Avicenna Medical Journal of Sirte
2026;1(1):1-4

Original article

Factors Affecting Levothyroxine Dose in Primary Hypothyroidism

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Abstract
Primary hypothyroidism is a deficiency of thyroid hormone due to diseases affecting the thyroid gland itself. Our objective was to determine whether age, gender, ideal body weight, and menstrual status affect levothyroxine dose in primary hypothyroidism to achieve euthyroidism. The study was performed retrospectively by reviewing the charts of patients being treated for primary hypothyroidism in the endocrinology clinic in Benghazi Diabetes Center, who had TSH values within a normal range. The selected patients were taking LT4 without any confounding medications and had no serious chronic conditions. All the subjects of primary hypothyroidism on maintenance dose for at least 12 months were considered. The total number of subjects with primary hypothyroidism was 539; only 100 subjects were eligible for the study. Subjects included both men & women between the ages of 24 & 88 years who have primary hypothyroidism. TSH parameters across study groups ANOVA test (P=0.058, no significant difference). Weight-based LT4 dose parameters across study groups. The difference is not statistically significant between men, premenopausal women, and menopausal women. Dot plot for the relationship between age, weight, and mean LT4 weight-based dose (statistically not significant relationship). Dot plot for the relationship between mean TSH level and mean LT4 weight-based dose (statistically not significant relationship). The LT4 dose is not primarily driven by a patient's Age, gender, or menstrual status, but it is by body weight. This knowledge may eventually improve the ability to predict a patient's dose requirement and thus more quickly attain a euthyroid status when initiating LT4 therapy.
Keywords. Levothyroxine, Hypothyroidism, Age, Sex. Body weight.

Introduction

Hypothyroidism, it is a syndrome caused by thyroid hormone deficiency, which may be primary due to diseases of the thyroid gland itself or, less commonly, secondary due to diseases of the pituitary glands or the hypothalamus which causing failure of thyroid-stimulating hormone (TSH) production. It is common, especially in women, although it can occur in either sex at any age, but it is more common in older people, particularly females. With normal ageing, thyroid hormone production, secretion, and degradation decline, and therefore older people with hypothyroidism have lower doses for levothyroxine (LT4) replacement than the younger population (1).

Replacement therapy with thyroid hormone is indicated as a lifelong therapy when the diagnosis of persistent thyroid hormone deficiency is confirmed (2). LT4 is considered to be the therapy of choice in hypothyroid patients and has long been used in TSH-suppressive doses in patients with nontoxic nodular or multinodular goiter (MNG) and differentiated thyroid cancer (DTC) to improve their prognosis **(3)**. LT4 represents one of the most commonly administered drugs in the world, and its use has been increasing over the last decade (4,5). This work aimed to study the factors affecting Levothyroxine dose in subjects with primary hypothyroidism.

Background: Body weight (BW) and age have been shown to affect the dose of levothyroxine (LT4) that results in normalization of serum thyroid-stimulating hormone (TSH) in hypothyroid patients. Our objective was to determine whether gender, menstrual status, and ideal body weight (IBW) also affect the LT4 dose required to achieve a serum TSH within the normal range.

Methods

Study design and setting

The study was performed retrospectively by reviewing the charts of patients being treated for primary hypothyroidism from 2007 up to 2016 who had TSH values within a normal range. The selected patients' ages were between 18–85 years who were taking LT4 without any confounding medications, and who had no serious chronic conditions. Euthyroidism was defined as a serum TSH within the range of 0.4–3.5 mIU/L. Their LT4 doses, referred to as LT4 dose requirements, based on both body weight and ideal body weight (IBW) were documented.

Patient selection

This was a retrospective chart review of patients being followed in endocrine clinic in Benghazi center for Diabetes mellitus and endocrinology between 2007 and 2016. Data were abstracted between 2016 and 2017. The total number of patients with primary hypothyroidism was 539. All cases of primary hypothyroidism on maintenance dose for at least 12 months were considered.

Subjects included both men and women between the ages 18 and 85years who have primary hypothyroidism. They were required to be on a minimum of 75mg LT4 a day for at least 1year, and to have been consistently euthyroid on a stable dose of LT4 for the past 6 months before the initial data point.

