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Levothyroxine Therapy Adequacy, Dose Estimation and Vitamin D Effect Assessment in a Sample of Iraqi Female Patients with Different Causes of Hypothyroidism

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Abstract

Exogenous levothyroxine dose modulation and euthyroidism achievement is a persistent challenge in clinical settings. This study strives to assess the adequacy of treatment and identify the patients' factors that can be used to estimate the euthyroid levothyroxine dose. A secondary objective was to assess vitamin D supplementation impact on thyroid status.

A review of a prospectively collected information from 142 female patients from Baghdad Center of Nuclear Medicine from June 2019 until March 2020 who were receiving levothyroxine for different causes was done. After a follow-up period, the patients' thyroid tests were assessed and the euthyroid doses for each cause category were statistically analyzed. Thyroid function was assessed before and after three months of vitamin D supplementation for 29 out of 50 patients who measured its level.

Sixty-six patients (47%) of the sample were inadequately replaced. Iatrogenic causes of hypothyroidism were associated with a higher levothyroxine dose than primary hypothyroidism. BMI was the most significant predictor of the euthyroid levothyroxine dose (r=0.601 and p=0.001 in those with total thyroidectomy). The euthyroid dose was also correlated with duration of treatment, and the presence or absence of iron and calcium supplements.Vitamin D supplementation resulted in a significant thyroid-stimulating hormone level decrease (–3.7 ± 4.7 µIU/ml, P-value= 0.001) without affecting thyroid hormones.

BMI can be used to predict a levothyroxine replacement dose that is approximate to that required to achieve euthyroidism. Vitamin D supplementation is associated with TSH reduction in hypothyroid subjects.

Keywords: Hypothyroidism, Levothyroxine, Thyroidectomy, Vitamin D.

تقييم العلاج بالليفوثيروكسين وتقدير جرعته ودراسة تأثير فيتامين د في عينة من المرضى العراقيات المصابات بأسباب مختلفة من قصور الغدة الدرقية

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الخلاصة

يعد تعديل جرعة الليفوثيروكسين تحديا مستمرا في الظروف السريرية. تسعى هذه الدراسة إلى تقييم مدى كفاية العلاج وتحديد عوامل المرضى التي يمكن استخدامها لتقدير جرعته. كان الهدف الثانوي هو تقييم تأثير مكملات فيتامين (د) على حالة الغدة الدرقية.

تم إجراء مراجعة لمعلومات تم جمعها مستقبليًا لـ ١٤٢ مريضة من مركز بغداد للطب النووي من يونيو ٢٠١٩ حتى مارس ٢٠٢٠، واللاتي كن يتلقين العلاج لأسباب مختلفة. بعد فترة المتابعة ، تم تقييم اختبارات الغدة الدرقية للمريضات وتم تحليل جرعات الليفوثيركسين إحصائيا في كل فئة. كما تم تقييم وظيفة الغدة الدرقية قبل وبعد ثلاثة أشهر من مكملات فيتامين د لتسع وعشرون مريضه من اصل خمسين مريضة قاموا بقياس مستواه.

ستة وستون مريضة (٤٧٪) من العينة لا يأخذون ليفوثيروكسين بشكل كافي. ارتبطت الأسباب العلاجية المنشأ لقصور الغدة الدرقية مع جرعات ليفوثريكسين أعلى مقارنة مع الأسباب الأخرى. كان مؤشر كتلة الجسم أهم عامل متنبئ لجرعة الليفوثيروكسين (r = 0.601 و p = 0.001 في أولئك الذين لديهم استئصال كلي للغدة الدرقية). كما ارتبطت الجرعة مع مدة العلاج ، ووجود أو عدم وجود مكملات الحديد والكالسيوم.

أدت مكملات فيتامين د إلى انخفاض كبير في هرمون تحفيز الغدة الدرقية (–٣,٧ ± ٤,٧ µIU/مل ، P = 0.001) دون التأثير على هرمونات الغدة الدرقية.

