

# Adherence to levothyroxine among patients with hypothyroidism in Lebanon

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## Abstract

**Background:** Non-adherence to medication schedules by patients with chronic illnesses can have serious consequences, including poor clinical outcomes, higher hospitalization rates, and increased healthcare costs. Hypothyroidism is a chronic illness with simple treatment, yet non-compliance is common.

**Aims:** This study aimed to evaluate treatment adherence to levothyroxine therapy in Lebanese population by estimating the proportion of adherent hypothyroidism patients and assess factors affecting the adherence to treatment.

**Methods:** A cross-sectional survey between May and July 2015 included 337 patients. Patients were approached by a community pharmacist during their visit to buy their levothyroxine drug and were asked to fill the questionnaire.

**Results:** Among these patients, 14.5% showed high adherence, 30.6% medium adherence, and 54.9% low adherence to medication. The mean adherence score was  $5.53 \pm 1.86$  points. The results of a logistic regression showed that age (ORa=1.036), visiting the endocrinologist once every month (ORa=2.777), and the fact that the physician gave the patient information about the disease (ORa=2.898) would significantly increase the adherence to the medication. In addition, having one (ORa=0.365) or two comorbidities (ORa=0.232) in addition to hypothyroidism, postponing/cancelling medical appointments at the last minute (ORa=0.358), the number of waterpipe smoked per week (ORa=0.621) and the number of alcohol glasses drunk per week (ORa=0.631) would significantly decrease the adherence score.

**Conclusion:** Educational programmes should be implemented, doctor-patient and pharmacist-patient relationship could be improved and new treatment regimens be considered in order to enhance patient adherence.

Keywords: medication adherence; hypothyroidism; levothyroxine; adherence score; Lebanon.

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## Introduction

Hypothyroidism is believed to be an important health issue in Lebanon, as it is worldwide. Studies in India have found a prevalence of hypothyroidism of approximately 11% (1) and 3.05% in Europe (2). According to a recent study conducted by Zreik and Nasralla, the prevalence of hypothyroidism in Lebanon was estimated at 0.6% (3).

Medication adherence is defined by the World Health Organization (WHO) as “the degree to which the person’s behaviour corresponds with the agreed recommendations from a healthcare provider” (4), with respect to timing, dosage, and the frequency of medication-taking during the prescribed length of time (5). Non-adherence is a major cause of treatment failures. Adherence is simultaneously affected by multiple factors. There are five interacting dimensions of non-adherence: healthcare system/team factors such as the access to care and the stress of healthcare visits; patient-related factors especially psychological factors; therapy-related factors that comprise the unpleasant side-effects; condition-related factors such as the duration of therapy; and finally

social and economic factors that include unstable living conditions, lack of family or social support, medication cost, and health insurance (6).

Adherence to therapy may be investigated by direct patient report, clinical impression or frequency of refills at the pharmacy. Non-adherence to medication schedules by patients with chronic illnesses has long been recognized as a problem. It is estimated that approximately only 50% of patients follow treatment recommendations (7). Hypothyroidism is a chronic illness with simple treatment, yet non-compliance is common. Little objective information is available about patient adherence to hypothyroidism medications, although most clinicians believe non-adherence is common. Estimates of non-adherence range from 22% to 82% of patients (8). A study done in the United States of America in 2008 showed that during the first year of drug therapy, 68.4% of individuals with hypothyroidism achieved adherence rates of 80% or better (7).

Since data about hypothyroidism in Lebanon are scarce, the major objective of this study is to evaluate

treatment adherence to levothyroxine therapy in a sample of the Lebanese population. Our study's secondary objectives were to investigate the knowledge of these patients about their disease and therapy and to assess factors affecting their adherence to treatment. Knowing these factors (comorbidities, cost of medicine, interaction with food or medication and patient's education) will provide a comprehensive knowledge for healthcare providers in order to improve medication adherence.

## Methods

### Study design and sampling

A pilot cross-sectional survey was carried out using a sample of Lebanese patients. Patients were approached by a community pharmacist during their visit to buy levothyroxine drug at community pharmacies. Before the start of the data collection process, all community pharmacists received a common training with the research team in order to ensure consistency. The pharmacist explained the study objectives to each patient. We had to obtain the permission of the pharmacist in charge in order to fill the questionnaires in his/her pharmacy. After a period of 12 weeks, questionnaires were placed in closed envelopes and collected from the pharmacies for data entry. The names of the patients were registered to ensure non-duplication of the same patient, but not entered in the database to ensure anonymity. The anonymity of the patients was guaranteed during the data collection process in order to avoid information bias. The study was performed over a period of 12 weeks between May and July 2015. The sample included patients from 22 pharmacies from four districts in Lebanon (Beirut, Mount Lebanon, North and South Lebanon).

### Compliance with ethical standards

The Lebanese University Institutional Review Board waived the need for an approval based on the facts that it was an observational study that respected participants' autonomy and confidentiality and induced minimal harm to them. A written informed consent was obtained from all participants prior to distributing the questionnaire to them.

### Inclusion and exclusion criteria

Eligible patients were Lebanese adults older than 18 years old, treated with any levothyroxine drug available in the Lebanese market for hypothyroidism since at least six months, regardless to other medicines that may be taken by the patient for the treatment of co-existing medical conditions. There were not any specific exclusion criteria except mental illness or dementia, which could affect the participant's ability to understand and answer properly the questionnaire and cause information bias. Patients assisted by a caregiver were not eligible to participate because they were not in charge of their own adherence to treatment.