Patients taking medications known to interfere with LT4 absorption or alter LT4 binding proteins (e.g., estrogen and testosterone) were excluded from participation.

Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026

Other medications leading to exclusion were iodine, propranolol, amiodarone, lithium, dopamine agonists or antagonists, somatostatin analogues, steroids, phenytoin, carbamazepine, sertraline, rifampin, bile acid sequestrants, antacids, kayexalate, cholestyramine, colestipol and raloxifene.

Times of LT4, meal, and coffee consumption if documented in the patient chart, were recorded. Patients taking calcium, iron, and multivitamins were excluded, unless there was documentation in the chart that the consumption of LT4 and these products was separated by at least 4 hours. Pregnant or lactating patients were not eligible.

Patients with chronic, serious diseases such as cardiac, pulmonary, gastro-intestinal, renal, and pituitary disease were ineligible for study participation. Patients were required to have been diagnosed with hypothyroidism at least 12 months prior to when their initial study data were collected. Patients with a fluctuation in weight of >15% in the previous 12 months were excluded from the study.

Data collection tool

Data was collected using a constructed perform including demographic characteristics, causes of hypothyroidism, presence of other diseases, obstetric and gynecological conditions, clinical and laboratory measurements, thyroid parameters and LT4 dose of the patient, age, duration on maintenance dose in months, gender, marital status, employment status, level of education, cause of Goiter, associations of Goiter (Chronic Diseases), obstetric and Gynecological Conditions, TSH level, T4 level and weight.

Statistical analysis

Using SPSS IBM 23.0 monovariate analysis made with t-test, one-way analysis of variance (ANOVA), and their non-parametric alternatives. Multivariate analysis was done using a Generalized Linear Model with a Gamma model and Log function. Descriptive statistics, such as mean, standard deviation (SD), minimum and maximum, were used. All of the results were considered significant at $P \leq 0.05$.

Ethics

Institutional review board approval was obtained before study commencement.

Results

Demographic characteristics

Descriptive analysis of the quantitative variable of the sample shows that the mean ± SD age of males and females were (53.33±19.27) and (53.3±10.57) years, respectively. The age ranges from 24 to 88 years with a mean of 53.3, SD 11.124. Age was normally distributed (*P* by Kolmogorov-Smirnov test = 0.2) and homogeneous across genders (Table 1).

Table 1: The age distribution of the study group

	Gender	Mean	SD	P by t-test
Age	Male	53.33	19.27	*0.997
	Female	53.30	10.57	

*Difference is not statistically significant **

Further descriptive analysis of the quantitative variable of the sample show that the mean± age of pre-menopausal women and menopausal women were (43.22±5.43) and (59.84±7.47) years, respectively and the minimum were (28), (50) and maximum were (49), (88) years, respectively (Table 3.2).

Table 2. The mean, median, SD, minimum and maximum age of the study group

Statistics	Study group		
	Men	Pre-menopausal women	Menopausal women
Mean	53.33	43.22	59.84
Median	57.50	45.00	58.00
SD	19.27	5.43	7.47
Minimum	24	28	50
Maximum	77	49	88

Descriptive analysis of the qualitative variable show that the distribution of male and female among the data was (6%), (94%), respectively (Figure 1).

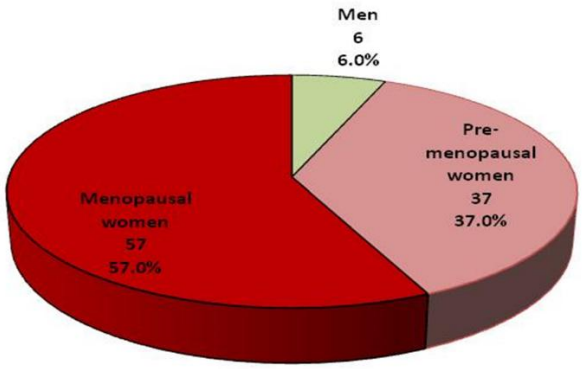

Figure 1. Sex distribution of the study group.

Figure 2 shows the residency distribution of patients among the group, about(37%) of Benghazi, (9%) out of Benghazi residents, and (54%) not defined.