يمكن استخدام مؤشر كتلة الجسم للتنبؤ بجرعة ليفوثيروكسين إستبدالية. ترتبط مكملات فيتامين د بتحسين مستوى TSH لمرضى الغدة الدرقية.

الكلمات المفتاحية: قصور الغدة الدرقية ، ليفوثيروكسين ، استئصال الغدة الدرقية ، فيتامين د.

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Introduction

Hypothyroidism, being one of the common thyroid dysfunctions, has a global variation in epidemiology with a prevalence ranging from 1 to 2% in iodine sufficient countries[1]. It is ten times more likely to affect females than males[2]. Among a wide range of possible etiologies, the most important are chronic auto-immune disease (Hashimoto's thyroiditis), iodine deficiency and iatrogenic consequences as a result of surgical resection of the thyroid gland to eradicate toxic thyroid nodules, multinodular goiter and to remove thyroid tumors, or after receiving radioactive iodine treatment (RAI) for Graves' disease[3]. The governments in most iodine-deficient countries have implemented the policy to use iodized salt following the world health organization recommendations, which is also the case in Iraq ever since the 1990s. In a study that was conducted on a sample of female Iraqi patients with different thyroid disorders in 2010, iodine deficiency was excluded as a major cause, while other aspects such as environmental contaminations and genetic defects were thought to be more substantial[4].

Regardless of the cause, levothyroxine (LT4) has been the cornerstone of thyroid replacement therapy for a long time because of its several advantages, such as efficacy and low cost [5]. The principle of its action is the enzymatic bioactivation of the exogenous pro-hormone T4 into its metabolite triiodothyronine (T3)[6]. The goal of treatment is to attain clinical and biochemical euthyroidism with the thyroid-stimulating hormone (TSH) level as a guide to achieve that[5].

LT4 is deemed as a narrow therapeutic index drug[7]. Under-treated hypothyroidism may lead to the untoward consequences associated with the disease such as an impaired health-related quality of life, psychiatric disturbances, cardiovascular diseases, and an increased incidence of type 2 diabetes mellitus[8,9]. On the other hand, excessive LT4 treatment can cause tachycardia, atrial arrhythmias, increased risk of atrial fibrillation, and osteoporosis, which are important considerations especially in older patients[6]. Both cases would be troublesome for the patient and may lead to increased health care costs.

Throughout the years, numerous factors have been studied for their possible influence on the body requirement and/or bioavailability of LT4. These included age, gender, hormonal status, pathology (benign or malignant disease), co-morbid diseases, supplements use, generic substitution, lean body weight (LBW), body mass index (BMI), body surface area (BSA) and vitamin D (VD) level[10–12].

The study aims to assess the LT4 treatment adequacy in a sample of female patients who are receiving LT4 and to find an approach to estimate the correct LT4 dose that keeps the patient in a euthyroid state. A secondary objective was to assess VD supplementation impact on thyroid status.

Patients and Methods

A request to conduct the study containing detailed information regarding the study aim and methodology was submitted to Medical City Directorate/Ministry of Health which has been reviewed and subsequently approved.

This was a prospective cohort study, which entailed enrolling and interviewing all the subjects who matched the study criteria consecutively (Table 1) from June 1st until October 2019 at the thyroid counseling clinic of Baghdad Center for Nuclear Medicine. Each patient was consequently followed-up for five or six months. During the interviewing process, a sub-group of 50 patients was randomly chosen for a serum VD level measurement.

Table 1. Criteria for sample selection

Inclusion Criteria	Exclusion Criteria
1- Adult female Iraqi resident.	**1-** Pregnant and lactating.
2- Able to give fully informed consent.	**2-** Acute illness and recent surgery.
3- Receive LT4 for at least two months	**3-** Thyroid cancer patients, since they may require to achieve TSH suppression.

The interviewing process was conducted face to face. For the objective of a thorough and uniform data collection, a special sheet was prepared in advance to be used in the patient interview. Its purpose was to acquire detailed information, including measured anthropomorphic data, socio-demographics, contact information, disease history, co-morbidities, and concurrent medications.

