Original Article

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Body Weight as a Major Determinant of Thyroxine Sodium Dosage in the Treatment of Primary Hypothyroidism

Internal Medicine Section

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ABSTRACT

Introduction: Several formulae have been proposed for optimising the dosage prerequisites of levothyroxine (LT4), and body weight and Body Mass Index (BMI) have been suggested to be broadly dependent on the formulae range.

Aim: To evaluate the role of body weight as a determinant of LT4 dosage in the treatment of primary hypothyroidism.

Materials and Methods: The present study was a prospective observational study conducted at Outpatient Department (OPD) Endocrinology, Patna Medical College Hospital, Patna, Bihar, India, on 100 patients diagnosed with untreated primary hypothyroidism between February 2020 and January 2021. Demographic details, anthropometric measurements, vital signs, and details of types and dosage of treatment received were collected. LT4 dose requirement for each individual patient was then generated as mcg per kg/body weight per day. Estimation of serum Thyroid Stimulating Hormone (TSH), Free T4 (FT4), creatinine and thyroid peroxidase levels were carried out as per standard diagnostic protocols and the dosage adjustment was conducted based on target TSH levels. Population characteristics were expressed as mean±standard deviation. The Python version 3.4.5 with the package seaborn was used for statistical analyses and preparation of figures, distribution and correlation plots.

Results: The study enrolled 100 individuals (88 women and 12 men) with mean age of 40.69 years (age range 17 to 72 years). A significant positive correlation was noted between the LT4 dose and total body weight (p-value <0.001). The association was also significant when the LT4 dose was correlated with BMI (p-value <0.001) and FT4 (p-value <0.001). However, the correlation of Thyroid Peroxidase Antibodies (TPO Ab), TSH, height and age with the LT4 daily dose (p-value >0.05) was found to be statistically non significant.

Conclusion: There exist a significant positive correlation between LT4 dosage and body weight. Hence, body weight should be considered as a key determinant while prescribing LT4 therapy for the treatment primary hypothyroidism.

Keywords: Body mass index, Levothyroxine, Obesity

INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders worldwide with potentially devasting consequences on the patients' well-being. The prevalence of hypothyroidism in iodine-deficient countries is estimated to be 1-2%. However, one-third of the world population lives in iodine-deficient regions and changes in diet and agricultural practices are the major causes for iodine deficiency [1]. A multi-centre cross-sectional study conducted across eight major Indian cities has estimated the prevalence of hypothyroidism to be around 11%. The study also identified significant association of the disease with female gender and older age [2]. However, there is a lack of data on the prevalence of primary hypothyroidism in Indian population. A 2019 study by Baruah MP et al., reported significantly high prevalence (33%) of primary hypothyroidism among adult population in Guwahati city [3]. The complications associated with untreated hypothyroidism include cardiovascular disease, goitre, infertility in women, cognitive dysfunction, growth retardation in children and myxoedema coma [4]. The effect of iodine deficiency on cognitive and neurological development of offspring has been well established [1].

Levothyroxine sodium (an isomer of T4, LT4) is the most commonly used thyroid replacement therapy. The optimisation of LT4 dosage remains critical for the well-being of patients. The dosage of LT4 depends on various factors namely age, gender, serum TSH level, and female menstrual and pregnancy status, the residual thyroid function retained by the patient, the body weight or lean body mass of the patient, and the target thyrotropin or TSH level to be achieved during therapy. Another important factor that affects LT4 dosage requirement is its absorption, which is influenced by certain medical conditions (e.g., Hashimoto's thyroiditis), medications (e.g., thyrosine kinase inhibitors), food and beverages, and the timing of LT4 administration [5-7]. According to American Thyroid Association's recommendation, dose adjustments should be made when there are large changes in body weight, with aging, and pregnancy, based on the assessment of LT4 levels 4-6 weeks after any dosage change [8].

A randomised, double-blind trial by Roos A et al., has recommended a full dose of LT4 of 1.6 µg/kg for young and healthy adults and a dose of 25 to 50 µg/d for old and cardiac patients [9]. Over the years, numerous researchers have proposed different formulae for optimising dosage prerequisites, and the formulae range is broadly dependent on the body weight and the Body Mass Index (BMI) of the patient [10-12]. The present study is intended to evaluate the role of body weight as a determinant of LT4 dosage in primary hypothyroidism therapy, as validation of this association would help to develop clear consensus on customisation of LT4 dosage based on body weight.

