# Introduction

Conventionally, calculated daily dose of levothyroxine (LT4) is recommended for otherwise healthy and middle-aged patients for initiating treatment for primary hypothyroidism. The recommended initiating dose of LT4 is 1.6 µg/kg body weight in overt primary hypothyroidism of autoimmune etiology. Lower dose of LT4 is required in the elderly and has been suggested to be related to the decline in the lean body mass (LBM). The dose recommended in subclinical hypothyroidism is lower in comparison to overt hypothyroidism. However, fixed dose of LT4 has been suggested as starting dose for overt hypothyroidism.

Hashimoto’s thyroiditis is the most common cause of primary hypothyroidism in iodine-sufficient areas and may have indolent course as suggested by studies in individuals of autoimmune subclinical hypothyroidism. The usual course of progression in Hashimoto’s thyroiditis is gradual loss of thyroid function. Follow-up studies of the individuals with subclinical hypothyroidism in the elderly showed that a significant proportion of subclinical hypothyroidism cases with elevated or normal thyroid peroxidase antibody had normalization of serum thyrotropin (thyroid-stimulating hormone [TSH]), while others progressed to overt hypothyroidism. Similar study in children showed a variable rate of progression of...
subclinical hypothyroidism to either overt hypothyroidism or normalization of thyroid profile.[5] Hence, it can be presumed that in overt autoimmune primary hypothyroidism cases, the degree of thyroid damage may be variable.

Studies have evaluated the magnitude of replacement doses in primary hypothyroidism based on body weight. The dose of LT4 varies with the etiology of hypothyroidism. Although the average replacement dose of LT4 is approximately 1.6 µg/kg body weight in autoimmune hypothyroidism, the range of required dose is wide and varies from 25–50 to ≥200–225 µg/kg body weight.[6] The recommended dose of 1.6 µg/kg is based on the assumption of minimal residual thyroid function. In addition, studies have shown that LT4 requirement in autoimmune thyroiditis is lesser when compared to complete athyrotic individuals.[7,8] Hence, it can be presumed that the LT4 requirement to maintain euthyroidism in autoimmune hypothyroidism cases depends on the residual functional thyroid tissue, and the current recommended dose of LT4 in autoimmune hypothyroidism, i.e., 1.6 µg/kg body weight, may not be required by all the individuals of primary hypothyroidism.

The aim of this study was to find the range of LT4 dose based on body weight (D/W) and LT4 dose based on ideal body weight (D/IBW), and to find the determinants of LT4 requirement needed to maintain euthyroidism in individuals of primary autoimmune hypothyroidism.

**METHODS**

**Study design**

The study was cross-sectional. The patients were enrolled prospectively.

**Patient selection**

Adults were enrolled prospectively from the follow-up cohort of the Outpatient Endocrinology Department of the Hospital visiting between May 2015 and January 2016. Individuals enrolled included men and women between ages 18 and 85 years with primary autoimmune hypothyroidism and on treatment for at least 1 year and on minimum dose of at least 25 µg of LT4 daily. Hashimoto’s thyroiditis was defined as clinically presence of firm diffuse goiter or positive thyroid peroxidase antibody. The inclusion criteria included stable ambulatory patients with primary hypothyroidism, currently biochemically euthyroid based on the latest TSH report from the central laboratory with reference range serum TSH (0.4–4.5 mIU/L), LT4 dose administration in the morning and empty stomach dosing, and maintenance of food and beverages gap of at least 1 h with the LT4.

Exclusion criteria included noncompliant individuals, other than morning empty stomach administration of LT4, food gap with LT4 of <1 h, being on medication known to hamper LT4 absorption within 4 h of LT4, hypothyroidism other than of autoimmune etiology like postradiiodine, thyroid cancer postsurgery, posttotal thyroidectomy, pregnancy, and central hypothyroidism. Euthyroidism was defined as a serum TSH within the range of 0.4–5. Historical values of serum TSH was not taken, and a recent value from the Central Laboratory was compulsory for enrollment. Good compliance for LT4 as Confirmed by history was needed for inclusion.

Institutional review board approval was taken for the study and written informed consent was obtained from all the participants before enrollment.