### Sample size

We fixed our expected frequency of adequate knowledge

at 68.4% in a similar study (7) and chose a precision level of  $\pm 7\%$ . The Epi-info software version 7.2 (a population survey) calculated a minimum sample size of 332 to ensure a confidence level of 95%.

### Data collection

Data were collected by using a well-designed questionnaire composed of different sections. These sections were chosen and organized based on the review of similar literature. The participants completed the self-administered anonymous questionnaire in the Arabic language. First, it was pilot-tested on nine patients for further modifications who were not included in the final study sample. This was done to check the questions were unambiguous and easily understood by the patients and that it was possible to complete in an appropriate time frame. The questionnaire which consisted of closed and open-ended questions was completed by the patients in an average time of 7 minutes.

### The questionnaire

In order to explore the views of a representative sample, the study questionnaire was designed to facilitate the collection of quantitative as well as qualitative data. The questionnaire used in this study had several parts, starting with numerous questions related to the socio-demographic characteristics of the patients such as age, gender, profession, marital status. The second part was about lifestyle characteristics and comprised of questions about cigarette and waterpipe smoking and their respective number of cigarettes/waterpipes smoked per day, alcohol and coffee drinking with the quantities consumed respectively, regular physical activity with the duration of exercise done per week and sleeping hours. The third part was about the general medical condition and included the thyroid drug taken by the participant with regards to timing, dosage, and frequency of medication-taking. The fourth part was specifically about thyroid problems, and included questions about the cause of hypothyroidism, starting and a secondary dose of treatment and the frequency of Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4) testing. The fifth part aimed to collect data on the relationship with the healthcare provider based on the frequency of the patient's visits to his doctor, and the education that the patient has received from his doctor/ pharmacist regarding his disease and treatment.

The following part was to elicit the information that the patients had about the importance of iodine intake for normal thyroid function. The adherence to thyroid drugs was assessed by asking the patients about the frequency, percent and rating response of their levothyroxine medication during the last month.

Concerning the frequency, we asked the patient "did you take all your medications all the time?" with the possible responses being divided as follow: 0% for none of the time, 20% for a little of the time, 40% for some of the time, 60% for a good bit of the time, 80% for most of the time and 100% for all the time. The percent item was checked using the question "what percent of the time

were you able to take your medications exactly as your doctor prescribed them?” The rating item was assessed using the following question “rate your ability to take all your medications as prescribed” with the possible answers being divided as follows: 0% = very poor, 20% = poor, 40% = fair, 60% = good, 80% = very good and 100% = excellent. The total score was calculated by summing all three answers and presented in a percentage (9–11). The total score obtained could be presented as a percentage (9–11).

**Statistical methodology**

Statistical analysis was performed using SPSS software version 21. Descriptive statistics, mainly mean values and standard deviation (SD), were presented for continuous quantitative variables, while frequencies and percentages were used for nominal and ordinal variables. We checked the distribution normality for all variables using the Shapiro Wilk test. Student’s t-test was conducted to examine differences between means in quantitative variables, while Chi-square analyses were used to compare qualitative and some categorical variables. ANOVA test

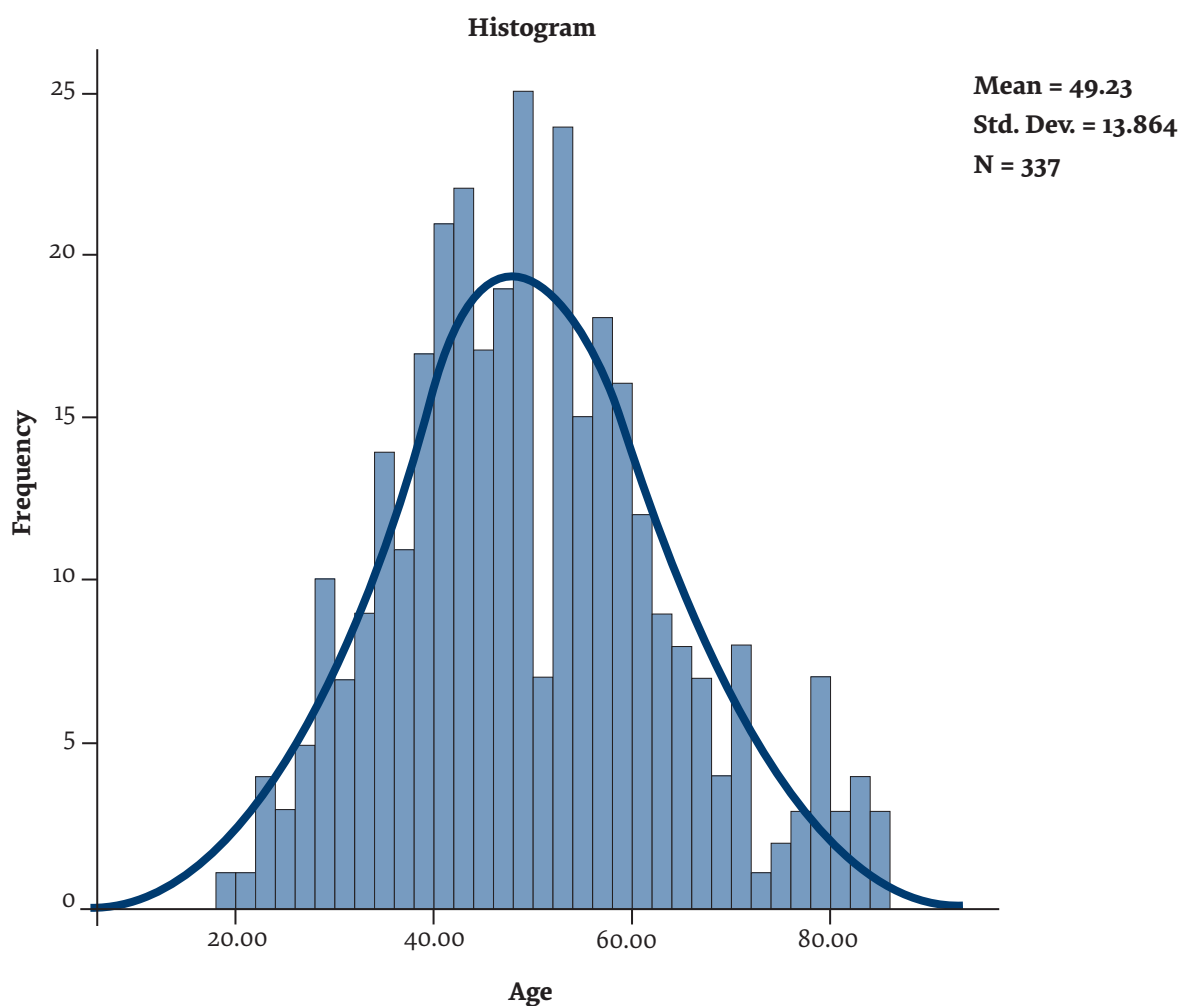
was used to compare between means of three or more groups. The correlation coefficients were used to evaluate the association between quantitative variables.  $P < 0.05$  was considered significant.

