

Lean body mass-based levothyroxine replacement in young athyrotic patients with differentiated carcinoma of thyroid

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ABSTRACT

Objective: The objective of this study was to optimize dose of levothyroxine (LT4) based on lean body mass (LBM) in young athyrotic patients with differentiated carcinoma of thyroid (DCT) which has not been properly addressed in Bangladesh before. **Materials and Methods:** Sixty patients with DCT (age, range: 20-39 years) having total thyroidectomy followed by radioiodine ablative therapy (RIT) and 23 euthyroid volunteers were recruited. Clinical, biochemical parameters were obtained from all patients after 2 months of RIT and on LT4 replacement at a dose of 200 µg/day as first follow up visit and also from control subjects. Then 60 patients were divided into two groups consisting of 30 patients each. Patients of Group-I received LT4 replacement based on LBM measured by dual energy X-ray absorptiometry (DXA) and Group-II continued LT4 replacement in conventional dose. Patients of both groups were assessed again for same parameters at 6 to 12 months at the second visit. **Results:** Optimized dose of LT4 based on LBM by DXA (131 ± 23 µg/day) significantly reduced thyroid hormones and kept thyroid stimulating hormone (TSH) in expected levels in patients of Group-I at the second visit compared to patients of Group-II who continued conventional LT4 dose (200 µg/day). Hyperthyroid symptom scale (HSS) was significantly reduced to 2 ± 1 in patients of Group-I but not in patients of Group-II, HSS, 8 ± 1 ($P < 0.001$). **Conclusion:** Optimization of LT4 dose based on LBM can avoid chronic exposure of mild excess of thyroid hormone in young patients with low risk DCT.

Key words: Differentiated carcinoma of thyroid, dual energy X-ray absorptiometry, lean body mass, levothyroxine

INTRODUCTION

Patients with differentiated carcinoma of thyroid (DCT) receive lifelong levothyroxine (LT4) replacement therapy after undergoing total thyroidectomy and subsequent radioiodine therapy (RIT). LT4 is given in

thyroid-stimulating hormone (TSH) suppressive dose to keep the patients in subclinical hyperthyroid state because low-level TSH prevents development of metastases by lowering the stimulus for cellular growth.^[1-4] Long-term administration of LT4 in TSH suppressive dose in patients with DCT has some ill effects on heart, impairs quality of life and psychometric functionality.^[5-13] In a study, it has been shown that individual requirement of LT4 supplement is mostly dependent on lean body mass (LBM) rather than total body weight as fat mass of body does not contribute in LT4 metabolism.^[14,15] The objective of the present study was to optimize the dose of LT4 depending on LBM and thereby reducing the side effects of chronic overdose of LT4 therapy on patients with DCT of the low-risk group.

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MATERIALS AND METHODS

Sixty patients with DCT of the low-risk group (T1, N0, and M0)^[16] between the age range of 20 and 39 years were consecutively enrolled in this prospective case-control study. All patients were diagnosed as papillary carcinoma of thyroid on histopathological examination. Patients with any signs of metastases, previous cardiac problems, and chronic disease were excluded. All patients had undergone total thyroidectomy and then received about 100 mci RIT and subsequently 200 µg LT4 daily for initial 2 months. Age, weight, height, body surface area (BSA), body mass index (BMI), and life style-matched 23 healthy euthyroid volunteers were also recruited as the control group. Each participant of the study was explained about the risk and benefit of the present study before participation and informed consent was collected in Bangla language. Clinical and biochemical parameters of control subjects were obtained to compare with patients with DCT after 2 months of RIT and on LT4 replacement on conventional 200 µg/day at first follow-up visit. Then 60 patients were divided into Group-I and Group-II, each group consisting of 30 patients. Thirty patients of Group-I had undergone dual energy X-ray absorptiometry (DXA) investigation to estimate their LBM (GE Health care, Lunar Prodigy Advance PA + 301470 at whole body version) at first follow-up visit. The study subject's body weight and height were measured. BMI was calculated by weight/(height)²(kg/m²). (Calculation of BSA = Total body weight (kg) 0.425 × Ht (m) 0.725 × 0.007184).^[14] Then, total body mass is calculated by DXA as follows: Total body weight (TBW) = total bone mineral concentration (BMC) + total fat mass (FM) + total lean mass. Thereby, lean body mass (LBM) = the total body mass – (total fat mass + total BMC) was obtained by above formula [Figure 1].^[14,17-19]

After 2 months of RIT, the patients of Group-I received LT4 dose depending on LBM (mean, 131 ± 23 µg/day, 3.5-4.0 µg/kg/LBM/day). After 3 months of this dosing, hormone assessment were done to see the adjustment. However, patients of Group-II continued the conventional fixed dose of LT4 (200 µg/day). Thereafter, patients of both groups were assessed by hormone estimation. Serum TSH concentration was measured by ultra-sensitive immunoradiometric (IRMA). Normal reference value of serum TSH is 0.3-5.0 mIU/L. Serum FT3 was measured by the radioimmunoassay (RIA) method. The euthyroid reference range of FT3 is 2.8-9.5 pmol/L. Serum FT4 was determined by RIA. The normal range of FT4 is 9.5-25.5 pmol/L.