MATERIALS AND METHODS

The one-year prospective observational study included patients with known hypothyroidism who visited the OPD section of Department of Endocrinology, Patna Medical College Hospital, Patna, Bihar, India, between February 2020 and January 2021. The study was conducted in accordance with the International Conference on Harmonisation (ICH-GCP) and regulations and guidelines of Helsinki declaration.

Inclusion criteria: Only those patients with first diagnosed, untreated primary hypothyroidism were included in the study and followed-up till nine months.

Exclusion criteria: Patients on medications that are known to interfere with LT4 absorption or adjust LT4 binding proteins and pregnant or lactating women were excluded from the study.

Study Procedure

A total sample of 100 patients was included in the study and were followed uptill nine months. The medical records of the patients were accessed for collecting demographic details (age, sex) anthropometric measurements (height, weight, BMI), vital signs (pulse, Blood Pressure (BP)), and details of types and amounts of medical treatments received by the patients. LT4 dose requirement for each individual patient was then generated as mcg per kg/body weight per day. Various studies have estimated the replacement dose of LT4 based on body weight in hypothyroid patients treated to achieve a normal TSH [13,14]. These estimates range from1.6 mcg to 1.8 mcg LT4 per kilogram of actual body weight. It is well established that the aetiology of patients hypothyroidism, which is closely linked to the amount of residual thyroid function that a patient has, affect the dose of LT4 that will normalise the patients TSH [15]. Estimation of serum TSH, FT4, creatinine and TPO Ab levels was carried out as per standard diagnostic protocols of the institute's laboratory and data of the same were collected during the four follow-up timepoints (baseline, 3rd, 6th and 9th month). The dosage adjustment was conducted based on target TSH levels (1 to 3 IU/mL).

STATISTICAL ANALYSIS

Characteristics of the study population were expressed as mean±standard deviation. The Python version 3.4.5 with the package seaborn and Excel 2103 (16.0.13901.20400) were used for statistical analysis and preparation of figures, distribution and correlation plots. Descriptive statistics of demographic and clinical data was calculated. Continuous variables were summarised as means and standard deviations, and categorical variables as counts. The effect of weight on LT4 doses was tested using a multiple linear regression model. The model was generated with LT4 dose as the dependent variables and with weight, height, TSH value, age, BMI, FT4, and TPO Ab included as independent variables. The p-value of <0.05 was considered significant and <0.01 was considered highly significant.

RESULTS

The study enrolled 100 individuals (88 women and 12 men) meeting the inclusion and exclusion criteria. The mean age of the individuals was 40.69 years, with a range of 17 to 72 years. The demographic characteristics of the enrolled subjects are shown in [Table/Fig-1].

Characteristics	Mean (SD)
Age (years)	40.6 (14.19)
Weight (kg)	64.1 (12.5)
Height (cm)	156.2 (6.47)
BMI (kg/m^2)	26.2 (4.97)

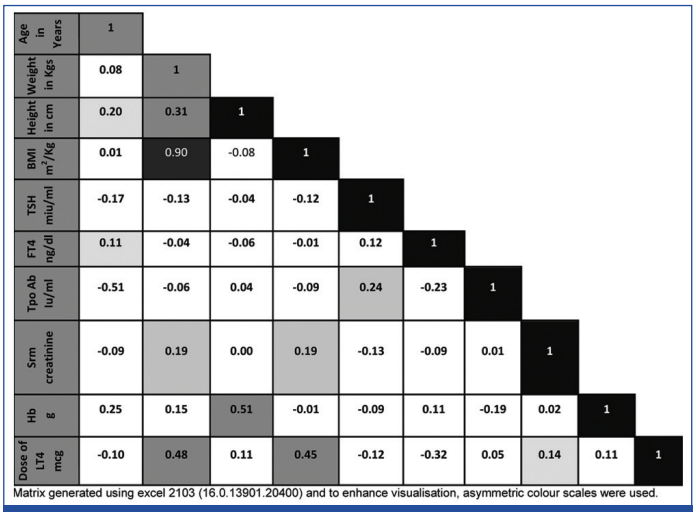
[Table/Fig-1]: Demographic characteristics of the study population.