Association between multiple factors including socio-demographic characteristics of study participants and adherence were evaluated, using both bivariate and multivariable analysis. A multiple logistic regression was carried out using variables that showed a  $P < 0.2$  in the bivariate analysis (12,13); potential confounders may be eliminated only if  $P > 0.2$ , in order to protect against residual confounding (14). In the multiple logistic regression, the dichotomized adherence score (based on a cutoff point = 60%) was used as the dependent variable. Significance was defined as a  $P < 0.05$ .

**Results**

Out of the 450 distributed questionnaires, 337 (75%) were filled and returned back. Thus, the sample size needed for sufficient power to conduct the analysis was met. Our sample was normally distributed, with a  $P$ -value of the Shapiro Wilk test of 0.263 and as shown in Figure 1.

Figure 1 Normal distribution of sample



## Descriptive analysis

### Socio-demographic characteristics

Table 1 describes the socio-demographic and socio-economic characteristics of the 337 participants. The mean age was  $49.23 \pm 13.86$  years and the mean Body Mass Index (BMI) was  $25.98 \pm 4.36$  kg/m<sup>2</sup>. Females' participation (75.7%) was higher than that of males (24.3%) and the highest percentage of the patients lived in Mount Lebanon (59.6%). Almost 37% of these patients had a university degree while 7% were not educated and 36% had no professional work. The monthly income of the house was mostly between LEB£ 1000 000 and 2 000 000 (42.4%) and only 5% of the patients reported living alone. Among the 337 study participants 15% did not have any medical insurance coverage, while 42% benefited from the National Social Security Funds (NSSF) and 29% had a private health insurance.

### Lifestyle characteristics

Lifestyle characteristics and social habits of the study participants were presented in Table 2. 42.1% of the patients were cigarette smokers whereas 21% reported waterpipe smoking. Coffee drinking was proclaimed by the majority (90.8%) unlike alcohol drinking that was reported by only 44% of the participants. Among these patients, only 27% practiced a regular physical activity.

### Health status and medication-related characteristics

Concerning the medical situation, Table 3 shows that more than half of the patients (56.7%) did not have a family history of hypothyroidism. Responses to the questions that aimed to reveal the manner in which Lebanese population took thyroxine drug showed that almost all patients (98.5%) took their levothyroxine medicine in the morning and 91% declared taking it before meals whereas only 49% reported taking this medicine away from food. Out of the 337 participants, 39% experienced a better medication adherence after the dose was increased while 58% maintained the same adherence rate.

Some of the surveyed patients suffered only from hypothyroidism (26.7%) but a higher proportion (44.5%) had one additional medical problem and 28.8% were suffering from at least two co-morbidities. The mean number of medicines taken by these patients was  $2.83 \pm 1.82$  drugs, while the mean duration of hypothyroidism reported was  $9.71 \pm 7.52$  years. Among this sample, 61% of the patients professed a regular testing of their thyroid function with a mean testing frequency of  $9.35 \pm 3.76$  months and 64% of them obtaining normal results. Only 22% of these patients admitted knowing the normal range of TSH.

### Relationship with a healthcare provider and knowledge of the importance of iodine supplementation

The highest frequency of endocrinologist's regular visit was the yearly visit (39.8%) and 26% of the participants admitted consulting their physician less than once per year. The majority of the patients (94.1%) revealed that their doctor/ pharmacist gave them the necessary explanation

