Developing formulas for calculating the dose of Levothyroxine in hypothyroidism patients treated at Hai Phong International Hospital in 2022

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ABSTRACT

Thyroid hormone replacement therapy has been used for more than a century to treat hypothyroidism [1]. As levothyroxine is usually administered over a patient's lifetime, physiological changes throughout life will affect the dose of levothyroxine required to maintain euthyroidism. This study conducted retrospectively on patients treated for hypothyroidism in the hospital Hai Phong International Hospital in 2022, aims to identify several factors that may affect a patient's daily dose of levothyroxine, including factors such as age, weight, comorbidities, along with several blood biochemical indicators including thyroid hormones and indicators of liver function and damage. From the 690 record samples collected and correlation results, we have come up with a regression equation calculating the dose of Levothyroxine for patients.

Keyword: *Dosage, hypothyroidism, Levothyroxine*

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INTRODUCTION

Hypothyroidism is a common endocrine disease, and its incidence and prevalence vary depending on the population being studied [1]. It is 10 times more frequent in women than men, and the prevalence increases with age. Most symptoms are nonspecific and the diagnosis is based on clinical evaluation and biochemical tests. [2]

Thyroid hormone replacement therapy has been used for more than a century to treat hypothyroidism [2]. Levothyroxine (LT4) is the standard therapy for hypothyroidism patients, affecting up to 5% of people worldwide. Despite the fact that since its invention in 1949, levothyroxine medication has significantly improved the lives of millions of hypothyroid patients, the difficulty of preserving biochemical and clinical euthyroidism in levothyroxine-treated patients cannot be understated.[3]

As levothyroxine is usually administered over a patient's lifetime, physiological changes throughout life will affect the dose of levothyroxine required to maintain euthyroidism.[4] Furthermore, dose adjustments may need to be made in patients with concomitant medical conditions, in patients taking certain medications, as well as in elderly patients. Patients who have undergone any weight or hormonal changes may require dose adjustments, and the majority of pregnant women require increased doses of levothyroxine. Optimal treatment of hypothyroidism requires a partnership between the patient and the physician. The physician is tasked with the vigilant appraisal of the patient's status based on a thorough clinical and laboratory assessment and appropriate adjustment of their levothyroxine therapy.[4]

It is believed that an inappropriate dose calculation may be the reason for the failure of drug potency at the clinical levels, though

highly effective in preclinical. Hence, it is necessary to have an accurate formula to calculate the dose of Levothyroxine for hypothyroidism patients. In this research, we evaluate the main factors influencing the dose of Levothyroxine to provide a practical equation, based on the existing literature and data analysis to allow optimal follow-up for these patients with two following objectives:

Finding patients' characteristics may affect the dose of Levothyroxine in patients treated for hypothyroidism at Hai Phong International Hospital.

Developing a formula for calculating the dose of Levothyroxine in hypothyroidism treated at Hai Phong International Hospital

Background

Treatment of hypothyroidism with thyroid extract was replaced by synthetic levothyroxine in the 1970s. A decade later, the development of sensitive thyroid-stimulating hormone (TSH) assays led to a reduction in the average daily dose of levothyroxine, following the demonstration that serum TSH was often suppressed, indicating overtreatment [35]. Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost.[36] Levothyroxine is one of the most commonly prescribed drugs on the planet. The World Health Organization considers it an important drug for basic health care.

Levothyroxine Dosage

The levothyroxine dose initially required by a patient depends primarily on at least two factors. These are the amount of residual endogenous thyroid function retained by the patient and the patient's weight, body mass index (BMI), or lean body mass [30]. Smaller dosages of Levothyroxine in the range of 25 to 75 mcg may be adequate in cases of moderate or SCH to make a patient euthyroid. The Levothyroxine dose is generally weight-based when the patient's innate capacity to generate thyroid hormone is low, with a patient who is athyreotic as a result of thyroidectomy indicating the entire loss of this function [30,54]. The optimal weight-based Levothyroxine dose for patients with limited thyroid function has been the subject of numerous investigations. Typical dose estimates range from 1.4 to 1.7 mcg/kg body weight [30,54]. If a patient's thyroid status is stable before replacement, the serum TSH is a good indicator of how much thyroid function is still there, with individuals with SCH still having some capacity to generate thyroid hormone. As a result, it is possible to anticipate the dosage of LT4 needed to induce euthyroidism from a patient's serum TSH levels. Patient sex impacts the dosage requirements for LT4 according to certain research, but not all of them. [55].