**Data collection**

All consecutive patients willing for enrollment and meeting the inclusion and exclusion criteria were enrolled in the study. The data collected included age, gender, height, body weight, menopausal status for women, compliance with medication, co-prescription within 4 h of LT4, and food gap with LT4. Body weight was recorded with electronic weighing scales. Ideal body weight (IBW) was calculated based on Devine formula as follows: women over 152 cm, 45 kg + 2.3 kg for each additional 2.5 cm; for women under 152 cm, 45 kg − 2.3 kg for each additional 2.5 cm; for men over 152 cm, 48 kg + 2.7 kg for each additional 2.5 cm.[9] Degree of overweight was calculated by dividing weight by IBW. The latest TSH done in the central laboratory of the institute and the current LT4 dose were noted.

**Biochemical analysis**

Serum TSH analysis was performed by chemiluminescence immunoassay method (Roche Cobas e411) with functional sensitivity of 0.005 mIU/L, and normal range 0.4–4.5 mIU/L. Lyophilized quality control material (Bio-rad) was used with mean values of three levels of controls – 0.46, 5.52, and 34.2 mIU/L. The inter- and intra-assay variability levels were 2.9 and 3 mIU/L, respectively.

**Statistical methods**

Continuous variables were summarized as means and standard deviations and range as minimum and maximum values. The percentile of LT4 absolute dose, D/W, and dose based on ideal body weight (D/IBW) was calculated at 25th, 50th, and 75th percentile. ANOVA was used to compare the groups, and Bonferroni correction was used as *post hoc* test. Correlation was assessed by Pearson’s method and all the correlation analyses were two tailed. Linear regression model was used for univariate and multivariate predictive regression analyses. Initially, all the variables were entered with stepwise, forward, and backward method of variable entry to find the best predictive independent variables and finally ENTER method was used with all the best predictive variables. Collinearity of independent variables was checked based on tolerance. *P* < 0.05 was considered statistically significant.

**RESULTS**

A total of 346 individuals (a total of 290 women; 214 premenopausal and 76 postmenopausal women, and 56 men) meeting the inclusion and exclusion criteria were enrolled in the study consecutively. The median duration of hypothyroidism and mean age of individuals were 4 years and 42.1 years,
The absolute LT4 daily dose (ADD) ranged from minimum of 25 µg to maximum of 200 µg with mean of 77.1 ± 30 µg. The dose at 25th percentile, 50th percentile, and 75th percentile was 50, 75, and 100 µg, respectively. The mean LT4 daily D/W was 1.16 ± 1.2 µg/kg and dose ranged from 0.3 to 2.82 µg/kg; dose at 25th percentile, 50th percentile, and 75th percentile was 0.8, 1.16, and 1.5 µg/kg, respectively. The mean LT4 daily D/IBW was 1.58 ± 0.63 µg/kg of IBW and dose ranged from 0.42 µg/kg to 3.5 µg/kg of IBW; dose at 25th percentile, 50th percentile, and 75th percentile was 1.13, 1.53, and 1.97 µg/kg, respectively.

The parameters of the individuals were compared between men, premenopausal women, and postmenopausal women as shown in Table 1. There was no significant difference in mean ADD or D/W between men, postmenopausal women, and premenopausal women, although premenopausal women required significantly higher D/IBW compared to men. The ADD, D/W, and D/IBW at 25th percentile, 50th percentile, and 75th percentile for men, premenopausal women, and postmenopausal women are shown in Table 2. Among the anthropometric measures, weight correlated positively and significantly with ADD (r = 0.2, P < 0.001) and significantly and negatively with D/W (r = −0.36, P < 0.001), although no correlation was found with IBW. Similarly, height correlated significantly and positively with ADD (r = 0.17, P < 0.001) and significantly and negatively with D/IBW (r = −0.23, P = 0.001), although no correlation was found with D/W.