**Table 1** Socio-demographic and socio-economic characteristics

Factor	Mean $\pm$ SD/ N (%)
<b>Age</b>	49.23 $\pm$ 13.86 years
<b>Gender</b>	
Male	82 (24.3)
Female	255 (75.7)
Weight (kg)	71.31 $\pm$ 13.83
Height (m)	1.65 $\pm$ 0.07
BMI (kg/m <sup>2</sup> )	25.98 $\pm$ 4.36
<b>Region</b>	
Beirut	95 (28.2)
Mount Lebanon	201 (59.6)
North	10 (3)
South	31 (9.2)
<b>Education</b>	
Primary	14 (4.2)
Complementary	73 (21.7)
Secondary	103 (30.6)
University	123 (36.5)
Not Educated	24 (7.1)
<b>Employment status</b>	
Unemployed	120 (35.6)
Employee/Liberal	208 (61.7)
Retired	9 (2.7)
<b>Monthly income</b>	
Less than 1M	117 (34.7)
Between 1M and 2M	143 (42.4)
More than 2M	77 (22.8)
<b>Live alone</b>	
No	320 (95)
Yes	17 (5)
<b>Medical coverage</b>	
Cash payer	51 (15.1)
NSSF	141 (41.8)
Mutual fund of civil servants	37 (11)
Army	6 (1.8)
Security forces	4 (1.2)
Private Insurance	98 (29.1)

about the way they should take their medicine while only 45% stated having enough information about their case and medicines. However, more than half of the participants (53%) admitted postponing medical appointments and in the case of only 29% of the patients, the doctor recommended a special diet for iodine supplementation, rich in sea food and iodized salt. The knowledge of the importance of iodine supplementation in hypothyroidism was

**Table 2 Lifestyle characteristics and social habits**

Factor	N (%)
<b>Smoking</b>	
No smoking	124(36.8)
Cigarette	142 (42.1)
Waterpipe	71 (21.1)
<b>Current alcohol drinking</b>	
No	190 (56.4)
Yes	147 (43.6)
<b>Current coffee drinking</b>	
No	31 (9.2)
Yes	306 (90.8)
<b>Regular physical activity</b>	
No	246 (73)
Yes	91 (27)

somehow good since almost 24% of the participants admitted that iodized salt is the main source of iodine and 54% of them knew that seafood is a significant source of this element. However, only 59% of the participants were aware that thyroid gland needs iodine for normal production of hormones and 44% of them declared not knowing the negative outcomes of iodine deficiency (Table 4).

#### Adherence patterns

Results revealed that 49 (14.5%) patients were classified into the High Adherence group, 103 (30.6%) were identified into the Medium Adherence group and 185 (54.9%) into the Low Adherence group. The mean adherence score was  $5.53 \pm 1.86$ . The score reliability was satisfactory, measured with Cronbach Alpha the given result was 0.7, which reflects a good internal consistency.

#### Statistical analysis

##### **Bivariate analysis for the factors associated with the medication adherence**

The results of the bivariate analysis showed that a significantly higher mean adherence score was found in retired patients ( $6.56$ ;  $P = 0.008$ ) compared to unemployed or employed patients; in those who schedule physician visits once every 2 months ( $7.15$ ;  $P < 0.001$ ); patients regularly testing their TSH ( $P < 0.001$ ), who know the normal range of TSH ( $P < 0.001$ ); and those who do not postpone their doctor's visit ( $P < 0.001$ ). In addition, a significantly lower mean adherence score was found in patients with one comorbidity compared to those without comorbidities ( $P = 0.002$ ) (Table 5).

Moreover, a significant and positive correlation was found between the adherence score and age ( $r = 0.155$ ;  $P = 0.004$ ), mean duration of hypothyroidism ( $r = 0.144$ ;  $P = 0.008$ ), whereas a significant negative correlation was found between the number of waterpipe smoked per week ( $r = -0.115$ ;  $P = 0.035$ ) and the number of alcohol glasses drunk per week ( $r = -0.227$ ;  $P < 0.001$ ) (Table 6).

#### Multivariate analysis

The results of a logistic regression showed that age ( $ORa = 1.036$ ), visiting the endocrinologist once every month ( $ORa = 27.77$ ), and the fact that the physician gave the patient information about the disease ( $ORa = 2.898$ ) significantly increased the adherence score. In addition, having one ( $ORa = 0.365$ ) or two comorbidities ( $ORa = 0.232$ ) in addition to hypothyroidism, postponing/cancelling medical appointments at the last minute ( $ORa = 0.358$ ), the number of waterpipe smoked per week ( $ORa = 0.621$ ) and the number of alcohol glasses drunk per week ( $ORa = 0.631$ ) significantly decreased the adherence score (Table 7).

#### Discussion

In this study of adult Lebanese patients suffering from hypothyroidism, we estimated the prevalence of non-adherence to levothyroxine therapy and we investigated the factors affecting this behavior and preventing good medication adherence. The overall percentage of non-adherent patients was 54.9%, greater than that reported adherence rate in Manchester, United Kingdom (22%) (15) and the United States of America (31.6%) during the first year of drug therapy (7). The true prevalence of non-adherence with levothyroxine therapy will be much higher than the self-reported non-adherence. Such questioning has a low sensitivity (55%) for ruling out non-adherence (16).

Older patients and males were found to be less adherent according to our results, while a study comparing adherence rates among seven different medical conditions including hypothyroidism, showed that in the comparison of adherence by gender, adherence rates showed little variation. In contrast, adherence rates considerably improved with increasing age particularly in hypertension, type 2 diabetes and hypothyroidism (7). This might be due to a lack of communication between the healthcare professional and the patient (17). Furthermore, with increasing age, subjects tend to have compromised physical dexterity, cognitive skill, and memory (18).

Patients having at least one or more additional medical problem had a worse adherence compared to those suffering only from hypothyroidism. Conversely, a study comparing adherence rates of subjects with hypothyroidism found that the influence of comorbidity burden was small (7). In addition, patients were more likely to achieve higher levels of adherence if their monthly income increased, which is understandable since high-income people can afford to pay for their medications as compared to low-income people. This is similar to findings of a study done in the United States of America (7). As a consequence, it is assumed that any governmental or private health plan policy that reduces copayments would enhance medication adherence (7). In Lebanon, the National Social Security Funds reimburses 80% of the price of the levothyroxine medications, whereas some private insurances have plans which cover medications.