Received: 08-03-2026 - Accepted: 06-05-2026 - Published: 30-06-2026

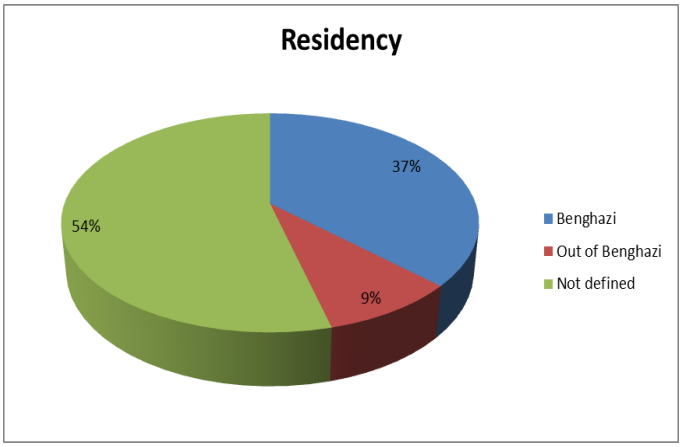

Figure 2. The residency of the study group.

Figure 3 shows the marital status of the study group of patients. Among the group where, about (21%) married, (4%) single (2%) divorced, and (73%) without data.

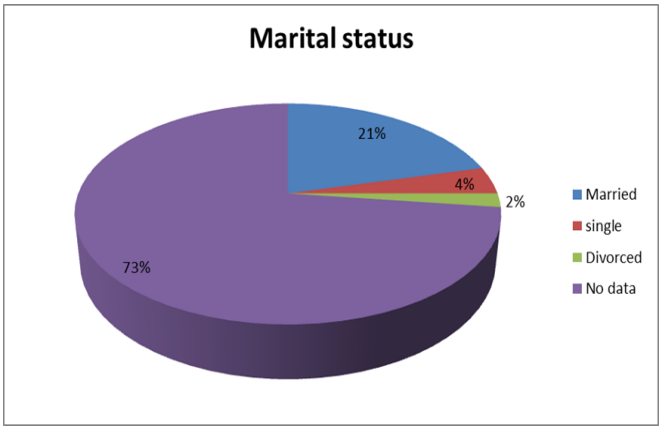

Figure 3. The marital status of the study group.

Figure 4 shows the causes of primary hypothyroidism of the study group of the patients among where, about (4.8%) operated goiter (total resection), (5.8%) operated goiter (subtotal resection), (6.7%) autoimmune goiter and (82.7%) non-identifiable causes.

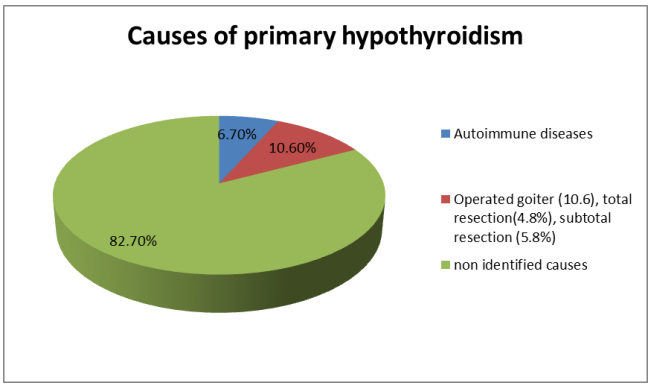

Figure 4. The causes of primary hypothyroidism of the study group.

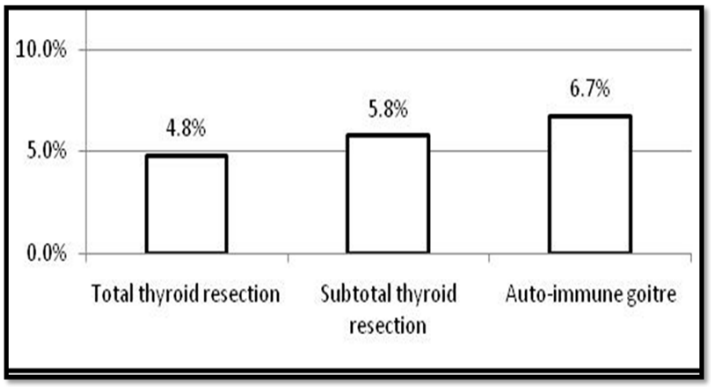

Figure 5. Rates of identified causes of hypothyroidism among study population.