A number of formulas or algorithms have been created in prospective studies to predict the ideal LT4 dose that will lead to post-thyroidectomy euthyroidism. Although these algorithms consider weight, BMI, and age, weight-based algorithms are frequently a more straightforward version of them [54,56]. In keeping with the finding that when weight-based formulas are used, those who are overweight, obese, or have a high BMI are over-replaced, some of these algorithms are tiered so that the weight-based dose is lower for patients with higher BMIs. [57] Di Donna and colleagues found that 68% of patients were euthyroid at the first follow-up after using age- and BMI-related nomograms to predict LT4 dose in advance. In another prospective trial, a regression equation including weight, age, and a baseline LT4 dosage of 125 mcg obtained 72% accuracy [54]. A Poisson regression model was developed and compared to other dosing regimens in the literature in a retrospective study of nearly 600 patients who had thyroidectomy [58]. One of the more complicated algorithms ever created, it took into account factors including weight, BMI, age, preoperative TSH, sex, and whether or not the patient took iron or multivitamins. Using a straightforward weight-based

calculation of 1.6 mcg/kg/day, it properly predicted a dose of LT4 that would cause euthyroidism in 64.8% of patients as opposed to 51.3% of patients. Additionally, it offered greater accuracy (59.7%) at higher patient BMI tertiles than the 38% accuracy obtained with 1.6 mcg/kg/day [30].

SUBJECTS AND METHODS

Research Subjects All medical records of patients who were treated at Hai Phong International Hospital from January 2022 to December 2023, fulfilling the following criteria:

Inclusion criteria

The medical records of patients of either sex older than 18 years of age with a diagnosis of hypothyroidism, using Levothyroxine.

Exclusion criteria

Patients <18 years old;

Patients with a history of thyroid cancer, gastric bypass surgery, thyroid surgery, intake of liothyronine (T3) preparations, irregular follow-ups, changing brands of levothyroxine

Research Contents

Finding patients' characteristics may affect the dose of Levothyroxine in patients treated for hypothyroidism at Hai Phong International Hospital.

Describe Patients characteristics General Clinical Characteristics: Age, Gender, Medical conditions (comorbidities), concomitant drugs, weight, and Pregnancy

Patients' subclinical tests:

+ Thyroid hormones tests: T3, T4, TSH

+ Liver function tests: GOT, GPT, Albumine

Finding the patient's characteristics may affect the dose of *Levothyroxine General Characteristic: Age, Gender, Medical conditions (comorbidities), concomitant drugs, weight, and Pregnancy*

Develop a formula to predict the Levothyroxine dose for hypothyroidism patients

- Clinical Characteristics of Factors as Variables: Age, Gender, Medical Conditions, weight, Concomitant drugs, and Pregnancy

- Subclinical test: Liver function tests (GOT, GPT, ALB)

Research method: Retrospective study

Method of data collection

The data collection method is a convenience sample method to select all medical records that meet the criteria throughout the study period.

During the research process, 868 electronic medical records satisfied the criteria in Hai Phong International Hospital from January 2022 to December 2022.

The study was conducted with 690 patients. Of those, all 690 patients had all the clinical characteristics and subclinical tests set out by the study.

To measure the characteristics of the patient to the studied dose used 2 methods. First, differential analysis is used to measure the relationship of each characteristic to the dose. Second, the study performed linear regression of patient-to-dose characteristics in order to build a model to measure the patient's simultaneous impact on the dose. To ensure high reliability of the results of the analysis, the study used an initial sample of 690 patients.

To investigate the relationship between the Levothyroxine dose and the subclinical tests, the study used correlation analysis to measure univariate, and regression analysis to measure the degree of concurrent effect. To carry out this section, the sample studied was 690 patients with all the tests mentioned.

After obtaining the results of univariate influence on the dose, I proceeded to formulate the dose calculation according to the patient's characteristics and according to laboratory indicators by means of multiple linear regression.

Method of data analysis

Data was collected and analyzed using Microsoft Excel 2016 software and SPSS version 22.

The qualitative variables are described by number and percentage (N, %). Continuous variables with normal distributions are described by mean ± standard deviations. Continuous variables with non-standard distributions are described by median and interval quartile ranges.

The differences among groups were analyzed using the χ^2 test for qualitative variables, the One-way ANOVA test for continuous variables with normal distributions, the non-parametric Kruskal - Wallis test for continuous variables with non-standard distributions

The difference is considered to be statistically significant if $p<0.05$.

RESULTS

Patient characteristics may affect the dose of Levothyroxine in patients treated for hypothyroidism at Hai Phong International Hospital.