Age correlated significantly with D/W (r = −0.2, P < 0.001) but not with ADD or D/IBW. On comparing age quartiles for D/W, a significant difference was found between 1st quartile versus 2nd, 3rd, and 4th quartile. The mean D/W in 1st age quartile was 1.4 µg/kg, 2nd quartile was 1.15 µg/kg, 3rd quartile was 1.13 µg/kg, and 4th quartile was 1.13 µg/kg. The correlation of age with body mass index (BMI) was also statistically significant (r = 0.29, P < 0.001), suggesting a potential role of change in body composition affecting the correlation of age with D/W. The partial correlation of age with D/W showed a significant trend (P = 0.05) even after adjusted for BMI.

Duration of hypothyroidism correlated significantly with ADD (r = 0.2, P = 0.001), D/W (r = 0.2, P < 0.001), and D/IBW (r = 0.2, P < 0.001). Individuals were divided into 4 groups based on quartiles of duration of hypothyroidism. On comparing the mean D/W, D/IBW, or absolute LT4 daily dose between the groups based on duration of hypothyroidism, 1st quartile was significantly different from 3rd and 4th and between 2 and 4th for D/W.

There was a significant correlation between BMI and ADD (r = 0.12, P < 0.02), D/W (r = 0.13, P = 0.01), and D/IBW (r = −0.38, P = 0.001). Individuals were divided into four groups based on BMI (Group 1 BMI < 18.5 kg/m², Group 2 BMI 18.5–23 kg/m², Group 3 BMI > 23–30 kg/m², and Group 4 > 30 kg/m²). On comparing the groups by repeated-measures ANOVA with post hoc Bonferroni correction, no significant difference was found between the BMI groups in ADD and D/IBW, but a significant difference in D/W was found between BMI Groups 1 and 3, 1 and 4, 2 and 3, 2 and 4, and 3 and 4. The mean D/W was as follows: Group 1: 1.6 µg/kg, Group 2: 1.5 µg/kg, Group 3: 1.2 µg/kg, and Group 4: 1.0 µg/kg.

The correlation coefficient of D/W and D/IBW with independent variables is adjusted for covariates [Table 3]. In univariate regression model, gender, height, weight, IBW, and BMI were significant predictors for ADD. For D/W, age,

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**Table 1: The descriptive clinical and biochemical data of the enrolled individuals in both the genders separately**

| Characteristics               | All women          | Premenopausal women (214) | Postmenopausal women (76) | Male (56) |
|-------------------------------|--------------------|--------------------------|----------------------------|-----------|
| Age (years)                   | 41.0±13.3^a        | 34.7±9.1^a               | 58.6±5.9^a                 | 48.0±14.8 |
| Weight (kg)                   | 64.2±14.0^a        | 63.1±14.7^a              | 67.0±11.7^a                | 73.6±14.0 |
| Height (cm)                   | 154±6.1^a          | 154.3±6.0^a              | 153.4±6.1^a                | 165.0±6.8 |
| IBW (kg)                      | 47.1±5.8^a         | 47.3±5.7^a               | 46.6±6.2                   | 61.5±7.2  |
| BMI (kg/m²)                   | 27.2±6.5           | 26.5±5.9^a               | 29.1±7.6                   | 27.0±4.2  |
| Degree of overweight          | 1.37±0.30^a        | 1.34±0.31^a              | 1.45±0.27^a                | 1.2±0.2   |
| Duration of hypothyroidism (years) | 5.9±3.9           | 5.2±4.2^a                | 7.8±6.6^a                  | 5.3±4.2   |
| TSH (mIU/L)                   | 2.3±1.2            | 2.3±1.3                  | 2.3±1.2                    | 2.4±1.2   |
| Levothyroxine (µg/day)        | 75.5±28.6^a        | 75.9±28.7^a              | 73.6±27.2^a                | 86.0±28.1 |
| D/BW (µg/kg/day)              | 1.22±0.51          | 1.30±0.31                | 1.13±0.46                  | 1.16±0.44 |
| D/IBW (µg/kg/day)             | 1.61±0.62          | 1.62±0.63                | 1.60±0.62                  | 1.39±0.59 |