Figure 6 shows the associated diseases of the study group of the patients among where, about (34) diabetics, (32.7%), (14) hypertensive (13.5%), (4) dyslipidemic (3.8%), (4) other major surgeries (3.8%), (2.8%), (3) pulmonary disease (2.9%) and (1%) neuro disorder, (4) other chronic disorders (3.8%).

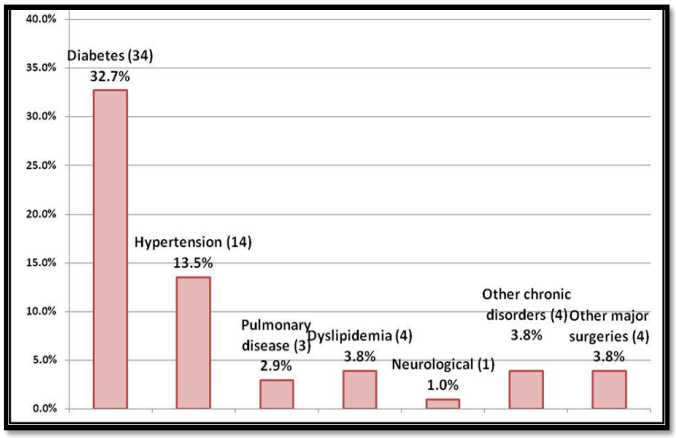

Figure 6. Rates of identified comorbid conditions among study population.

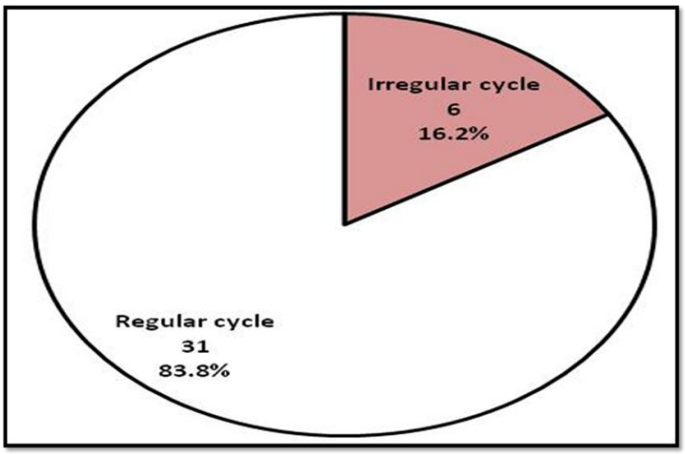

Figure 7. Rate of irregular cycle among pre-menopausal women in study population.

Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026

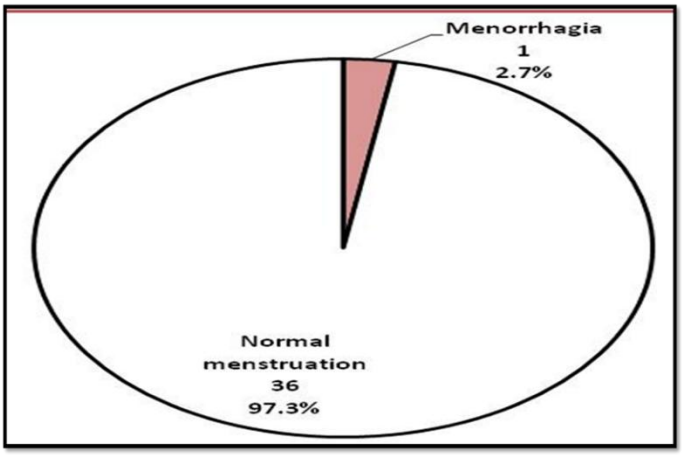

Figure 8. Rate of menorrhagia among pre-menopausal women in the study population.

weight parameters across the study group. Weight ranged from 55 to 168 kilograms (mean=78.3 Kg, SD=18.7 Kg). Weight parameters across study groups ANOVA test (P=0.238, no significant difference.