Patients' characteristics Table 3*: Patient's clinical characteristics (n=690)*

Characteristics	Quantity	Percentage%
Gender		
Female	618	89.6%
Male	72	10.4%
Concomitant drugs		
PPI	101	14.6%
NSAIDs	17	2.5%
ACEIs	26	3.7%
Diuretics	37	5.4%
Cardiovascular drugs	243	35.2%
Diabetes drugs	127	18.4%
Aspirin	21	3%
Comorbidities		
Heart diseases	257	37.2%
Diabetes	152	22%
Hyperlipidemia	413	60%
CKD	6	0.9%
Gastrointestinal diseases	32	4.6%
BMI (kg/m^2)		
<25	567	82.2%
25 to <30	119	17.2%
>30	4	0.6%
Pregnant	30	4.3%

In the table above, it can be seen that, in 690 medical records filtered from more than 1400 cases of the hospital, the number of female patients with hypothyroidism and receiving levothyroxine is more than that of men, specifically the number of female patients accounts for 89.6%. Meanwhile, the proportion of men accounts for only 10.4%. And the number of patients who are pregnant women accounted for 4.3%, namely 30 patients.

Moreover, among the patients investigated for the prevalence of comorbidities, the largest proportion of patients with hyperlipidemia, according to the study results, the number of patients suffering from these diseases was 413 (60%) out of a total of 690 patients, followed by patients with cardiovascular diseases, diabetes and diseases of the gastrointestinal tract.

The patients in this study were mostly people with a normal BMI, less than 25, with a large rate of 82.2%, of which patients with a BMI diagnosed with obesity were only 0.6%, specifically 4 patients.

In this study, we also investigated more drugs that patients were receiving concomitantly with Levothyroxine, in which the proportion of patients taking drugs for cardiovascular disease accounted for the highest proportion with 243 out of 690 patients (35.2%), followed by patients using diabetes drugs, with a population of 127 patients (18.4%). The lowest were patients using aspirin and NSAIDs at 3.1% and 2.5%, respectively.

Table 4: *Patients age and Levothyroxine dose (n=690)*

	Min	**Max**	**Mean**	**St. Deviation**
Age (years)	18.0	91.00	52.55	14.405
Levothyroxine dose (mcg/day)	25.0	150.0	73.55	28.663

During the patient age investigation, since we only investigated patients taking the drug over the age of 18, the youngest age in the study was 18 years, and the oldest patient was 91 years old. Thus, the average age of the study patients was 52.55 years with a standard deviation of 14.12.

Correspondingly, the lowest dose patients took was 25.0 mcg/day, and the highest was 150 mcg/day, with an average patient dose of 73.55 mcg/day.

In addition, we have also tabulated statistics describing the distribution and percentage of thyroid hormone levels of patients at the hospital.

Table 5: *Descriptive Statistics of thyroid hormones serum levels*

	Min	**Max**	**Mean**	**SD**
T3 (nmol/L)	1.00	12.14	2.02	1.23
T4 (nmol/L)	38.74	398.48	127.48	49.12
TSH (mIU/L)	0.005	65.17	2.04	3.46

Table 6*: Percentage of patients according to thyroid hormone concentration ranges (%)*

	Low	**Normal**	**High**
T3	6.55	80.9	12.55
T4	2.0	80.0	18
TSH	3	88.9	8.1

According to the literature I have studied, the normal levels of T3, T4, and TSH are: 1.2 – 2.7 nmol/L, 60 – 150 nmol/L, 0.37 – 4.7 mIU/L, respectively.

From table 5 and table 6, it can be seen that the smallest T3 hormone concentration is 1 nmol/L, the largest is 12.14 nmol/L, with an average of 2.02 nmol/L, the number of patients with normal T3 serum level is 80.9%.

With T4 concentrations, the lowest T4 concentration was 38.74 nmol/L, the highest was 398 nmol/L, with an average of 127.48 nmol/L, the number of patients with an index within the therapeutic target was 80%.

For TSH, the smallest concentration was 0.005 mIU/L, the largest was 65.17 mIU/L, and the average TSH concentration was 2.04 mIU/L with the number of patients within the normal range of 88.9% of the total number of patients.

***Table 7**: Probability distribution of the comorbidities (n =690)*

Number of comorbidities	Frequency	Percent	Cumulative percent (%)
0	220	31.9	31.9
1	192	27.8	59.7
2	172	24.9	84.6
3	100	14.5	99.1
4	6	0.9	100.0

One of the risk factors affecting the dosage of the drug, is the comorbidities of patients, during the research I found that there are patients with not one but many comorbidities, in particular, the number of cases of patients with 1 to 2 concomitant diseases with hypothyroidism accounts for almost the same proportion (27.8% and 24.9%). The number of patients with up to 4 comorbidities accounts for only a very small percentage (0.9%).

Correlation between Levothyroxine doses and the characteristics

To compare dose differences with patient demographic characteristics, the study used a t-test for traits with 2 groups and ANOVA for traits of patients with more than 2 groups. If the analysis result has p(t) for the t-test and p(F) for Anova <0.05 (5% significance level), then there is a statistically significant difference in mean dose between groups in patient characteristics. This means that different groups of patients have different average doses, or that patient trait is related to the dose.