Hyperthyroid symptom scale (HSS) is a potentially useful scale to assess the severity of known hyperthyroid symptoms and their response to therapy. HSS is an observer rated scale, which includes 10 items of clinical features of hyperthyroidism.^[20] Every control subjects and patients were evaluated according to HSS and biochemical parameters were obtained at the first visit and patients of both groups were evaluated after 6-12 months at the second visit.

Statistical analyses

Two-tailed unpaired Student's *t* test was used to compare basal data between control subjects and patients. One-way ANOVA was used to compare all the clinical and hormone data between patients of Group-I and Group-II at the first visit and the second visit and between two visits. The *post hoc* covariates were analyzed at Tukey's HSD (honestly significant difference) test. Statistical analysis was performed by using SPSS, version 13 software packages for windows. Data were expressed as mean ± SD. A probability (*P*) value less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences between patients and control subjects in terms of age, height, weight, BSA, and BMI (*P* > 0.05) [Table 1]. The mean age of control subject was 30 ± 5 yrs (range, 20-39 yr), which did not differ significantly with patient group of 28 ± 6 yrs (range, 20-39 yrs) (*P* > 0.05) [Table 1].

Subjects of the control group had height ranging from 145 to 168 cm and in the patient group ranging from 139 to 170 cm. Control subjects and patients had comparable mean weight in the present study, the control group, range: 40-63 kg and in the patient group, range: 33-70 kg. Control subjects and patients had similar sedentary lifestyle. Control subjects had BMI, range: 17-26 kg/m² and the patient group showed similar BMI, range: 15-31 kg/m². Comparable

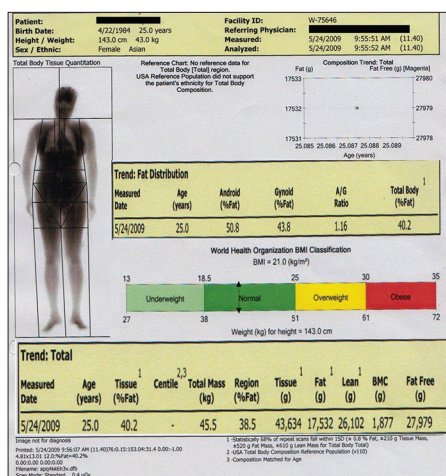


Figure 1: Whole body DXA for lean body mass of a 25-year-old female patient with DCT

weight and height in control subjects and patients groups in the present study showed similar BSA (control subjects, range: 1.32-1.72 m²; patients, range: 1.18-1.8 m²).

LBM was measured in each patient of Group-I. Comparative TBW and LBM of patients of Group-I were shown in Figure 2. Control subjects showed serum FT3, FT4, and TSH within normal reference ranges. All patients who received LT4 on conventional dose (200 µg/day for initial 2 months) showed high FT3, FT4, and suppressed TSH. Significant differences ($P < 0.001$) were noted where hormone status compared between control subjects and patient groups [Table 2].

For keeping the patients with DCT at low TSH level (0.04-0.1 mIU/L) and within normal ranges of FT3 and FT4, the dose of LT4 was optimized on the basis of LBM of each patient of Group-I after the first visit. After 3 months, the repeat hormone assay of Group-I patient showed normal thyroid hormone levels and expected TSH level (0.1 ± 0.01 mIU/L). The mean dose of LT4, 131 ± 23 µg/day, range: 120-220 µg/day, 3.5 to 4 µg/kg/LBM was found optimum. Patients of Group-I showed high serum FT3, FT4, and low TSH when they were on conventional dose of LT4 at the first visit. After optimization of dose of LT4, hormone levels became normal and the TSH level was increased in patients of Group-I at the second visit. Serum FT3 and FT4 values were higher and TSH was suppressed in patients with DCT of Group-II, who continued conventional LT4 dose (200 µg/day) compared to healthy control subjects and patients with optimized dose of LT4 of Group-I at the second visit [Tables 1 and 3]. Significant differences ($P < 0.05$) were noted in hormone levels of Group-I and Group-II at the second visit.