Table 3. Weight parameters across study groups.

Study group	**Mean**	**SD**	***P* by t test (across genders)**	***P* by one-way ANOVA***
Men	92.50	18.83	**0.723**	0.238
Pre-menopausal women	83.05	17.40		
Menopausal women	89.96	19.45		

Table 4 shows the mean TSH parameters across the study group. TSH parameters across study groups ANOVA test (P=0.058, no significant difference).

Table 4. Mean TSH parameters across study groups

Study group	Mean	SD	***P* by t test (across genders)**	***P* by one way ANOVA***
Men	2.56	1.68	**0.238**	**0.058**
Pre-menopausal women	1.92	0.83		
Menopausal women	2.37	0.94		
Total	2.21	0.97		

Table 5. Weigh-based T4 dose parameters across study groups

Study group	Mean	SD	***P* by Mann-Whitney U test**				***P* by Kruskal-Wallis test**
Men	1.85	1.04	*0.323	*0.405	*0.292	*0.525	*0.51
PMW	1.28	0.38					
MW	1.33	0.47					
Total	1.33	0.47					

The difference is not statistically significant. MW=Menopausal women, PMW=pre-menopausal women.

Table 6. Result summary of multivariate analysis of predictors for weight-based LT4 dose.

Parameter	B	Hypothesis Test		
		Wald Chi-Square	df	.Sig
(Intercept)	1.577	27.501	1	0.001> a
[Gender=Male]	0.143	0.751	1	0.386
Premenopausal women	0.223-	5.016	1	0.025b
Age	0.007-	2.267	1	0.132
Mean TSH	0.031-	0.685	1	0.408
Weight	0.009-	25.415	1	0.001> b

A *Poorly explained model. Some other factors and covariates should be included in further study.* ***B*** *Statistically significant .predictor at level of confidence of 95%*

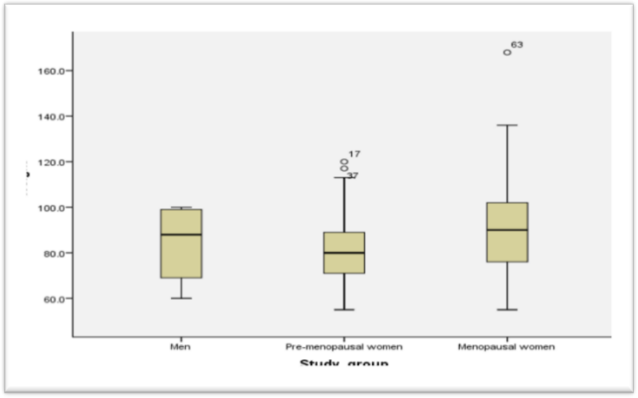

Figure 9. Weight parameters across study groups.

Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026

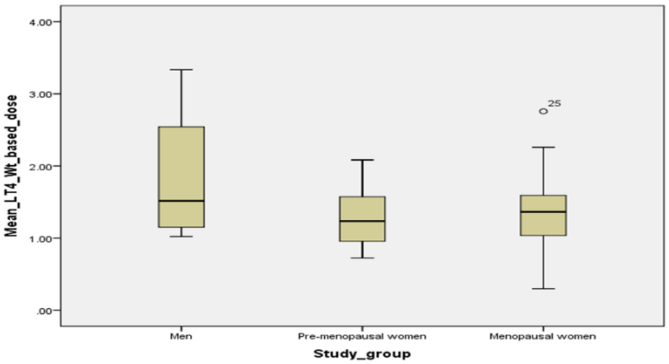

Figure 10. The mean LT4 weight based- dose among the study group.

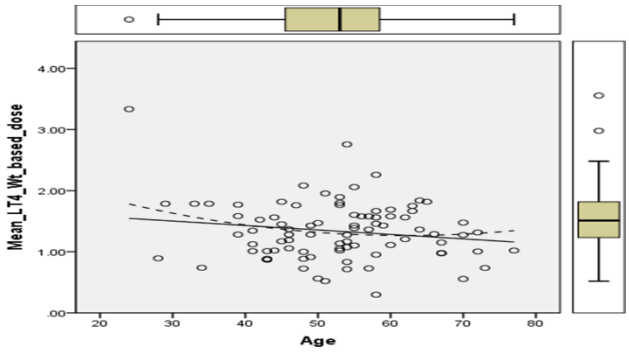

Figure 11. Scatter plot relationship between age and mean LT4 weight-based dose.