***Table 8**: Correlation between Levothyroxine dose and patients' clinical characteristics (n=690)*

Characteristics		Levothyroxine dose (mcg/day)		Test	
		Mean	SD	t	p-value
Gender	Female	74.01	27.99	-4.19	<0.001*
	Male	86.81	31.11		
Concomitant drugs					
PPI	No	74.62	29.03	2.37	0.018*
	Yes	67.33	25.68		
NSAIDs	No	73.40	28.74	-0.85	0.39
	Yes	79.41	25.36		

Characteristics		Levothyroxine dose (mcg/day)		Test	
		Mean	SD	t	p-value
ACEIs	No	74.17	28.79	-4.09	<0.001*
	Yes	57.69	19.17		
Diuretics	No	73.66	28.86	0.42	0.67
	Yes	71.62	25.11		
Cardiovascular drugs	No	74.50	28.28	1.18	0.24
	Yes	71.81	29.33		
Diabetes drugs	No	72.87	28.45	-1.32	0.188
	Yes	76.57	29.50		
Aspirin	No	73.02	28.77	-4.17	<0.001*
	Yes	90.48	18.50		
Comorbidities					
Heart diseases	No	75.23	28.46	2.00	0.046*
	Yes	70.72	28.83		
Diabetes	No	72.21	28.45	-2.32	0.021*
	Yes	78.29	29.01		
Hyperlipidemia	No	74.82	28.39	0.95	0.34
	Yes	72.70	28.85		
CKD	No	73.72	28.56	1.67	0.096
	Yes	54.17	36.80		
Gastrointestinal diseases	No	73.78	28.71	0.97	0.33
	Yes	68.85	27.68		
Anova (F-P)					
BMI	<25	72.80	28.58	1.51	0.37
	25 to <30	76.89	28.03		
	>30	81.25	55.43		
Pregnant	No	72.95	28.29	-2.57	0.01*
	Yes	86.67	33.95		

With the characteristics of patients divided into 2 groups yes and no, after evaluating the difference in Levothyroxine dosage between the 2 groups of each characteristic, we found the following special features:

There was a difference in the dose of Levothyroxine between male and female patients, specifically, female patients received an average dose of 71.01 mcg/day, and male patients were 86.81 mcg/day.

Similarly, there were differences in the dose of levothyroxine between patients taking and not taking PPIs, ACEs, and aspirin.

For patients without cardiovascular diseases, diabetes, the average levothyroxine doses of these groups differed from those without.

There was a difference in LT4 dose between pregnant and non-pregnant patients, specifically, pregnant patients received an average dose of 86.67 mcg/day, while non-pregnant patients received only an average dose of 72.95 mcg/day.

In other words, whether the patient was of any gender, taking PPIs, ACEIs, or aspirin, whether the patient had cardiovascular diseases, diabeteor s, and whether the patient was pregnant were all significantly related to the dose of levothyroxine that the patient took.

To find the relationship between age and the total number of diseases associated with the dose, I use univariate linear regression, if the regression results give p value <0.05 then they are related to the dose. In addition, the impact factor also indicates the magnitude and dimension of the relationship, if the impact factor – means they are related in opposite directions, whereas if the impact factor (+) they are related in the same direction.

***Table 9**: Correlation between age, the total number of comorbidities, and Levothyroxine dose*

	Impact factor	**t**	**p-value**	**CI 95% U**	**CI 95% U**
Age (years)	-0.206	-2.728	0.009*	-0.354	-0.058
Total number of comorbidities	-0.782	-0.773	0.44	-2.767	1.203

I noticed that age has an impact on the patient's dose of Levothyroxine, namely age having the opposite effect on the dose of the drug, it can be understood that, if age increases to 1 year, the dose is reduced by 0.206 mcg/day (p = 0.009).

Correlation between Levothyroxine doses and the subclinical tests

To measure the correlation between the factors, the study uses the Pearson correlation coefficient in the covariance matrix. The covariance matrix measures the correlation of 2 factors with each other where the magnitude of the Pearson correlation coefficient indicates the magnitude of the relationship, i.e. larger the correlation coefficient indicates the tighter the relationship fad; the sign of the Pearson correlation coefficient indicates the direction of the relationship, if they bear the sign (+) it means that those 2 elements are related in the same direction to each other, on the contrary, they correlate in the opposite direction; In addition, in the correlation analysis, it also shows whether the relationship of 2 certain factors is statistically significant or not, the Sig value (p-value) <0.05, the correlation is statistically significant.