Postponing the physician's visits had in this study the greatest impact on adherence score by decreasing

**Table 3 Health status and medication-related characteristics**

Factor	Mean ± SD/ N (%)
<b>Family history</b>	
No	191 (56.7)
Parents	94 (27.9)
Siblings	52 (15.4)
<b>Timing of medication intake</b>	
Morning	332 (98.5)
Not in the morning	5 (1.5)
<b>Intake of drugs concerning the meals</b>	
Before meals	308 (91.4)
After meals	29 (8.6)
<b>Intake of drugs away from food</b>	
No	169 (51.1)
Yes	162 (48.9)
<b>Better adherence after dose increase</b>	
No	13 (3.9)
Yes	130 (38.6)
Same adherence	194 (57.6)
<b>Presence of comorbidities</b>	
No comorbidity	90 (26.7)
One comorbidity*	150 (44.5)
2+ comorbidities**	97 (28.8)
Duration of hypothyroidism (in years)	9.71 ± 7.52
Number of medication taken	2.83 ± 1.82
<b>TSH test regularly</b>	
No	132 (39.2)
Yes	205 (60.8)
Period of testing (months)	9.35 ± 3.76
<b>Result of testing***</b>	
Normal	215 (63.8)
Not normal	28 (8.3)
Don't know	94 (27.9)
<b>Knowing the normal range of TSH</b>	
No	263 (78)
Yes	74 (22)

\*Patients with one disease.

\*\*Patients with two or more diseases.

\*\*\*Normal TSH levels defined as a range from 0.4–4.0 milli-international units per litre (mIU/L) (<https://www.nlm.nih.gov/medlineplus/ency/article/003684.htm>).

it significantly. Indeed, many factors of non-adherence were related to patients' education which included unawareness, ignorance, patient's feeling of being fine or not in need of the pills any longer (19). Those factors are all potentially preventable and health providers should do their best to correct them by educating their patients about their treatments (19).

Following surgery, levothyroxine non-compliance is a common problem even in high income and well-educated societies (19). Schifferdecker et al. had shown that following thyroidectomy, 17% of German patients

**Table 4 Description of factors related to the healthcare provider and patient's knowledge about the disease**

Factor	N (%)
<b>Frequency of physician's visit</b>	
Monthly	11 (3.3)
Once every 2 months	5 (1.5)
Once every 3 months	21 (6.2)
Once every 6 months	78 (23.1)
Once per year	134 (39.8)
Less than once per year	88 (26.1)
<b>Physician's explanation</b>	
No	20 (5.9)
Yes	317 (94.1)
<b>Do you think you have enough information about the disease?</b>	
No	187 (55.5)
Yes	150 (44.5)
<b>Postponing / cancelling medical appointments at the last minute</b>	
No	158 (46.9)
Yes	179 (53.1)
<b>Following a recommended diet</b>	
No	240 (71.2)
Yes	97 (28.8)
<b>Main source of iodine</b>	
Iodized salt	80 (23.7)
Seafood	183 (54.3)
Don't know	74 (22)
<b>Which part of the body needs iodine</b>	
Thyroid gland	199 (59)
Don't know	138 (41)
<b>The most negative outcome for iodine deficiency</b>	
Impaired growth	31 (9.2)
Hypothyroidism	157 (46.6)
Don't know	149 (44.2)

decided to stop therapy without the knowledge of their treating physicians (20). The opposite is true according to our study where the bivariate analysis demonstrated that patients having a history of thyroidectomy had a better adherence score, probably because of a better understanding of the consequences of the ablation of the thyroid gland.

In line with earlier reports, having enough information about the medical condition was found to improve the adherence score. In fact, educating the patient about the medication is not enough since a randomized controlled trial of levothyroxine adherence showed that distributing booklets about levothyroxine medication did not improve adherence between the study group and the control group (15,20). The doctor–patient relationship plays a key role in adherence to medication regimens. Physicians who use understandable language and encourage open doctor–