The sample was divided into three main categories according to the etiology: post-thyroidectomy, post-RAI (both of which is considered as an iatrogenic cause of hypothyroidism), while the other causes were labeled as primary.

Following the interview, thyroid function tests (serum thyroid-stimulating hormone TSH, total T4 (TT4), and total T3 (TT3)) were performed using patients' serum inside the laboratory of the center on a fully automated ADVIA Centaur™ analyzer (Siemens, Germany). The principle was two-site sandwich immunoassay[13]. Each TSH reading was tabulated with the corresponding LT4 dose, which was being taken prior to their enrolment in the study, along with TT4 and TT3 levels. The reference range for TSH was (0.4-5.5μIU/ml) while that for TT4 and TT3 was (41.3-162.5 nmol/L and 0.92-2.79 nmol/L), respectively. Using the same device, the serum level of calcidiol for 50 patients was

measured based on a one-pass 18-minute competitive immunoassay and a level of 30 ng/ml or higher was considered to be sufficient[14]. LT4 dose was adjusted by physicians empirically.

Medication counselling regarding the correct way of administration was provided to the patients so as to obtain a maximum benefit for the patients in the future and optimal results for the study in the upcoming tests. These included encouraging adherence, taking the drug at least 30 minutes prior to breakfast and minimizing caffeine in the subsequent meal, also, separating the medications that are proven to interact with LT4 such as ferrous and calcium salts by at least four hours and using the same drug brand consistently if possible.

All the key information was then organized into a database along with the calculated BMI [actual body weight (kg)/height^2 (m^2)][15]. The database was being updated throughout the follow-up period. The follow-up was performed online using the patients' given contact information through social media and included their most recent thyroid function tests' results at the center, new weight, and medication counseling.

All the statistical analyses and related graphs were developed using IBM SPSS® software version 23. Categorical data were presented as frequencies and percentages while continuous data were summarized in the form of mean($\overline{X}$) and standard deviation (SD). A value ≤ 0.05 was assumed for statistical significance and the rejection of the null hypothesis. The thyroid function tests' results were analyzed and compared between the study groups during the initial encounter and at the end of the follow-up. Analysis of variance (ANOVA) and paired t-test were applied for comparisons wherever applicable.

Out of the entire database, euthyroid doses were selected and linear regression models were generated for each of the studied groups. The euthyroid LT4 dose was considered the dependent variable and the other factors (BMI, age, duration of treatment, presence or absence of diabetes, hypertension, anemia, and supplements use) were included as independent variables. The fittest models and their coefficients were identified.

Results

Patients' characteristics

A total sample of 142 female patients was recruited and followed-up in the study. The group distribution was: 76 with primary hypothyroidism, 52 post-thyroidectomy, and only 14 as a result of RAI ingestion. The age range was 18-72 years with a mean of 44 ±11.5 years. The calculated BMI had a mean of 30.7 ±6.02 kg/m^2 and followed Gaussian distribution. BMI was very significantly correlated with age (r=0.238, p=0.000). The period of time they were on LT4 had a mean of 51.7 ±70 months. A large proportion of the patients (68.3%) were suffering from one or more types of comorbidities (Table 2). Twenty-six patients were taking iron and/or calcium supplements, eighteen of which had primary hypothyroidism.

Table 2. Patients' characteristics and statistics

Descriptive Statistics	**$\bar{x} \mp$ S. D**
Age (years)	44 ± 11.5
Weight (kg)	78.2 ± 16.2
Height (cm)	159.8 ± 5.8
Duration of LT4 treatment (months)	51.7 ± 70
BMI (kg/m^2)	30.7 ± 6.02
Characteristic	**No (%)**
Etiology	
Primary causes	76 (53.5%)
Post-thyroidectomy	52 (36.6%)
Post-RAI	14 (10%)
Co-morbidities	
Musculoskeletal diseases	58 (40.8%)
Hypertension	40 (28.2%)
Iron deficiency anemia	20 (14.1%)
Diabetes mellitus	11 (7.7%)

Total sample: 142 female patients

BMI: body mass index, LT4: levothyroxine, RAI: radioactive iodine

Initial encounter data

Only 76 patients (53%) were within the TSH reference range, while 53 were under-replaced and 13 were being over-replaced. The replacement dose was the only factor with a statistically significant difference between the study groups (P <0.001).