***Table 10**: Correlation between Levothyroxine dose and subclinical tests (n=690)*

		Levothyroxine dose/day	**GOT**	**GPT**	**ALB**
Levothyroxine dose/day	Pearson Correlation	1			
	Sig. (2-tailed)				
	N	690			
GOT	Pearson Correlation	.200**	1		

		Levothyroxine dose/day	GOT	GPT	ALB
	Sig. (2-tailed)	.000			
	N	690	690		
GPT	Pearson Correlation	.162**	.449**	1	
	Sig. (2-tailed)	.000	.000		
	N	690	690	690	
ALB	Pearson Correlation	.177**	.083*	.015	1
	Sig. (2-tailed)	.000	.030	.695	
	N	690	690	690	690
**. Correlation is significant at the 0.01 level (2-tailed).					
*. Correlation is significant at the 0.05 level (2-tailed).					

In the tests we studied that evaluated the correlation with the patient's Levothyroxine dose, it was found that GOT, GPT, and ALB had a Sig < 0.05, i.e. these variables were statistically significant correlated with the intraday dose of LT4. These variables were correlated in the same direction with LT4 doses.

It is understandable that, if the dose of LT4 increases by one unit, these variables, in other words, these laboratory indicators also increase by one unit.

Developing a formula to predict Levothyroxine dose in hypothyroidism patients.

After evaluating the correlation between qualitative and quantitative variables that affect the patient's daily dose of Levothyroxine, we obtained the following results: with the clinical characteristics of the patient, we determine the gender, age, status of pregnancy, diabetes, the use of Aspirin, ACEI, and PPIs were factors that demonstrated a statistically significant effect on the patient's dose of the drug; with subclinical tests, all 3 laboratory indicators of liver injury and function, GOT, GPT, and Albumine, have an impact on the patient's dose.

From the above results, I proceeded to build a multiple linear regression model between the dose and the variables evaluated to have a meaningful effect on the dose, the model was built entirely on 690 filterable patients to optimize the sample size, increasing the accuracy and reliability of the equation.

***Table 11**: Correlation Coefficients table of multiple linear regression model of the factors affect the dose of Levothyroxine (n=690)*

		Unstandardized Coefficients		Standardized Coefficients		
Model		**B**	**Std. Error**	**Beta**	**t**	**Sig**
Levothyroxine dose/day	(Constant)	44.744	7.330		6.100	.000
	GOT	.278	.083	.134	3.338	.001
	GPT	.135	.062	.087	2.171	.030

ALB	.790	.174	.163	4.543	.000
Sex (Male)	11.674	3.427	.124	3.399	.001
Pregnant (yes)	10.816	5.303	.077	2.040	.042
Diabetes (yes)	6.906	2.711	.100	2.547	.011
Aspirin (yes)	18.225	6.206	.109	2.937	.003
ACEIs (yes)	-13.870	5.425	-.092	-2.557	.011
PPI (yes)	-6.997	3.085	-.086	-2.268	.024
Age	-.186	.084	-.094	-2.214	.027
R2				0.145	
F				11.428	
P (F)				.000	

The model has P(F) <0.05 so R^2 is non-0 (0.145), hence this regression model exists.

After implementing the multiple linear regression model, we found that in the variables included in the equation, factors cardiovascular disease status no longer had a statistically significant influence (p>0.05), so this factor was not included in the model. Of the remaining influencing factors, the use of ACEI, PPIs and age had the opposite effect on the dose of the drug.

After synthesizing and putting the elements into the linear model, I came up with the following equation:

Levothyroxine dose (mcg/day) = 44.744 + 11.674 (Male) + 10.816 (Pregnant) + 10.816 (Diabetes) + 18.225 (Aspirin) – 13.870 (ACEIs) – 6.997 (PPI) – 0.186*Age + 0.273* GOT+ 0.137*GPT + 0.786*ALB + ε

The patient's dose of Levothyroxine is calculated as the regression constant (44.744), plus Age, GOT, GPT, ALB multiplied by the corresponding regression coefficient, respectively, in case the patient has any of the clinical features mentioned in the general equation (Sex Male, Pregnant, having diabetes, using aspirin, ACEIs or PPIs), then plus the regression coefficients corresponding to that characteristic.

DISCUSSIONS

Patients' characteristics may affect the dose of Levothyroxine in patients treated for hypothyroidism at Hai Phong International Hospital.

General characteristics of patients.

During the research conducted at Hai Phong International Hospital from January 2022 to December 2022, we recorded all 690 electronic medical records that satisfied the requirements.