Co-morbidities were present in 31% of the subjects and the corresponding number of subjects noted with hypertension, diabetes, and both hypertension and diabetes were 9%, 8% and 14%, respectively. Comparison of changes in biochemical characteristics from baseline to nine months is depicted in [Table/Fig-2]. A significant reduction in mean serum TSH level (p-value <0.0001) and increase in FT4 levels (p-value <0.0001) were noted in subjects following the treatment.

Parameters	Baseline (mean)	3 months (mean)	6 months (mean)	9 months (mean)	p-value
TSH (mIU/mL)	34.62±1.94	3.17±4.39	2.33±0.68	2.36±0.46	**<0.0001**
FT4 (ng/dL)	0.91±0.28	1.41±0.23	1.47±0.10	1.49±0.08	**<0.0001**
Dose of levothyroxine sodium (mcg/day)	90.88±23.83	92.13±25.29	92.13±25.17	92.13±25.17	**<0.0001**

[Table/Fig-2]: Biochemical characteristics of the study population.
The p-value calculated by using Analysis of Variance (ANOVA) test. The p<0.05 considered level of significance

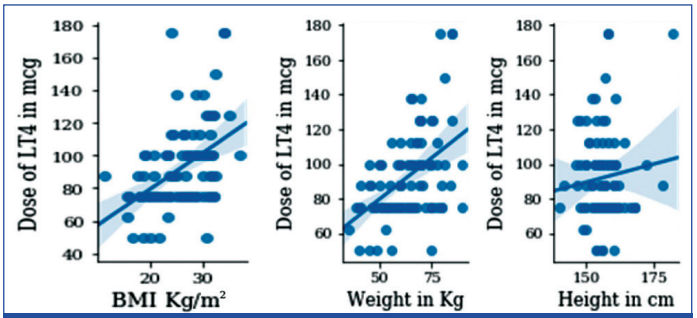
Heat-map was used for the visualisation of correlation matrix between the input and output data. High correlation was observed in the upper rows of [Table/Fig-3], indicating a correlation of dosage of LT4 with BMI (0.45), height (0.11) and body weight (0.48).



Matrix generated using excel 2103 (16.0.13901.20400) and to enhance visualisation, asymmetric colour scales were used.

[Table/Fig-3]: Correlation matrix for demographic and biochemical characteristics.

The distribution pair plot of three variables against the outcome variable is depicted in [Table/Fig-4]. The scatter plot displayed the data set containing quantitative variables. The trendline in the figure has shown corresponding increase in dosage of LT4 with weight, height, and BMI.



[Table/Fig-4]: Distribution plot between the daily dose of LT4 and total body weight, BMI, and height.
Pair plot graph generated using Python seaborn code (Python version 3.7.4)

The relationship between the total daily dose of LT4 and body weight was analysed using multiple linear regression, and a significant positive correlation between the LT4 dose and total body weight was noted (p-value <0.01, [Table/Fig-5]). The association was also significant when the LT4 dose was correlated with BMI (p-value <0.001) and FT4 (p-value <0.001). A statistically non significant correlation was observed for TPO Ab, height and age with the LT4 daily dose (p-value >0.05).

Variables	Slope	Intercept	R-value	p-value	Std. Error
Age (years)	-0.18	99.36	-0.1	0.32	0.18
Weight (kg)	0.95	32.1	0.48	**<0.001**	0.18
BMI (kg/m^2)	2.25	33.98	0.45	**<0.001**	0.45
Height (cm)	0.42	26.09	0.11	0.3	0.4
TSH (mIU/mL)	-1.54	102.59	-0.12	0.24	1.3
FT4 (ng/dL)	-29.48	119.02	-0.32	**<0.001**	8.72
TPO Ab (IU/mL)	0	91.22	0.05	0.62	0.01

[Table/Fig-5]: Regression analysis of LT4 dose on body weight in hypothyroid patients.
Significance level at p<0.05

DISCUSSION

Studies have reported that many elderly patients are being treated with a large dosage of T4 or inappropriate TSH goals [16,17]. Due to the age-related reduction in thyroxine degradation and in lean

body mass, there is a gradual decrease in the LT4 requirement with age [18]. Hence, several studies have agreed upon the need to consider the factors like patient weight and lean body mass for the determination of LT4 dose [19,20]. The present study has evaluated the effect of LT4 therapy in hypothyroid patients focusing on the body weight with regular intervention testing of TSH and FT4 levels. Various studies have estimated the replacement dose of LT4 based on body weight in hypothyroid patients treated to achieve a normal TSH.