**Table 5 Bivariate analysis for the qualitative factors associated with the adherence to medications**

Adherence scores / Factor	Total Number N=337 (100%)	Mean adherence score $\pm$ SD	P-value
<b>Gender</b>			0.187
Male	82 (24.3)	5.30 $\pm$ 1.85	
Female	255 (75.7)	5.61 $\pm$ 1.86	
<b>Employment status</b>			0.008
Unemployed	120 (35.6)	5.86 $\pm$ 1.90	
Employee/ liberal	208 (61.7)	5.30 $\pm$ 1.82	
Retired	9 (2.7)	6.56 $\pm$ 1.39	
<b>Monthly income</b>			0.085
Less than 1M	117 (34.7)	5.82 $\pm$ 1.86	
Between 1 and 2 M	143 (42.4)	5.45 $\pm$ 1.85	
More than 2M	77 (22.8)	5.25 $\pm$ 1.84	
<b>Disease status</b>			0.002
No comorbidity	90 (26.7)	5.97 $\pm$ 1.86	
One comorbidity	150 (44.5)	5.15 $\pm$ 1.85	
2+ comorbidities	97 (28.8)	5.72 $\pm$ 1.79	
<b>Frequency of physician visits</b>			< 0.001
Monthly	11 (3.3)	6.48 $\pm$ 1.22	
Once every 2 months	5 (1.5)	7.15 $\pm$ 1.41	
Once every 3 months	21 (6.2)	5.95 $\pm$ 1.35	
Once every 6 months	78 (23.1)	6.21 $\pm$ 1.72	
Once per year	134 (39.8)	5.46 $\pm$ 1.80	
Less than once per year	88 (26.1)	4.74 $\pm$ 1.95	
<b>Testing thyroid function regularly</b>			< 0.001
No	132 (39.2)	4.91 $\pm$ 1.99	
Yes	205 (60.8)	5.94 $\pm$ 1.66	
<b>Has your doctor explained how to take your medication</b>			0.121
No	20 (5.9)	4.71 $\pm$ 2.37	
Yes	317 (94.1)	5.59 $\pm$ 1.82	
<b>Do you think you have enough info regarding your medical condition</b>			< 0.001
No	187 (55.5)	5.14 $\pm$ 1.82	
Yes	150 (44.5)	6.02 $\pm$ 1.81	
<b>History of thyroidectomy</b>			0.182
No	239 (70.9)	5.38 $\pm$ 1.89	
Yes	98 (29.1)	5.65 $\pm$ 1.83	
<b>Do you know the normal range of TSH?</b>			< 0.001
No	263 (78)	5.31 $\pm$ 1.87	
Yes	74 (22)	6.32 $\pm$ 1.61	
<b>Do you postpone the doctor's visit?</b>			< 0.001
No	158 (46.9)	6.16 $\pm$ 1.66	
Yes	179 (53.1)	4.98 $\pm$ 1.86	
<b>Has your doctor advised to follow a diet?</b>			0.068
No	240 (71.2)	5.43 $\pm$ 1.94	
Yes	97 (28.8)	5.81 $\pm$ 1.63	

patient communication in friendly, caring environments are more likely to foster participation by patients in their own medical care, increasing the likelihood of adherence (21).

Poor adherence is the most likely explanation of TSH remaining above the normal range (22). Repeating this test every six weeks is appropriate until the dose is stabilized. However, this time interval can be increased if the patient

**Table 6 Correlations between quantitative variable and the adherence score.**

Adherence score/ factor	Mean ± SD	Correlation coefficient	P-value
Age	49.23 ± 13.86	r= 0.155	0.004
Mean duration of hypothyroidism	9.71 ± 7.52	r= 0.144	0.008
Number of medication taken	2.83 ± 1.82	r= 0.077	0.158
Number of cigarettes per day	4.03 ± 6.73	r= -.007	0.899
Number of waterpipe per week	0.46 ± 1.11	r= - 0.115	0.035
Number of alcohol glasses per week	0.95 ± 1.36	r= - 0.227	<0.001
Number of cups of coffee per day	2.84 ± 2.04	r= -.015	0.786
Number of exercising times per week	0.78 ± 1.38	r=0.058	0.286
Number of sleeping hours per day	7.08 ± 1.17	r=0.014	0.794

is approaching a euthyroid state and is feeling well. After the dose is stabilized an annual TSH measurement is usually adequate monitoring unless a problem arises (23). Our findings match those of a study done in the United Kingdom in which compliant participants were more likely to have had their TSH checked within the previous 12 months and for their most recent TSH to be within the reference range (24).

Moreover, knowing the normal range of TSH was shown to improve the adherence score. This is consistent with the guidelines of the American Association of Clinical Endocrinologists that suggest during follow-up assessments an appropriate interim history to be recorded, and physical examination to be performed in conjunction with pertinent laboratory tests. Involving the patient in the levothyroxine treatment by explaining the thyroid disease and potential consequences should result in improved adherence (25).

Our study demonstrated that following a recommended diet improved the adherence rate and that the knowledge of the importance of iodine supplementation among the participants was not satisfactory. The knowledge of iodine distribution in nature, its metabolism, its recommended daily allowances and its supplementation will help understand the problems of the thyroid hormones (26).

Health care professionals (physicians and pharmacists) can play an important role in explaining to the patient that iodine cannot be stored for a long period in the body; thus, it must be supplied regularly in the diet (26).

### Limitations

This study had several limitations. First, it was designed to be an observational study, relying on the reports made by the participants without independent verification. In addition, given that patients were from four districts of Lebanon, mostly from Mount Lebanon and Beirut, our results may not be extrapolated to the whole Lebanese population suffering from hypothyroidism. Hence, the extent of generalization from this study results is limited. Selection bias might be possible because of the 25% refusal rate. Self-reporting was used as the only method of measuring adherence, which has potential disadvantages concerning recall and information bias and eliciting only socially acceptable responses. However, we did not include any question about depression, which can be a potential factor for non-adherence to medications. Given these possibilities, adherence levels among participants may be overestimated. The study was also limited by the broad inclusion criteria, which permitted the inclusion of patients with a wide variety of conditions resulting in hypothyroidism. However, the use of the broad inclusion

**Table 7 Multivariable analysis: Logistic regression taking the dichotomus adherence score (cut-off of 60%) as the dependent variable**

Factor	P-value	OR <sup>a</sup>	Confidence Interval	
Age	.028	1.036	1.004	1.068
Disease status*	.025			
One comorbidity	.026	0.365	0.150	0.972
2+ comorbidities	.011	0.232	0.076	0.713
Visiting the endocrinologist once every month	.022	27.777	1.631	42.136
Postponing / cancelling medical appointments at the last minute	.015	0.358	0.156	0.821
Physician explained about the disease	.021	2.898	1.173	7.142
Number of waterpipe per week	.094	0.621	0.356	1.084
Number of alcohol glasses per week	.010	0.631	0.444	0.896

\*Compared to no comorbidities



criteria can also be considered as strength, as it allowed the study to reflect the adherence status of the Lebanese.