Regarding HSS, score was significantly higher in patients with DCT compared to control subjects. HSS and heart rates were significantly higher in Group-II compared to control subjects and patients of Group-I at the second visit [Table 1]. HSS showed a significant clinical improvement of patients who received optimized dose of LT4 at the second visit [Table 3].

DISCUSSION

DCT are potentially curable cancers. Properly treated patients with DCT have almost normal life expectancy.^[1-2,21,22] In young patients with DCT, total thyroidectomy and RIT may ensure a survival rate of more than 95% at 30 years.^[2] Subsequent follow up strategies and prognosis vary according to the patient's individual risk. LT4 replacement protocol differs among

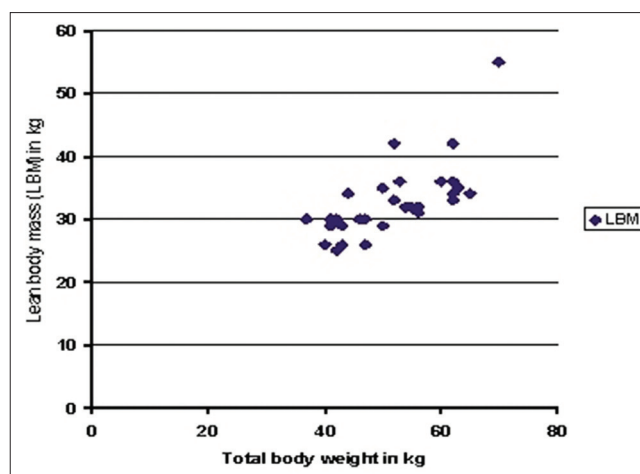


Figure 2: Lean body mass and total body weight in patients of Group -I

Table 1: Biophysical characteristics of control subjects and patients

Parameters	Control (n=23) (F/M-13/10) mean±SD	Patients (n=60) (F/M-55/5) mean±SD
Age (years)	30±5	28±6
Weight (kg)	55±6	53±10
Height (cm)	156±6	153±5
BSA (m ²)	1.53±0.10	1.48±0.14
BMI (kg/m ²)	23±2	23±4

$P > 0.05$ Control versus patients (no significant difference), $P < 0.05$ is considered significant difference, BSA: Body surface area, BMI: Body mass index

Table 2: Clinical characteristics and hormonal status of control subjects and patients at first visit

Parameters	Control (n=23) m±SD	Patients (n=60) m±SD
Pulse (bpm)	76±5	94±12*
SBP (mmHg)	117±6	115±8
DBP (mmHg)	72±3	76±10
HSS	1±1	8±1*
FT3 pmol/L	5.3±1.04	9.5±0.66*
FT4 pmol/L	17.13±3.12	28.55±2.56*
TSH (mIU/L)	1.95±0.42	0.08±0.017*

* $P < 0.05$ Control versus patients, TSH: Thyroid stimulating hormone, HSS: Hyperthyroid symptom scale

Table 3: Clinical characteristics and hormonal status of patients of group-I and group-II at first and second visits

Parameters	Group-I (n=30) mean±SD		Group-II (n=30) mean±SD	
	At first visit	At second visit	At first visit	At second visit
Pulse (bpm)	95±11	87±14*	93±12	100±20†‡
SBP (mmHg)	116±7	114±7	114±9	119±8
DBP (mmHg)	77±5	75±7	76±5	78±4
HSS	8±1	2±1*	8±1	8±1‡
FT3 pmol/L	9.4±0.7	5.5±1.3*	9.6±0.6	10.1±0.7‡
FT4 pmol/L	29.5±2.9	17.9±1.9*	27.56±1.6	27.4±0.94‡
TSH (mIU/L)	0.08±0.04	0.1±0.01*	0.08±0.05	0.09±0.05‡

* $P < 0.05$ Group-I vs Group-I between first and second visits; † $P < 0.05$ Group-II vs Group-II between first and second visits; ‡ $P < 0.05$ Group-I vs Group-II at second visit, HSS: Hyperthyroid symptom scale, TSH: Thyroid stimulating hormone

institutes of different countries considering the different recommendations of international guidelines. American Thyroid Association (ATA) and other authors advocated that maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mIU/L) is appropriate for low risk patients with DCT.^[3-5,21,22] This recommendation has not been followed uniformly in different institutes throughout the world. Patients with DCT with high and low risk are usually kept in subclinical hyperthyroid state irrespective of risk of metastases.^[5,6] The objective of the present study was to optimize the dose of LT4 based on LBM to prevent over exposure to it and thereby reducing the signs and symptoms of hyperthyroidism and deleterious effect on heart and quality of life.