The use of a serum TSH and body weight-based calculations of LT4 dose usually produces similar dose estimates. The dose of LT4 also depends on lean body mass, age, gender, de-iodinase polymorphism and pregnancy [21,22]. The current study has shown that the body weight, FT4 and BMI have a significant influence on LT4. In concurrence with the current findings, a study by Younis IR reported that it is important to consider body weight while prescribing LT4 and the recommended initial dose should be higher for patients with more weight [22]. A 2021 comparative study has highlighted the need to adjust the LT4 dosage based on the body weight in patients with primary hypothyroidism, keeping in mind to monitor the TSH and FT4 levels at regular intervals [18].

Fletcher A and Weeman A have noted that hypothyroidism is often overlooked as a cause of hypertension and the restoration of euthyroid status assists in the reduction of both systolic and diastolic pressure [23]. Gronich N et al., showed that the risk of developing diabetes mellitus is higher in patients with hypothyroidism. These findings concur with the present study results, that has reported diabetes and hypertension as the comorbidities noted in the study participants [24].

The present study has considered an average dosage requirement of 92.125 mcg daily of LT4 for both the genders with an approximate weight of 63 kg. However, Chandra AK and Kumar M have used 125 µg daily for an average man weighing 75 kg, separately and 100 µg daily for an average-sized woman weighing 60 kg [18]. Literature review shows that most of the studies have reported 3-6 months as the period of normalisation of the clinical signs and symptoms and quality of life and this is in line with the present study timeline of 3-9 months [9].

The current study has found a statistically non significant correlation of TPO Ab, TSH, height and age with the LT4 daily dose (p-value >0.05). Sawin CT et al., have noted that individual LT4 dosage requirement is dependent on lean body mass. The study has shown that middle-aged elderly men have age-related decrease in the LT4 requirement, as opposed to the same age female counterparts [25]. Another study has reported the age-related decrease in LT4 in older menopausal women not in premenopausal women [26]. However, the present study did not categorise women into different groups based on age or menopausal status. A review by Athanassiou KI and Ntalles K, has noted that the daily LT4 dosing may depend on factors such as age, body weight, presence of coronary artery disease and cardiac arrhythmias. The recommended dosing in adult is about 1.8 µg/kg body weight and in the elderly, it is about 0.5 µg/kg body weight [27]. An interventional audit of a large community database has highlighted poor compliance, drug impedance, parietal cell antibodies (as a marker of atrophic/autoimmune gastritis), and celiac disease as the causes requiring high-dose levothyroxine replacement in patients with hypothyroidism [28]. Okuroglu N et al., have reported a positive association between LT4 and antibody titres in patients with autoimmune thyroiditis; in contrast, the present study has noted a non significant association [29]. Another study by Bakker B et al., found that the plasma TSH and FT4 concentrations reached the age-related normal range within a few days after diagnosis in congenital hypothyroidism following the LT4 treatment [30]. Although the current study has reported a non significant association between TSH and LT4 daily dose, it did not estimate the number of days required to normalise serum TSH and FT4 levels.

Prospective design and evaluation of biochemical characteristics in a standard clinical laboratory are the major strengths of the present study. The study corroborating body weight as a significant determiner of LT4 dosage, highlights the need to bring necessary consensus in daily practice to avoid undertreatment or overtreatment.

Limitation(s)

Smaller sample size and lesser number of men potentially limit the generalisation of the present results. In addition, the impact of gender on LT4 dosage requirement was not evaluated in the study.

CONCLUSION(S)

A significant positive correlation was observed between LT4 dosage and body weight. The present study has corroborated the role of body weight as a key determinant while prescribing LT4 therapy. This is beneficial to shorten the time required to attain a stable dose, and to avoid undertreatment or overtreatment. Future research focusing on dosage adjustment based upon age and pregnancy status in a larger cohort is highly warranted.

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