Values expressed as mean±SD. Difference in mean between the groups was done by ANOVA and post hoc analysis was done by Bonferroni correction, P<0.05 was considered statistically significant. Significant difference between women (all) and men, *Significant difference between premenopausal women and men, **Significant difference between premenopausal and postmenopausal women, ***Significant difference between postmenopausal women and men. SD: Standard deviation, BW: Body weight, IBW: Ideal body weight, TSH: Thyroid-stimulating hormone, D/W: Levothyroxine daily dose based on weight, D/IBW: Levothyroxine daily dose based on IBW.
Table 2: The percentile of age of individuals, doses of levothyroxine, and duration of hypothyroidism in both genders separately

| Percentile       | Dose (µg/day) | D/W     | D/IBW    |
|------------------|---------------|---------|----------|
| **25th percentile** |               |         |          |
| Male             | 50            | 0.79    | 0.90     |
| Premenopausal women | 50         | 0.89    | 1.16     |
| Postmenopausal women | 50       | 0.87    | 1.16     |
| **50th percentile** |               |         |          |
| Male             | 91.1          | 1.15    | 1.40     |
| Premenopausal women | 75        | 1.21    | 1.56     |
| Postmenopausal women | 75       | 1.10    | 1.64     |
| **75th percentile** |               |         |          |
| Male             | 107.1         | 1.54    | 1.84     |
| Premenopausal women | 100       | 1.55    | 2.05     |
| Postmenopausal women | 85.7     | 1.38    | 1.90     |
| **Mean dose**    |               |         |          |
| Male             | 86.1          | 1.17    | 1.40     |
| Premenopausal women | 75.9      | 1.25    | 1.62     |
| Postmenopausal women | 73.6     | 1.13    | 1.59     |

D/W: Levothyroxine daily dose based on weight, D/IBW: Levothyroxine daily dose based on IBW, LT4: Dose levothyroxine absolute daily dose, IBW: Ideal body weight.

Table 3: The partial correlation of exploratory variables after adjusting for covariates for levothyroxine daily doses

| Variable                     | Adjusted for          | R for D/W | P   | R for D/IBW | P   |
|------------------------------|-----------------------|-----------|-----|-------------|-----|
| Age                          | BMI, IBW              | 0.1       | 0.05| 0.1         | 0.05|
| Duration of hypothyroidism   | Age, BMI, gender      | −0.23     | 0.001*| 0.24        | 0.001*|
| BMI                          | Age, gender and IBW   | −0.35     | 0.001*| 0.14        | 0.001*|
| Gender                       | Height                | 0.01      | 0.8  | 0.01        | 0.9  |

*P value is significant. R: Correlation coefficient, D/W: Levothyroxine daily dose based on weight, D/IBW: Levothyroxine daily dose based on IBW, BMI: Body mass index, IBW: Ideal body weight

Table 4: Multivariate model predicting levothyroxine dose/kg body weight, age, duration of hypothyroidism, and body mass index as independent variables

| Independent variables | Standardized β coefficient | P   | 95% CI          |
|-----------------------|----------------------------|-----|----------------|
| **Levothyroxine daily dose** |                           |     |                 |
| Duration of hypothyroidism | 0.251                   | 0.001| 0.879-2.074    |
| Weight                | 0.143                     | 0.004| 0.129-0.576    |
| IBW                   | 0.448                     | 0.02 | 0.090-0.877    |
| **D/W**               |                           |     |                 |
| Age                   | −0.157                    | 0.002| −0.009−0.002   |
| Duration of hypothyroidism | 0.217                  | 0.001| 0.012-0.031    |
| BMI                   | −0.344                    | 0.001| −0.04−0.02     |
| **D/IBW**             |                           |     |                 |
| Duration of hypothyroidism | 0.245                   | 0.001| 0.018-0.042    |
| Weight                | 0.170                     | 0.002| 0.003-0.012    |
| Height                | −0.285                    | 0.001| −0.033-0.015   |

*The final result of the multivariate regression analysis is based on “ENTER” method. P<0.05 considered significant. BMI: Body mass index, CI: Confidence interval, D/W: Levothyroxine daily dose based on weight, D/IBW: Levothyroxine daily dose based on IBW, IBW: Ideal body weight.