Biophysical characteristics regarding female to male ratio in patients of the present study population have reflected the incidence of sex pattern of the disease. There female to male ratio is 9:1.^[23] In previous studies, similar sex patterns had been observed by other researchers.^[7,12,24,25] The patients and control subjects were matched for age, height, weight, BSA, and BMI in the present study. Patients with DCT were consecutively recruited from the younger age group. Other reasons to select the younger age groups were to avoid any existing cardiac problems and also to avoid chronic diseases and any kind of disability affecting the different parameters of the present study. Biondi, *et al.*, (1993), also recruited the patients of the younger age group having mean age of 36 ± 11 year. In contrast, other authors studied LT4 requirement in population of higher age group with the mean age of 45 ± 17 year, ranging from 22 to 85 years.^[22] Regarding height and weight of the population of the present study, they were lower compared to other studies where their people were taller and having more weight.^[5,7,24,25] Subjects of the control group and patients with DCT were recruited from similar lifestyle, all had sedentary life style. During selection of control subjects, persons engaged in significant physical activity had been deliberately avoided because they could have differed in their muscular build.^[14,15] In a study, the mean BSA of Japanese men between age group 20 and 39 years was 1.8 ± 0.1 m² and that of women was 1.5 ± 0.1 m².^[26] The mean BSA of female control subjects of the present study was comparable to Japanese healthy adult female.

It is a matter of great concern; the physicians of our country have been practicing LT4 at dose of 200 µg/day in post-radioiodine-ablated patients with DCT. This dose pattern does not consider age, sex, body weight of patients, and classification of DCT. This dose appears higher in the low-risk group of DCT, especially young patients having relatively low body weight. In our neighboring country India, physicians have been practicing 300 µg/day dose

of LT4 as initial dose, however, 100 µg dose reductions (200 µg/day) is advised for older patients with DCT having cardiac problems.^[27] There are several recommendations about requirement of daily dose of LT4.^[5,7,21,22] However, LBM measurement is superior to other measures of body size descriptor for dosage of many drugs, especially for those which are hydrophilic and used for lifelong. Pharmacokinetic parameter such as clearance is mostly dependent on LBM of an individual. Success rate of drug administration increases when given considering LBW rather than TBW.^[13] LT4 is water soluble and its pharmacokinetics is dependent on lean portion of body. LT4 is deiodinated to T3 (active form of hormone) in muscle, kidney, and liver. T4 is deiodinated to rT3 (reverse T3, inactive form) in skin. Fatty tissue has no role in metabolism of LT4.^[14,15] Comparative TBW and LBM were shown in patients of Group-I [Figure 2]. Regarding dose of LT4, it was optimized on the basis of LBM of each patient of Group-I at the first visit. After 3 months, the repeat hormone assay of Group-I patients were done. The dose of LT4 131 ± 23 µ gm/day (ranging from 120 to 220 µg/day) i.e., 3.5 to 4 µg/kg/LBM was found optimum to obtain normal thyroid hormone levels and expected TSH level (0.1 ± 0.01 mIU/L) in this group. This dose was comparable to LT4 dose calculated depending on LBM by DXA in a previous study.^[15]

Daily dose of LT4 based on TBW ranged from 2.2 to 3.0 µg/kg in different previous literatures.^[5,7,21,22] Regarding dose of LT4 calculation depending on TBW, arbitrarily it would have varied from 111 to 210 µg/day (mean, 156 ± 27 µg/day) in patients of Group-I of the present study, if 3 µg/kg/TBW/day were considered. This mean dose of LT4 is quite high compared to daily dose depending on LBM used in the present study [Figure 3] and also in a previous study by Santiny, *et al.*, (2005), in which

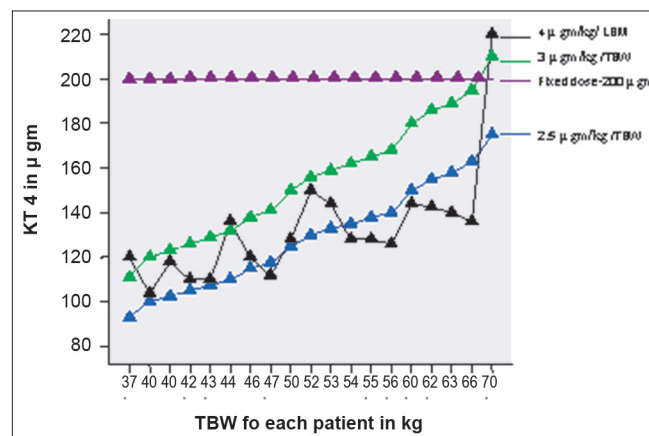


Figure 3: Daily dose requirement of LT4 in each patient of Group-I to attain TSH level range 0.04-0.1 m IU/L based on lean body mass and different recommendations based on total body weight