## Conclusion and recommendations

To our knowledge, there are no previous studies analyzing the adherence to thyroxine medication among Lebanese patients suffering from hypothyroidism. Many factors have been identified to affect adherence, either by improving adherence such as higher monthly income, comorbidities, history of thyroidectomy, having enough information about the medical condition, the duration of treatment, regular testing of TSH, knowing the normal range of TSH, following a recommended diet or by decreasing it as though male gender, young age and postponing medical appointments, leading to poor treatment adherence.

We conclude that even though effective drug therapy is available for hypothyroidism. It is challenged by non-

adherence which is a universal problem. The clinical implication of these findings is that patient educational programmes could be implemented in order to increase the awareness about the importance of medication adherence. Furthermore, the doctor-patient relationship could be improved in order to encourage the participation of the patients in their own medical care, increasing the likelihood of adherence. The community pharmacist can have a huge impact on patient adherence by counseling patients and teaching them about the drug-drug and drug-food interactions of thyroid medications and by coaching patients about the consequences of non-adherence. In addition new treatment regimens, such as the once weekly oral levothyroxine, could be considered as an alternative in patients having difficulty to adhere to their life-long daily medication.

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## Observance du traitement par lévothyroxine chez des patients atteints d'hypothyroïdie au Liban

### Résumé

**Contexte :** La non-observance des horaires de prises médicamenteuses par les patients atteints de maladies chroniques peut avoir de graves conséquences, tels que de mauvais résultats cliniques, des taux d'hospitalisation plus élevés et une augmentation des coûts de santé. L'hypothyroïdie est une maladie chronique dont le traitement est simple. Pourtant, la non-observance médicamenteuse est courante.

**Objectifs :** La présente étude avait pour objectif de déterminer l'observance du traitement par lévothyroxine dans la population libanaise en estimant la proportion de patients qui respectent le traitement et en évaluant les facteurs qui affectent l'observance thérapeutique.

**Méthodes :** Une étude transversale conduite entre mai et juillet 2015 incluait 337 patients. Des patients ont été contactés par un pharmacien communautaire lors de leur visite pour acheter leur traitement et il leur a été demandé de remplir un questionnaire.

**Résultats :** Parmi ces patients, 14,5 % ont montré une observance élevée, 30,6 % une observance moyenne et 54,9 % une faible observance médicamenteuse. Le score moyen d'observance était de  $5,53 \pm 1,86$  points. Les résultats de la régression logistique ont montré que l'âge (ORa = 1,036), la visite chez un endocrinologue une fois par mois (ORa=27,77) et le fait que le médecin ait informé le patient de la maladie (ORa=2,898) augmenteraient considérablement l'observance médicamenteuse. De plus, le fait d'avoir une (ORa=0,365) ou deux comorbidités (ORa=0,232) en plus de l'hypothyroïdie, de reporter/d'annuler les rendez-vous médicaux à la dernière minute (ORa=0,358), le nombre de pipes à eau fumées par semaine (ORa=0,621) et le nombre de verres d'alcool consommés par semaine (ORa=0,631) réduiraient considérablement le score d'observance.

**Conclusion :** Des programmes éducatifs devraient être mis en œuvre, la relation médecin-patient et pharmacien-patient pourrait être améliorée et de nouveaux schémas thérapeutiques devraient être envisagés afin d'améliorer l'observance du patient.

## الالتزام بتناول ليفوثيروكسين بين المرضى المصابين بقصور الغدة الدرقية في لبنان

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### الخلاصة

الخلفية: يؤدي عدم التزام المرضى الذين يعانون من أمراض مزمنة بمواعيد الأدوية إلى عواقب خطيرة، بما في ذلك ضعف المخرجات السريرية ومعدلات أعلى للدخول إلى المستشفى، وارتفاع تكاليف الرعاية الصحية. ويُعد قصور الغدة الدرقية مرضًا مزمنًا وعلاجه بسيط، ولكن يشيع عدم الالتزام بتناوله.

الأهداف: هدفت هذه الدراسة إلى تقييم الالتزام بتناول دواء ليفوثيروكسين بين السكان اللبنانيين من خلال تقدير نسبة المرضى بقصور الغدة الدرقية الملتزمين وتقييم العوامل المؤثرة في الالتزام بالعلاج.

طرق البحث: أُجري استطلاع مقطعي في الفترة بين مايو/ أيار ويوليو/ تموز ٢٠١٥ وشمل ٣٣٧ مريضاً، حيث تحدث الصيدادلة المجتمعيون مع المرضى أثناء زيارتهم لشراء دواء ليفوثيروكسين، وطلب منهم ملء الاستبيان.

النتائج: من بين هؤلاء المرضى، أظهر ٥, ١٤٪ التزاماً كبيراً، وأظهر ٦, ٣٠٪ التزاماً متوسطاً، وأظهر ٩, ٥٤٪ التزاماً منخفضاً بتناول الدواء. وكان متوسط درجات الالتزام هو ٨٦, ٥٣ ± ١, ٥ نقطة. وأظهرت نتائج الارتباط المنطقي أن العمر ( $ORa=1, 036$ )، وزيارة أخصائي الغدد الصماء مرة واحدة شهرياً ( $ORa=27, 77$ )، وحقيقة أن الطبيب أعطى المريض معلومات حول المرض ( $ORa=2, 898$ ) تزيد بشكل كبير من الالتزام بتناول الدواء. إضافة إلى ذلك، الإصابة بحالة مرضية مصاحبة واحدة ( $ORa=0, 365$ ) أو حالتين ( $ORa=0, 232$ ) بالإضافة إلى قصور الغدة الدرقية، وتأجيل/ إلغاء مواعيد الزيارات الطبية في اللحظة الأخيرة ( $ORa=0, 358$ )، وعدد مرات تدخين النرجيلة (الشيشة) التي تم تدخينها في الأسبوع ( $ORa=0, 621$ )، وعدد كؤوس الكحوليات التي تم شربها في الأسبوع ( $ORa=0, 631$ ) يؤدي إلى تقليل درجة الالتزام بشكل كبير.