In my study, the majority of patients were female with the number of patients was 618 patients (89.6%) and the number of patients was male at 72 patients (10.4%). According to the provided research results, there is a higher prevalence of hypothyroidism in women compared to men. The prevalence of hypothyroidism in women is reported to be around 4-6 times higher than in men [12]. However, the reasons for this gender difference are not fully understood. Some studies suggest that the higher prevalence of

hypothyroidism in women may be due to hormonal factors, such as estrogen, which can affect thyroid function. Other studies suggest that lifestyle factors, such as diet and physical activity, may also play a role [15]. It is important to note that the prevalence of hypothyroidism varies across different populations and regions, and further research is needed to fully understand the gender differences in hypothyroidism prevalence.

According to the study, the average age of the patients was 52.55, with the youngest being 18 years old and the oldest being 91 years old. Our study only selected patients who were over the age of 18. This time we only have statistics on the average age of patients with hypothyroidism who use the drug, we have not delved into carefully studying the dose of Levothyroxine by age. The prevalence of hypothyroidism varies across different age groups. According to the provided research results, the highest prevalence of hypothyroidism is observed in elderly people [18]. The prevalence of thyroid dysfunction increases with age, and changes in thyroid hormone levels lead to neuromuscular deficits.

35.2% of patients getting concurrent levothyroxine were taking cardiovascular medications, 18.4% had diabetes, and 14.6% were taking PPIs. Simultaneously, following the survey, I discovered that 60% of patients had dyslipidemia, 37.2% had cardiovascular disease, and 22% had diabetes. From there, it can be seen that the number of patients in the study with chronic diseases and underlying diseases is quite large; however, while the number of patients using cardiovascular drugs is higher, the number of patients with dyslipidemia is the highest; this may be due to patients using these drugs to reduce their risk of cardiovascular disease. Studies show that hypothyroidism tends to be high in older adults, and these diseases are also common in people who are experiencing or older than middle age. According to the studies I found, hypothyroidism is often associated with several diseases [27], the highest rate is CKD, in addition, hypothyroidism is closely associated with an increased risk of cardiovascular diseases, in addition to metabolic diseases and lipid disorders. In this report, the number of patients with the above 3 diseases accounts for the largest proportion.

Among the patients studied, the number of patients with BMI was large (82.2%), and the proportion of pregnant patients was 4.3% (30 patients).

The study found that the majority of patients had no or 1, 2 comorbidities (31.9%, 27.8%, and 24.9%, respectively), which may be because, as I mentioned above, patients with hypothyroidism often have several metabolic and cardiovascular diseases.

Regarding the patient's thyroid hormone levels T3, T4 and TSH, according to the above results, most patients have test results that are within the normal range. 80.9% of patients had normal T3 results (mean 2.02 nmol/L). The number of patients with normal T4 results reached 80% (mean concentration was 127.48 nmol/L). Of the 690 patients, 88.9% of patients had TSH results within the threshold for treatment outcomes (mean concentration was 2.04 mIU/L. After collecting data, I noticed that in fact, the number of patients of Hai Phong International Hospital who come to test these indicators is quite small, and often only once tested, at different stages of treatment, patients often do not have a second test.

Influence of the patient’s characteristics on Levothyroxine dose

After evaluation to compare dose differences with patient demographic characteristics, the study used a t-test for traits with 2 groups and ANOVA for traits of patients with more than 2 groups, we found that there were statistically significant differences between age, gender factors, use of PPIs, ACEIs, aspirin, patient development of cardiovascular diseases, diabetes and pregnancy status.

According to the article "Sex and Age Differences in Levothyroxine Dosage Requirement"[96], the weight-based dosage requirement of premenopausal women for LT4 is greater than either menopausal women

or men when actual body weight is used. Also, when ideal weight is used, the dosage requirement of all women is greater than that of men, and this study also showed that gender had a strong influence on the dose, namely the mean LT4 dose difference between men and women (86.97 mcg/day and 71.41 mcg/day), but in this study, the dose of male patients was higher than that of women.

According to the studies we gathered, PPIs are one of the drugs that have a strong ability to affect the absorption of Levothyroxine, prospective study was conducted to compare the effect of PPIs and histamine-2 receptor antagonists (H2RAs) on the pharmacokinetics of levothyroxine in hypothyroid patients. The study found that PPIs significantly decreased the absorption of levothyroxine, leading to lower serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) compared to H2RAs [46]; and ACEIs and Aspirin, Aspirin is not known to interfere with the absorption of levothyroxine, but ACE inhibitors (angiotensin-converting enzyme inhibitors) have been recommended for the appropriate use of cardioprotective drug therapies in coronary patients. However, there is no evidence to suggest that ACE inhibitors interfere with the absorption of levothyroxine.