Table 3. LT4 Dose and biochemical characteristics during first encounter

	Post-operative	Primary	Post-RAI	ANOVA P-value
	$\bar{x} \pm S.D.$			
Serum TSH level (µIU/ml)	13.6±30.7	5.8±7.2	6.6±5.8	0.079
Serum TT3 level (nmol/L)	1.56±0.36	1.63±0.4	1.64±0.38	0.632
Serum TT4 level (nmol/L)	120.93±43.62	113.27±34.56	140.3±52.63	0.106
LT4 Dose (mcg/day)	100.0±40.3	70.2±33.8	113.3±38.2	0.000*

Total number: 142 patients

$\bar{x}$: Mean, S.D.: Standard deviation, RAI: radioactive iodine, ANOVA: analysis of variance, TSH: thyroid stimulation hormone, TT3: total triiodothyronine, TT4: total thyroxine, LT4: levothyroxine. * significant (P-value ≤ 0.05)

End of Follow-up Data

Euthyroid results were obtained for 118 patients. Unlike the post-RAI group, the primary and post-thyroidectomy groups had a significantly higher mean dose after the follow-up as compared to the first encounter (P-value= 0.019 and 0.037, respectively). The dose and TT4 were significantly different among the study groups (Table 4).

Table 4. LT4 Dose and biochemical characteristics at follow-up

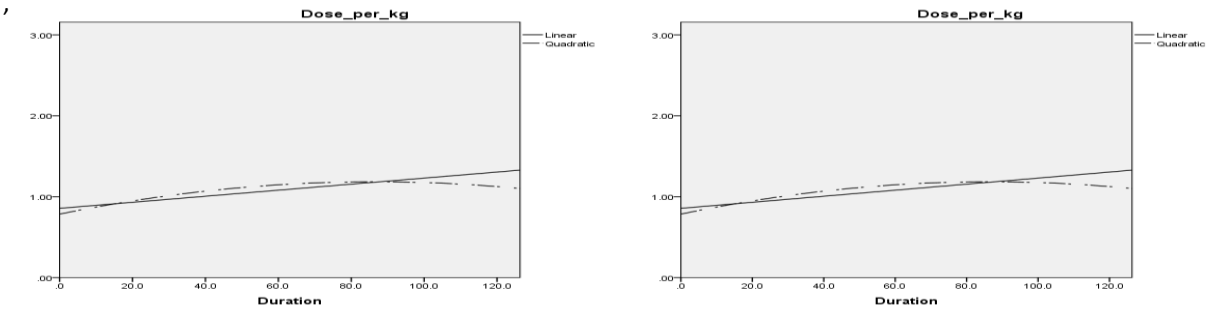
	Post-operative	Primary	Post-RAI	ANOVA P-value
	$\bar{x} \pm S.D.$			
Serum TSH level (µIU/ml)	7.7±21.8	3.6±3.4	4.5±4.4	0.234
Serum TT3 level (nmol/L)	1.56±0.61	1.67±0.47	1.73±0.32	0.774
Serum TT4 level (nmol/L)	124.05±43.4	109.97±30.9	149.75±46.02	0.001*
LT4 Dose (mcg/day)	107.2±42.4	76.8±35.0	110.7±37.6	0.000*

Total number: 142 patients

$\bar{x}$: Mean, S.D.: Standard deviation, RAI: radioactive iodine, ANOVA: analysis of variance, TSH: thyroid stimulation hormone, TT3: total triiodothyronine, TT4: total thyroxine,
LT4: levothyroxine. * significant (P-value ≤ 0.05)