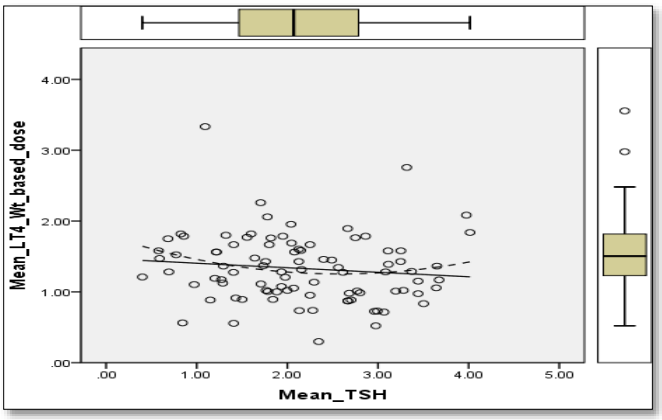

Figure 12. Scatter plot of relationship of mean TSH and mean LT4 weight-based dose

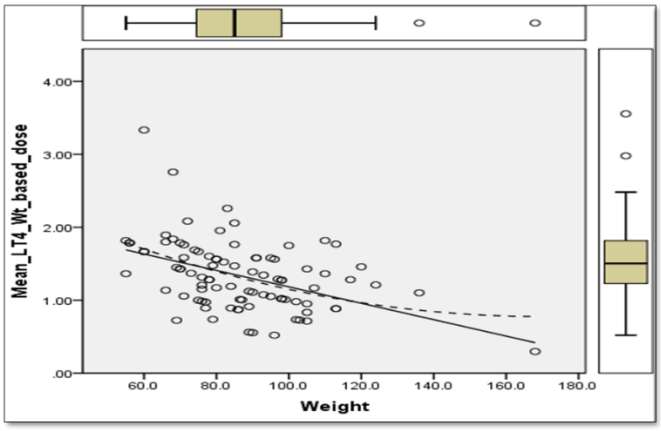

Figure 13. Scatter plot of the relationship between weight and mean LT4 weight-based dose

Discussion

Primary Hypothyroidism is a frequent disorder in the general population, with a prevalence 2-3%. It is well known that thyroid hormone production rates in individuals with endogenous thyroid function are under tight control and are affected by a variety of situations. Primary hypothyroidism is a permanent disease in most subjects and requires lifelong thyroid hormone replacement. Replacement with synthetic LT4 is the mainstay of therapy (6,7). Since the 1960s, levothyroxine, a synthetic L-isomer of thyroxine (LT4), has become the gold standard in the treatment of hypothyroidism. Recent evidence suggests that the dose of LT4 replacement is dependent on sex and body mass but not age, as was previously thought (8). In fact, hypothyroidism, a common chronic disorder, is managed by many specialists, including endocrinologists, internists, primary care physicians, surgeons, and paediatricians, who would likely be interested in an update on thyroxine therapy. For all of these reasons, the present study aimed to provide an update on levothyroxine therapy, with an emphasis on the factors affecting LT4 dose in primary hypothyroidism subjects.

The goal of treatment in patients with primary hypothyroidism is to attain euthyroidism guided by the TSH levels within the stipulated range to minimize any potential long-term adverse effects. However, various factors may result in both under and over-replacement of LT4 in these patients, ranging from physician factors such as inadequate dosing and monitoring to patient factors such as adherence to the treatment regimen (9).

A prospective study performed by Jonklaas (2010) followed euthyroid participants aged 18 to 65 years who were followed up after total thyroidectomy at 4 time points: 6-8 weeks, 12-16 weeks, 6 months, and 1 year. Patient weight, serum thyrotropin (TSH) concentration, and LT4 dosage required were recorded at each time point. The post-operative starting LT4 dosage was 1.7µg/kg daily for patients with benign thyroid disease and 2.2 µg /kg daily for patients with thyroid cancer (10).

Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026

Actual body weight was used to calculate the initial dosage. At steady state, adjustments were made in each patient's LT4 dosage until the target thyrotropin (TSH) concentration was reached. The LT4 dosage required to achieve this goal was documented. Fifty patients were included (37 women, 13 men). Formulae based on actual body weight were accurate in achieving a normal thyrotropin concentration in 48% to 75% of participants. He found that Final dosages to achieve normal thyrotropin values were similar in men (1.43 µg /kg daily) and menopausal women (1.68 µg /kg daily), but higher in premenopausal women (2.10 µg /kg daily). When a formula based on ideal body weight was used, the requirement for menopausal women (2.34 µg /kg daily) was similar to that of premenopausal women (2.44 µg /kg daily), but the requirement for men (1.73 µg /kg daily) remained lower than that observed in both female groups. When actual body weight was used to calculate LT4 dosage requirement, premenopausal women appeared to have a greater requirement than either menopausal women or men. When ideal body weight was used, the requirement of all women was greater than that of men. Perhaps with formulae using actual weight, this apparent sex difference is masked by the greater weight, older age, or altered hormonal milieu of menopausal women (10).

As a general guide in the continuous search for an optimal daily dose of LT4, Centanni et al. (2007) reviewed the literature and they found that 1.5 to 1.6 µg /Kg of body weight/day is appropriate to lower TSH into the normal range and 2.0-2.2 µg /Kg body weight/day to reduce TSH below its normal range. Despite this a number of patients do not show good responses to this range of doses (11). A clinical study of patients with non-toxic multinodular goiter provided a mild suppression of TSH at a median dose of 1.53 µg /Kg body weight/day (11). According to Benvenga et al. (1995) peak values of T4 are absorbed within 30 to 60 minutes with most absorption within 90 minutes. Food was shown to interfere with thyroxine absorption if not postponed from 15 minutes to 1 hour after taking T4. This suggests that T4 absorption is improved by fasting conditions. Thus, the current therapeutic procedure for hypothyroidism is mainly focused on hormone replacement therapy by sodium LT4. Patients are usually advised to take the medication in the morning, 30-60 minutes before breakfast (12).

Devdhar et al. (2011) found that just correlating body weights with dose was not adequate but could be corrected by using Ideal Body Weight (IBW). This was calculated by the Devine Method (women over 5ft (152cm) 100# plus 5# (2.3kg) for each additional inch (2.5cm), women under 5ft (152cm) 106# (48Kg) minus 5 # (2.3Kg)/inch. Men over 5ft (152cm) 106# (48Kg) plus 6 # for each additional inch. The authors found the following correlations with body weight. Requirements for older people were approximately the same, but seemed apparently less because they are mediated by reduced weight and the altered degree of overweight (8).

Limitations

are primarily based on its retrospective nature & the need to exclude many patients. The retrospective study design did not allow us to control over several factors. These factors include weighing patients in standardized clothing, prescribing a specific brand name of LT4, controlling the time of ingestion of LT4, or employing a central laboratory for TSH measurements. Also, we used actual body weight instead of ideal body weight, which is not available. During our chart review, we excluded 80% of patients, primarily because their LT4 dose had been changed or because they were taking medications that affected LT4 absorption, binding, or metabolism.... etc. & also poor patient compliance. These exclusions improve the accuracy & reliability of the data, but also reduce its generalizability.

Conclusion

However, under conditions of a stable LT4 dose, stable body weight, and absence of confounding medications, it could be concluded that the LT4 dose is not primarily driven by a patient's Age, gender, or menstrual status, but it does with body weight. This finding provides a basis for studying the physiologic underpinnings that determine an individual patient's LT4 dose requirement. This knowledge may eventually improve the ability to predict a patient's dose requirement and thus more quickly attain a euthyroid status when initiating LT4 therapy. It may also enhance our ability to maintain euthyroidism in our patient population. However, under conditions of a stable LT4 dose, stable BW, and absence of confounding medications, it could be concluded that the LT4 dose is not primarily driven by a patient's Age, gender, menstrual status, but it does with body weight.

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Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026

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Received: 08-03-2026 - **Accepted**: 06-05-2026 - **Published**: 30-06-2026