daily dose of LT4 was calculated on the basis of LBM. The dose of LT4 based on TBW increases linearly with the increment of TBW^[15] shown arbitrarily in Figure 3 in patients of Group-I. BMI always depends on fat accumulation.^[15,18] LBM does not increase linearly with the increase of body weight rather depends mainly on muscular activity and individual body build.^[14,15,18] Dose of LT4 increased linearly with the increase of TBW/BMI, but calculated dose based on LBM did not increase linearly. In Figure 3, remarkable nonlinearity/fluctuations of doses of LT4 were noted in LBM based dose pattern with a small difference of TBW. If 25 µg/day have been minimized from the daily total dose of LT4 based on LBM, several adverse effects would have been avoided.^[5,12,28] If 2.5 µg/kg/TBW of LT4 were considered for patients of Group-I, then dose would have varied from 93 to 175 µg with a mean dose 130 ± 22 µg/day, which also has increased linearly corresponding with body weight. A study^[15] recommended that patients with higher body weight comparatively are to be prescribed low dose (1.8 µg/kg/TBW) compared to patients with low body weight (2.56 ± 0.5 µg/kg/TBW) considering high fat accumulation in obese patients (analyzed by DXA whole body composition). Patients having different TBW may need the same dose of LT4 to attain same TSH value because of having same LBM. In this context, LBM appears as the best correlate of LT4 daily requirements, in which fat mass has little or no effect.^[15]

HSS was found as a good assessor to follow up hyperthyroid state after treatment.^[5,20] HSS showed a significant clinical improvement in patients with DCT who received optimized dose of LT4 at the second visit [Table 3] compared to the patients who received conventional dose of LT4 at first and second visits. Tachycardia, palpitations, heat intolerance, anxiety tremor, and nervousness were more evident features among patients with DCT on conventional LT4 dose and these symptoms are similar to those present in hyperthyroid state.

Optimization of LT4 produced expected influence on blood levels of FT3, FT4, and TSH evidenced by normal levels of FT3 and FT4 and low level of TSH. After optimization of LT4, moreover, signs and symptoms of hyperthyroid state were reduced in patients of Group-I [Table 3]. These findings of the current study were comparable to Biondi, *et al.*, (2000), where the study population was in endogenous subclinical hyperthyroid state for at least 6 months. This study is also in agreement with another study by the same author.^[7] Excessive LT4 replacement produce signs and symptoms of hyperthyroidism and patients continually suffer from impairment of emotional and physical health.^[6] It is now clear from previous published data and from the present

study that TSH suppressive dose of LT4 inevitably deteriorates patients condition worsening their quality of life.^[6,25]

Strength of the present study includes selection of young, low-risk group of patients with DCT who had comparable BMI along with healthy volunteers without having any cardiac problems. DXA has been found as a precise and reproducible method to measure body composition including measurement of LBM.

Limitation of the present study was comparatively short follow-up time after administration of high LT4 dose and optimization of dose of LT4 in one group of patients with DCT.

Further studies are recommended by consuming extended period of time for evaluation of quality of life in patients with DCT. Patients with DCT of the low-risk group are recommended to give replacement of LT4 depending on measurement of LBM (dose, 3.5-4 µg/kg/LBM). This will ensure expected replacement of LT4 especially in young patients with DCT. It will also cover the low-risk group and patients with diverse ethnicity irrespective of weight and BMI. Thereby, untoward side effects from chronic exposure to mild overdose can be avoided. This study documents that suppressive dose of thyroxine following thyroid carcinoma could be different in other ethnic groups with variations in body mass index. Therefore, the dose requirement obtained in the present study can be employed as a guide for determining comparable doses in individuals with similar body structure and weight.

CONCLUSION

Expected therapeutic suppression of TSH with LT4 replacement in athyrotic patients with DCT of the low-risk group requires optimization of LT4 dose. LBM-based LT4 therapy (3.5-4 µg/kg/LBM/day; 131 ± 23 µg/day) keeps the TSH in desired level. LT4 replacement used in the present study improves quality of life by reducing signs and symptoms of hyperthyroid state in patients with DCT. It prevents chronic exposure of mild overdose of LT4. Thereby statistically significant improvement of HSS of patients initiated among those who received optimized dose of LT4 compared to patients with DCT on conventional dose of LT4.

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