Euthyroid dose estimation

The model with the most significant euthyroid dose predicting power for the primary causes group was obtained with the dose per kg as the dependent variable and the BMI (r= –0.297, p= 0.014), duration of treatment (r= 0.260, p= 0.033), and supplements (iron and calcium) (r= 0.312, p= 0.012) as the independent variables. The resultant model had an R and R^2 values of 0.51 and 0.26, respectively. A linear equation was derived: Y= -$0.026X_1$ + $0.004X_2$ + 0.271X3 + 1.482 where X_1 is the BMI, X2: the duration of treatment in months and X3 is either 0 or 1, indicating the presence or absence of concurrent supplements. The relationship between the dependent and the independent variables was linear and not quadratic until a certain point, (Figure 1). The mean euthyroid dose was 73±35 mcg/day (1±0.5 mcg/kg/day).



a **b**

Figure 1. Regression analysis curves for primary causes of hypothyroid patients

a: Body mass index (kg/m^2) vs dose mcg/kg. b: Duration of disease (months) vs dose mcg/kg.

The number of euthyroid patients who had been receiving LT4 post-RAI treatment was very insignificant (only 10), the regression model was dismissed. The mean euthyroid dose was 110±41 mcg/day (1.5±0.5 mcg/kg/day).

In the post-thyroidectomy population, the LT4 dose correlation with time since the surgery was variable. Those who have had the surgery within the prior year had the strongest correlation (r=0.539, p=0.003) but after that, the correlation dissipated and became very insignificant and hence two models were created. The most powerful model for those who have had the surgery within a year was obtained by using the dose (mcg) as the dependent variable versus time since surgery and BMI (r=0.601, p=0.001) as the predicting variables. The resultant R-value was=0.762 and R^2 was=0.581. The equation derived was: $Y = 4.072X_1 + 2.613X_2 – 58.061$. Where Y is the predicted dose (mcg/day), X1 and X2 represent the BMI and time since surgery (months) respectively. The mean euthyroid dose was 104±39 mcg/day (1.2±0.4 mcg/kg/day).

While in those who had thyroidectomy more than a year ago, the highest predicting power model revealed that only the BMI had a significant contribution to the prediction model (r=0.658, p=0.000). The model had an R-value of 0.612 and R^2 of 0.354, the equation was: Y= 3.991X- 8.991 where Y represents the predicted dose (µg/day) and X is the BMI of the patient. The mean euthyroid dose was 111±31 mcg/day (1.4 ±0.3 mcg/kg/day).

A change in the linear relationship into a rather quadratic one was noted in the post-operative group when BMI was above 45 kg/m^2, (Figure 2). The same change in the relationship was also seen in the primary hypothyroid group model below a BMI of 20 kg/m^2 and when the BMI reaches 40 kg/m^2 and beyond (Figure 1). This could partly be due to a limited number of patients beyond those values and thus the study models and equations cannot accurately estimate the dose in these cases. The mean doses and prediction equations for the entire sample are summarized in Table 5.

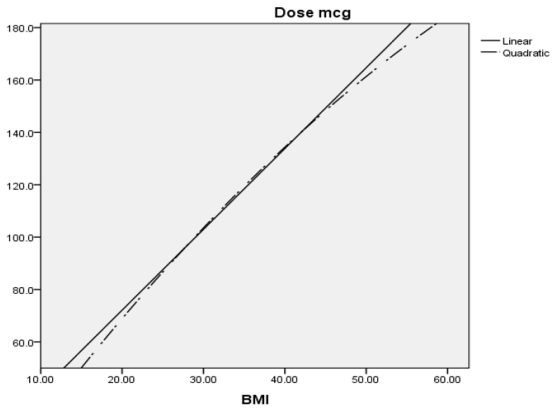


Figure 2. Body mass index (kg/ m^2) vs Dose (mcg) regression curve in post-thyroidectomy