DiscussiOn

LT4 is given as a replacement therapy for hypothyroidism, and the dose depends on the demand which in turn dependent on endogenous thyroid hormone production. The level of thyroid hormones in the blood circulation is determined by the endogenous secretion of thyroid hormones, their metabolism, and exogenous replacement therapy. To maintain euthyroid range of serum TSH and T4, the replacement dose of LT4 is determined by the residual thyroid function. Conventionally, the recommended starting dose of LT4 in autoimmune hypothyroidism cases is 1.6 µg/kg D/W.[1] Patients with minimal residual thyroid function due to autoimmune etiology require 1.6–1.8 µg/kg of actual body weight,[10] although some studies suggest a higher dose of 2.0–2.1 µg/kg.[8,10,11] The etiology of a patient’s hypothyroidism affects the D/W and may reflect degree of residual function as suggested by higher D/W requirement in athyreotic patients posttotal thyroidectomy versus patients with Hashimoto’s thyroiditis.[7]
This study showed age-related decline in D/W as shown by significant negative correlation between age and D/W, and significantly higher D/W requirement in individuals in 1st age quartile versus 2nd, 3rd, and 4th quartile, although no similar difference was for ADD and D/IBW. Devdhar et al.\(^\text{[12]}\) showed that age-based difference in LT4 dose is due to difference in body weight and gender, while study by Santini et al. showed a significant negative correlation (\(P < 0.03\)) of age with D/W which disappeared when adjusted for LBM\(^\text{[13]}\) and hence suggested that the age-related decrease in LBM is responsible for decrease in LT4 dose. The findings of this study are similar to the above-mentioned studies that the significance of age for D/W decreased when adjusted for BMI, but a trend of significance was still seen although lean muscle mass was not analyzed in this study.

This study enrolled long-standing cases of spontaneous onset primary hypothyroidism for which Hashimoto’s thyroiditis is the most common cause. At least 75% of cases in this study required dose \(\leq 1.5\) \(\mu\)g/kg of LT4 D/W that is lesser than recommended starting dose of 1.6 \(\mu\)g/kg of LT4. This finding can be explained by the variable residual thyroid function reserve. A study of long-term follow-up of adults with subclinical hypothyroidism for more than 9 years showed that on an average, 28% of patients progressed to overt hypothyroidism, while 68% patients remained in the subclinical state, suggesting a variable course in each patient.\(^\text{[14]}\) In the same study, it was shown that residual thyroid reserve and high titer of thyroid peroxidase antibody were significant predictors for development of overt hypothyroidism on follow-up. This study showed that duration of hypothyroidism was predictors of ADD, D/W, and D/IBW. In addition, individuals in the lowest quartile of duration of hypothyroidism (1–2.3 years) had significantly lower mean either ADD, D/W, or D/IBW compared to 3rd and 4th quartile, and 2nd quartile from 4th quartile. The findings of this study suggest progressive decrease in residual thyroid function and that not all cases have minimal residual thyroid function at the onset.

The gender-based significant difference in the mean ADD and D/IBW was seen in this study, although no gender difference was seen in mean D/W. The significantly higher D/IBW in premenopausal compared to male became insignificant when adjusted for height, suggesting that the difference in the gender-based difference in D/IBW is mainly due to difference in anthropometry. Similar gender-based difference was found in other studies.\(^\text{[13,14]}\)

Although BMI was not significantly different between male and female, IBW was significantly higher in men compared to postmenopausal or premenopausal women due to greater height in men. D/W was similar between male and female, but D/IBW was lower in men compared to premenopausal
or post-menopausal women. The lower D/IBW requirement in males, and almost similar dose requirement for D/W in both gender suggests that LT4 requirement of fat mass exists, although much lower than that of LBM.\(^2\)

Hence, this study suggests that the D/W or D/IBW requirement is variable and not one size and varies between individuals probably depending on the residual thyroid function reserve. Duration of hypothyroidism was a significant determinant of LT4 daily doses. This study has strengths such as large population size, confirmed compliance with medication, and recently confirmed euthyroidism, although it has many limitations as being cross-sectional, and functional reserve and LBM were not evaluated.

**Conclusion**

Primary autoimmune hypothyroidism patients require a variable dose of LT4, and the dose progressively increases with duration of hypothyroidism. Gender has no direct effect on LT4 dose, and the difference in dose is based on difference in anthropometry between both the genders.

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**Conflicts of interest**

There are no conflicts of interest.

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