According to statistics, the dose of the drug is affected by the patient's medical condition, namely cardiovascular disease. According to Roos et al. (2005), "cardiac responses of patients with hypothyroidism to thyroid hormone therapy can vary from precipitating acute coronary syndromes in patients without previous cardiac symptoms to controlling or even abolishing preexisting angina." This means that heart disease can affect how well the body absorbs this medication, leading to fluctuations in thyroid hormone levels. The impact of heart diseases on the metabolism of Levothyroxine can result in changes in dosing requirements, according to Jabbar et al (2020). This effect is particularly concerning given that subclinical hypothyroidism, which is often treated with Levothyroxine, has been associated with an increased risk for atherosclerosis and myocardial infarction (Fazio et al, 2004, p.1166).

There is currently no definitive evidence of the effect of diabetes and CKD on the dose of levothyroxine, so I hope this study can serve as a reference for future in-depth studies.

Regarding the pregnancy status of patients, the study showed that LT4 doses were significantly affected by this condition, which is consistent with the previous research literature, women being treated for hypothyroidism typically require a 20% to 30% increase in their LT4 dose early in the first trimester of pregnancy. This increased need is triggered by factors such as increased hepatic TBG synthesis and metabolism of thyroid hormone by the placental type 3 deiodinase [74].

In this study, when we divided BMI into 3 intervals to assess differences, we did not find statistically significant results. Although many tools or studies have shown that levothyroxine is calculated in part based on the patient's BMI, and age has been shown to have an adverse effect on the dose, specifically, if the patient increases by one year the dose must be reduced by 0.206 mcg/day several studies have shown that the levothyroxine dose requirement is decreased in older individuals [36,75].

Influence of serum Biochemistry tests on Levothyroxine Dose

We analyzed the effect of the factors on the subclinical laboratory test (and there was a statistically significant impact of GOT, GPT, Albumin serum levels.

Biochemical markers GOT, GPT, and Albumin are relevant indicators of the liver, as discussed in the review, which has only been evaluated in previous clinical case studies. I have read and researched and I noticed that in a study by Ohmori et al., a clinical case study suspected the possibility of patients with impaired liver function due to the effects of Levothyroxine, another study by Shiho Kang et al. (2015) [97], which

studied 1 case, the patient was a 54-year-old woman who suffered liver damage when the dose of Levothyroxine was increased from 25 mcg to 50 mcg. According to our study, these indicators are statistically significant in the same direction correlated with Levothyroxine doses.

Specifically, as shown in the results, we tested on the sample size of each variable was 690 samples, the correlation indicators GOT (r = 0.200, Sig = 0.000), GPT (r = 0.162, Sig = 0.000), Albumin (r = 0.177, Sig = 0.000) which showed that these indicators were significantly related to the dose, although this level of correlation lies in the weak level of correlation.

Developing a formula to predict the Levothyroxine dose for hypothyroidism patients

After obtaining the results of the multivariate effect on the patient's daily dose of Levothyroxine from qualitative and quantitative variables, I proceeded to build a regression model from the collected data.

This equation was built on a sample size of 690 patients, the variables included were all significant variables identified in the first target of the study. The factor of cardiovascular disease after inclusion in the regression model was no longer statistically significant (Sig > 5%). The equation is left with only gender (male), concomitant drugs (PPI, Aspirin, ACEIs), diabetes, pregnancy, and the subclinical tests (GOT, GPT, ALB).

When conducting influencing factors research, I did mention BMI. Previously, I searched through several studies, and I noticed the study by Hemmat et al. (2019) [98] that gave a method of calculating LT4 dose for patients after thyroid surgery that mentioned BMI as one of the variables, and the study of Dipan et al. (2011) that studied the correlation between Levothyroxine dosage and BMI showed this indicator has a significant correlation with the patient's Levothyroxine dose. However, when assessing the difference in patient doses between the different BMI ranges of outpatients at Hai Phong International Hospital, I did not find a statistically significant difference. So this variable was not included in the regression equation.

Levothyroxine dose (mcg/day) = 44.744 + 11.674 (Male) + 10.816 (Pregnant) + 10.816 (Diabetes) + 18.225 (Aspirin) – 13.870 (ACEIs) – 6.997 (PPI) – 0.186*Age + 0.273* GOT+ 0.137*GPT + 0.786*ALB + ε

Equation as explained in the results, the drug dose is calculated by adding the regression constant with the products of the variable with the corresponding regression coefficient, especially for qualitative variables, only in cases where the clinical characteristics of the patient coincide with the variables mentioned in the equation will the products of that variable and the coefficient be added corresponding regression.