Table 5. Euthyroid LT4 Dose Summary

Group	Mean Dose	Prediction Equation	Model Prediction Accuracy
1.Primary causes	73±35 µg/day 1±0.5 µg/kg/day	LT4 mcg/kg/day= – 0.026(BMI)+ 0.004(t) + 0.27(S) + 1.5	26%
2.Post-RAI	110±41 µg/day 1.5±0.5 µg/kg/day	Unattainable due to low number	
3.Post-operative (<1 year)	104±39 µg/day 1.2±0.4 µg/kg/day	LT4 mcg/day = 4(BMI) + 2.6(t) – 58	58%
4.Post-operative (≥1 year)	111±31 µg/day 1.4±0.3 µg/kg/day	LT4 mcg/day = 4(BMI) - 9	35%

LT4: levothyroxine, RAI: radioactive iodine, BMI: body mass index, t: months (treatment duration or time since surgery), S: 0 or 1 corresponding to the presence or absence of concomitant supplements

Vitamin D supplementation effect on thyroid status

The mean serum VD level for the 50 patients who have measured it was 16.5ng/ml ±13.6. Forty-one patients were deficient (<30 ng/ml) and were prescribed cholecalciferol 5,000 IU daily. Out of those 41 patients, 29 had a new follow-up thyroid function test after receiving the supplement for at least three months. Two patients had a TSH reduction but still fell outside the reference range, nine achieved euthyroidism, 13 had a reduction within the "normal range" while five had a small TSH increase within the reference range. While controlling for LT4 dose, the resulted TSH difference was significant without affecting thyroid hormones (Table 6).

Table 6. Vitamin D supplementation effect

	Before supplementation	Three months after supplementation	Difference	p-value
	Mean ± Standard Deviation			
TSH (µIU/ml)	5.5 ± 4.9	2.3 ± 2.1	-3.2 ± 4.7	0.001*
LT4 dose mcg/day	82.7 ± 36	81.4 ± 36.3	1.2 ± 25	0.783
TT3 (nmol/L)	1.5 ± 0.3	1.6 ± 0.4	0.04 ± 0.3	0.555
TT4 (nmol/L)	126 ± 41.2	129 ± 42.4	3.5 ± 41.8	0.685

TSH: thyroid-stimulating hormone , p-value for paired t-test, 29 patients , *significant difference, less than 0.05

Discussion

Serious adverse effects associated with hypothyroidism treatment can be avoided by proper LT4 dosing along with close monitoring of serum TSH values in conjunction with clinical evaluation during therapy and adjusting the dose accordingly[16].

On the first encounter, the current study showed that in this sample, 47% were either under- or over- replaced due to incorrect dose. The same ratio has been repeatedly reported in various populations and persistently for a long time.[1,17–19] Okosieme et al. reported that over a third of LT4 treated patients (37%) in United Kingdom had abnormal TSH values. But in contrast to the current study, the majority were over-treated in that one[17].

The postoperative patients were particularly difficult to control, demanded higher doses, more frequent testing, and dose adjustments. As seen in tables 3 and 4, even after multiple frequent physician visits, their TSH still fell outside the reference range (7.7±21.8 µIU/ml). Iatrogenic hypothyroidism required higher doses compared to primary causes because of the total removal or destruction of thyroid tissue in the iatrogenic causes, whereas in the primary group there is a remaining functioning thyroid gland that produces intrinsic hormone and decreases exogenous LT4 requirement[16].

The postoperative and post-RAI also required a higher TT4 concentration in order to achieve a similar TT3 to the primary group. Since the thyroid hormones are secreted normally from the thyroid gland with a T4/T3 ratio that is 14:1 and these groups lack their innate thyroid and the 6.5 µg of T3 from the normal gland[20].

