will contribute to raising awareness about the deficiencies in the management of hypothyroidism therapy by levothyroxine in primary care. For improving public health, FPs who encounter chronic diseases most frequently, should follow current guidelines and publications on the management of these diseases. Effective training programs for FPs and for patients to ensure the correct application of standard protocols are the key for effective treatment of hypothyroidism.

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