I investigated and developed this equation with the goal of optimizing the patient's treatment of hypothyroidism with Levothyroxine hormone replacement therapy. Yes, Levothyroxine dose can easily be affected by many factors. The optimal dosing of levothyroxine is influenced by many factors, including occult medical conditions, other factors that may affect the absorption of levothyroxine, and the ingestion of food. Patients receiving physiological doses of levothyroxine may have decreased bone density, and excessive doses may lead to osteoporosis in postmenopausal patients. Episodes of overtreatment and not the initial dose of levothyroxine are a risk factor for alertness deficit, and subtle inhibitory control deficit seems to be a permanent problem with the current therapeutic approach. Levothyroxine dosage requirement during pregnancy appears to be indispensable in the majority of patients with well-controlled hypothyroidism, especially in the first trimester. Survival improves when levothyroxine is administered promptly in large doses, even in patients with cardiac disease. Drug-induced malabsorption may potentially increase the levothyroxine dose requirement.

This equation covers the suspicion factors mentioned in previous studies, gender, age, pregnancy, patient characteristics (diabetes), and also patient medication (aspirin). These factors have been shown to affect a patient's ability to absorb Levothyroxine. Furthermore, this equation has addressed liver enzyme tests, according to the literature, levothyroxine is metabolized by deiodination and glucuronidation, and it is eliminated mainly through the liver and kidneys, if we can base on the patient's liver condition to calculate the dose, it is possible to avoid the risk of long-term negative effects on the patient, because levothyroxine is usually administered over a patient's lifetime to replace deficient thyroid hormones and prevent postoperative thyroid hypofunction. Moreover, given the fact that patients who visit the doctor rarely undergo thyroid tests before and during treatment, it is often difficult to rely on these indicators to calibrate the dose of levothyroxine for patients. Therefore, the equation I came up with could solve this problem and prescribe the right dose of levothyroxine for patients without hormone testing.

However, this equation does not mention the factors of the patient's BMI. Historically, the patient's dose of Levothyroxine has been calculated based on weight, which is a very important indicator in calculating the dose of the drug, the unit of dose is usually 1.6mcg/kg/day. About age, as other literature has demonstrated, as the patient gets older it is necessary to have certain dose corrections. But in our study, in terms of BMI because the majority of patients are in the BMI group < 25, overweight patients are too little, the data is not representative and the dose of the drug is only assessed according to the average age, so it is not possible to carefully assess the influence of these two variables on the dose of the drug.

Although it has been demonstrated that cardiovascular diseases have a statistically significant effect on Levothyroxine doses when assessing univariates, when included in the multivariate model, due to the influence of the remaining variables, it is no longer statistically significant, so this factor is not included in the regression model. The model has a low R^2 (0.145) but this is an acceptable limitation, and I will try to overcome this limitation in further studies.

Limitations of the study

As a retrospective study with an outpatient database, our study has some drawbacks in terms of data missing. Our study just collected available information in electronic medical records. Some detailed information about patients including the history of concomitant intake of foodstuffs, food supplements, and compliance, …may also have affected the delay in achieving euthyroidism.

In addition, in this research paper, we have not shown the influence of the patient's weight on the dose and included it in the dose calculation equation. Conditions that affect the dose are common comorbidities, the drugs used are also drugs with high frequency. This study has only stopped at the level of evaluating the correlation of monovariate to the dose of the drug, not delving into the evaluation of the effect related to the pathogenesis. The equation we gave is missing a factor that affects the dose of the drug, which is related to cardiovascular diseases, and the R^2 of the equation is low. We will continue our research on this issue in the future.

CONCLUSIONS

I collected outpatient medical records of 690 patients with hypothyroidism who took levothyroxine which satisfied the conditions of the study.

In finding patients' characteristics may affect the dose of Levothyroxine in patients treated for hypothyroidism at Hai Phong International Hospital, we identified statistically significant factors. About the characteristics of the patient, including gender, age, concomitant drugs (PPIs, ACEIs, Aspirin), comorbidities (cardiovascular diseases, diabetes mellitus) and pregnancy status of the patient. In our

tests, we have determined that GOT, GPT, and ALB all have an impact on the dose of Levothyroxine. And we have formulated an equation:

Levothyroxine dose (mcg/day) = 44.744 + 11.674 (Male) + 10.816 (Pregnant) + 10.816 (Diabetes) + 18.225 (Aspirin) – 13.870 (ACEIs) – 6.997 (PPI) – 0.186*Age + 0.273* GOT+ 0.137*GPT + 0.786*ALB + ε

This equation builds on a sample size of 690 patients, which covers the factors that affect dose based on the study results. In it, I included factors related to liver function tests and some clinical features of patients in the patient's dose calculation equation. What's more, this equation can help doctors prescribe more accurate doses without relying on a patient's thyroid hormone test readings. Since there is a narrow therapeutic window for levothyroxine, consistent and optimal absorption is essential.

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CONFLICTS OF INTEREST

It is confirmed that there will be no conflict of interest to arise.

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