الاستنتاجات: يجب تطبيق برامج للتوعية، ويمكن تحسين العلاقة بين الطبيب والمريض وبين الصيدلي والمريض، كما يمكن البحث في نظم علاج جديدة لتحسين التزام المرضى بتناول الدواء.

## References

- Unnikrishnan AG, Bantwal G, John M, Kalra S, Sahay RK, Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian J Endocrinol Metab.* 2013;17(4):647. <http://dx.doi.org/10.4103/2230-8210.113755>
- Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, Galofre JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):923–31. <http://dx.doi.org/10.1210/jc.2013-2409>
- Zreik RS, Nasrallah MP. The prevalence of endocrinopathies among Lebanese women presenting with hirsutism to an endocrine clinic. *J Med Liban.* 2014;62(1):27–32. <http://dx.doi.org/10.12816/0002624>
- Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant.* 2005;9(3):381–90. <http://dx.doi.org/10.1111/j.1399-3046.2005.00356.x>
- Agency for Healthcare Research and Quality. 2012. Medication Adherence Interventions: Comparative Effectiveness, Closing the Quality Gap: Revisiting the State of the Science. ([https://www.effectivehealthcare.ahrq.gov/ehc/products/296/1248/EvidenceReport208CQGMedAdherence\\_FinalReport20120905.pdf](https://www.effectivehealthcare.ahrq.gov/ehc/products/296/1248/EvidenceReport208CQGMedAdherence_FinalReport20120905.pdf)).
- Ramadhan A, Tamilia M. Treatment-refractory hypothyroidism. *CMAJ.* 2012;184(2):205–9. <http://dx.doi.org/10.1503/cmaj.110994>
- Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy.* 2008;28(4):437–43. <http://dx.doi.org/10.1592/phco.28.4.437>
- Okosieme OE. Thyroid hormone replacement: current status and challenges. *Expert Opin Pharmacother.* 2011;12(15):2315–28. <http://dx.doi.org/10.1517/14656566.2011.600307>
- Preston CC, Colman AM. Optimal number of response categories in rating scales: reliability, validity, discriminating power, and respondent preferences. *Acta Psychol (Amst).* 2000;104(1):1–15. [http://dx.doi.org/10.1016/S0001-6918\(99\)00050-5](http://dx.doi.org/10.1016/S0001-6918(99)00050-5)
- Lu M, Safren SA, Skolnik PR, Rogers WH, Coady W, Hardy H, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav.* 2008;12(1):86–94. <http://dx.doi.org/10.1007/s10461-007-9261-4>
- Garfield S, Eliasson L, Clifford S, Willson A, Barber N. Developing the Diagnostic Adherence to Medication Scale (the DAMS) for use in clinical practice. *BMC Health Serv Res.* 2012;12(1):350. <http://dx.doi.org/10.1186/1472-6963-12-350>
- Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989;129(1):125–37. <http://dx.doi.org/10.1093/oxfordjournals.aje.a115101>
- Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med.* 2008;3(1):17. <http://dx.doi.org/10.1186/1751-0473-3-17>
- Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* 1993;138(11):923–36. <http://dx.doi.org/10.1093/oxfordjournals.aje.a116813>
- Crilly M. Thyroxine adherence study: a randomised controlled clinical trial in primary care. Manchester: University of Manchester (MD thesis). 2003.
- Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is this patient taking the treatment as prescribed? *JAMA.* 1993;269(21):2779–81. <http://dx.doi.org/10.1001/jama.1993.03500210079036>
- Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. *N Engl J Med.* 2003;348(16):1556–64. <http://dx.doi.org/10.1056/NEJMs020703>
- Salzman C. Medication compliance in the elderly. *J Clin Psychiatry.* 1995
- Aradaib MM, Ahmed SA, Mahdi SI, Nasr A, Ahmed MEM. Near total thyroidectomy and compliance of patients on levo thyroxine therapy for life. *Sudan Med J.* 2012;48(1)

20. Schifferdecker E, Balz F, Jungmann E, Schoffling K. [Compliance problems in therapy with levothyroxine]. *Med Klin (Munich)*. 1990;85(8):477–80.
21. Kandukuri RC, Khan MA, Soltys SM. Nonadherence to medication in hypothyroidism: a case report. *Prim Care Companion J Clin Psychiatry*. 2010;12(3)
22. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001;26(5):331–42.
23. Davoren P. Modern management of thyroid replacement therapy. *Issues*. 2008;31(6):159-61.
24. Crilly M, Esmail A. Randomised controlled trial of a hypothyroid educational booklet to improve thyroxine adherence. *Br J Gen Pract*. 2005;55(514):362–8.
25. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8(6):457–69. <http://dx.doi.org/10.4158/1934-2403-8.6.457>
26. Alam Khan V, Khan MA, Akhtar S. Thyroid disorders, etiology and prevalence. *J Med Sci*. 2002;2(2):89–94. <http://dx.doi.org/10.3923/jms.2002.89.94>