In the current study, it was found that among all the studied factors, BMI was the most significantly associated with the euthyroid LT4 dose. However, the correlation was stronger in the post-thyroidectomy population and the regression models produced a higher R and R^2 values than the primary causes. This means that in the primary causes patients who have a remaining functional thyroid gland, BMI had a smaller influence on the required dose due to their different confounding physiological variables that affect the replacement dose[5]. When BMI was correlated with LT4 dose per kg in the primary causes group, the correlation was negative, i.e., the higher the BMI the lower the calculated dose per kilogram of body weight. This relationship between BMI and LT4 dose can be explained by the fact that adipose tissue has a small influence on LT4 requirements and that LT4 consumption is mainly accomplished in the lean body compartments[21]. This also explains why weight-based dosing fails to optimally replace hypothyroid patients.

Other studies that attempted to use BMI to predict LT4 dose were mostly conducted on patients with total-thyroidectomy. Ojomo et al.[11] established a linear relationship between BMI and euthyroid dose until BMI of 50 kg/m^2 and derived an equation to estimate an initial LT4 dose for total-thyroidectomy patients (mcg/kg/d= $^{-}0.018\times$BMI +2.13).

Di donna et al.[22] also used BMI in addition to age to predict the post-thyroidectomy LT4 dose and proposed an initial dose of 1.4-1.8 mcg/kg/day. Jin et al.[23] found that a dose of 1.5 µg/kg/day was optimal while 1.3 µg/kg/day for patients who are ≥55 years or BMI ≥30 kg/m^2.

Maghsudi et al. compared the efficacy of actual weight, LBM, and BMI based dosing and concluded that BMI had the strongest correlation with LT4 dose and derived a dose calculation formula: Y= –0.013 +0.005 BMI for benign pathology in total thyroidectomy patients[24]. On the other hand, Al-Dhahari et al. [25] identified Body Surface Area (BSA) as the most significant predictor and proposed a model accordingly.

The duration of treatment was also a significant LT4 dose predictor, which was probably influenced by the necessary dose titration while starting LT4 therapy[5]. Another explanation is the progressive autoimmune thyroid destruction with time[26]. However, its effect on the calculated dose was low.

The abundance of euthyroid patients who were being treated for primary hypothyroidism and receiving supplements concurrently with LT4 among this study sample demonstrated their effect on the LT4 dose. All three calcium salts (carbonate, citrate, and acetate) are confirmed to decrease the absorbed LT4 dose by 20-25%[27]. Iron sulfate is also notorious for its negative effect on LT4 absorption[28]. Despite the patients' claiming compliance with the instructions of four hours of

separation between the two, they were associated with a higher LT4 dose. No clear explanation exists for this but unconfirmed compliance may play some part. Although, a case has been reported with increased LT4 requirements despite their separation[29].

The current study demonstrated the positive impact of VD supplementation on thyroid status and specifically decreased TSH levels. The mechanism by which this occurs is still uncertain. A study by Zhang et al. also showed that higher VD status was linked with lower TSH after governing the other factors like age, thyroid hormones, gland tissue volume, and presence of nodule(s), [30]. A recent clinical trial also showed that three months of 50000 IU weekly VD supplementation produced a significant reduction in anti-thyroglobulin antibodies and TSH levels compared to placebo[12].

The most important limitation that may have hampered the study from obtaining even more accurate results is the absence of electronic medical records or any type of registry containing numbers, clinical or demographic information of the hypothyroid patients which made the process of information gathering rather tedious and less efficient and prevented the collection of high amount of data in order to produce more powerful models and to include the minority of male patients. Little information regarding thyroid antibodies levels was also a limitation.

Conclusion

Under-treatment is very common among hypothyroid Iraqi female patients. BMI is significantly correlated with the euthyroid dose and can be used to estimate a dose approximate to that required to achieve euthyroidism. Three months of VD supplementation is associated with decreased TSH levels without affecting thyroid hormones. A recommendation for future research is to expand the scope of the investigated factors such as physiological, pharmacological or genetic ones that may produce LT4 dose interindividual variation because the current approaches fail to attain high individualization and reproducibility.

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