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Prediction of LT4 Replacement Dose to Achieve Euthyroidism in Subjects Undergoing Total Thyroidectomy for Benign Thyroid Disorders

Ranjith Sukumar · Amit Agarwal · Sushil Gupta · Anjali Mishra · Gaurav Agarwal · A. K. Verma · S. K. Mishra

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Abstract
Background Total thyroidectomy is becoming the preferred choice of treatment in patients with benign disorders of the thyroid gland; hence, an optimal method of replacing thyroxine is essential to avoid the ill effects of over- and under-replacement of thyroxine in such patients.
Patients and methods We analyzed three methods of thyroxine replacement: replacement per kilogram of lean body mass (LBM) (2.5 mcg/kg LBM per day), per kilogram of body weight (1.6 mcg/kg body weight per day), and empirical replacement of thyroxine.
Results The thyroxine requirement in thyroidectomized patients was 2.04 mcg/kg per day, with an increasing requirement of thyroxine with increments of weight. On multivariate analysis we found that the thyroxine requirement was strongly correlated both with body surface area (BSA) and with body weight. On subsequent correlation testing, we found that BSA was more strongly associated than weight with the thyroxine requirement.
Conclusions Patients undergoing total thyroidectomy may require higher doses of thyroxine to achieve euthyroidism when compared to patients with similar anthropometric parameters having primary hypothyroidism. The method of replacing thyroxine based on LBM is the ideal method, but replacement based on fixed-dose regimens could be a good method if the body weight is taken into consideration.

Ranjith Sukumar and Amit Agarwal contributed equally to this research.

R. Sukumar · A. Agarwal (✉) · A. Mishra · G. Agarwal · A. K. Verma · S. K. Mishra
Department of Endocrine Surgery, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, India
e-mail: amit@sgpgi.ac.in; amitsgpgi@rediffmail.com

S. Gupta
Department of Endocrinology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, India

Introduction

As more and more centers advocating total thyroidectomy as a standard of care for various benign disorders of thyroid gland, it becomes imperative to find an optimal way of replacing its function to overcome the inevitable hypothyroidism. At present there is only one study in the reported literature that deals with this issue directly. Current practice mostly involves thyroxine replacement by empirical methods decided by the treating surgeon or physician or, in some cases, by per/kg dosing, which is described for nonsurgical hypothyroidism. A few studies have suggested lean body mass (LBM) as a better measure of thyroxine replacement in nonsurgical cases; however, the same does not hold true for post total thyroidectomy patients. Most of the studies that mention a thyroxine requirement in hypothyroid individuals report on cases of medical hypothyroidism, where the intact thyroid gland may still be contributing in some degree to the serum thyroxine levels. Various adverse effects of hyperthyroidism include an increased chance of atrial fibrillation, reduced bone mineral density, and a deranged lipid profile, along with reduced endothelial function in hypothyroidism, all of which are clearly described in the literature. Hence it is imperative to keep the thyroxine levels in the physiological range.

The surgical literature mostly deals with thyroxine given in suppressive doses for thyroid malignancies or to reduce the size of a benign goiter. The present study assumes the relevance of thyroxine when the prevalence of goiter is

taken into consideration and as more and more surgeons are convinced of the safety and efficacy of total thyroidectomy in treating various benign disorders of thyroid. As the number of patients requiring thyroxine replacement grows, there is a need to reduce the overall costs of maintaining these patients and limiting the inconvenience of repeated testing, which necessitates multiple visits to the hospital for routine T4 and thyroid-stimulating hormone (TSH) testing.

The aim of the present study was to compare various methods of thyroxine replacement: (1) fixed dose or empirical replacement, (2) per/kg dose replacement, (3) per/kg LBM replacement.

Materials and methods

A total of 60 patients who underwent total thyroidectomy for various benign thyroid disorders were randomized into three groups by the random card technique: the empirical group (EM group), the lean body mass replacement group (LBM group), and the per/kg body mass replacement group (PBM group), with 20 patients in each group. In the LBM group lean body mass was assessed by a dual absorption X-ray densitometry machine (Hologic Discovery QDR series). In this group thyroxine replacement was done at 2.5 mcg/kg per day [1]. In the PBM group, replacement of levothyroxine was accomplished at 1.6 mcg/kg per day [2], and patients in the EM group received fixed-dose regimens from 75 to 150 mcg according to the rough estimate of the weight of the patient. The follow-up was scheduled at 6–8-week intervals for further titration of dose of thyroxine in each group. The doses were titrated with reduction/increment of doses of 25–100 mcg/visit according to the TSH values recorded at follow-up. The first point of normalization of TSH between 0.3 and 5.5 μIU/l was taken as the end point of the study. In patients with hyperthyroidism and suppressed pituitary axis, the attainment of a normal free T4 level in serum was taken as the end point of the study. The free T4 and TSH assays were done in three laboratories that employ comparable assay methods and similar normal range values. Levothyroxine was supplemented with Thyronorm tablets (Abbott Laboratories). These subsets of patients were subsequently checked for normalization of TSH at the end of 3 and 6 months. Statistical analysis was done with SPSS software version 10 (SPSS, Chicago, IL).

Results

The study participants included 29 females and 31 males. The patients in the three groups studied (EM, LBM, and PBM) were identical in age and weight (Table 1). Various clinical and biochemical parameters of the patients were also assessed (Table 2). When groups were analyzed for among-group differences, the only factors found to be significant were number of visits required before achieving euthyroidism ($p = 0.001$) and the final weekly dose of thyroxine required in each group ($p < 0.001$).

Hence an intergroup comparison was done to determine possible advantages of each of the groups in comparison with the others. When the EM group was compared with the LBM group, the TSH level achieved at the end point of the study was considerably higher in the LBM group ($p = 0.037$), and the final weekly thyroxine dose required was higher in the EM group.

Similarly, when the EM group was compared with the PBM group, the groups differed only in the number of visits required before achieving biochemical euthyroidism ($p = 0.043$). In contrast, for the LBM and PBM group comparison, the patients in the PBM group tended to be younger ($p = 0.024$) and had significantly more hospital visits before euthyroidism could be established ($p < 0.001$). In addition, patients in the PBM group required significantly more thyroxine doses than patients in the LBM group ($p = 0.001$).

When the whole group of 60 patients was analyzed for correlation between final thyroxine dose required and body weight of the patient, we found that the thyroxine requirement increased with increments of weight (Fig. 1).

Table 1 Demographic parameters of the three study groups

Parameter (median)	EM (max–min)	LBM (max–min)	PBM (max–min)
Age, years	45.0 (19–65)	44.0 (30–62)	35.0 (16–60)
Weight, kg	52.5 (38–75)	57.0 (35–85)	58.0 (35–85)

EM Empirical group; *LBM* lean body mass group; *PBM* per/kg body mass group

Table 2 Clinical and biochemical parameters among the three study groups

Parameter (median)	EM (range)	LBM (range)	PBM (range)
Number of medical visits	2.0 (1–4)	1.5 (1–3)	3.0 (1–5)
Final TSH achieved, μIU/l	1.60 (0.45–5.3)	3.27 (0.46–5.4)	2.25 (0.3–4.4)
Final dose of thyroxine achieved, mcg/week	800 (500–1,050)	775 (500–850)	837 (550–1,150)

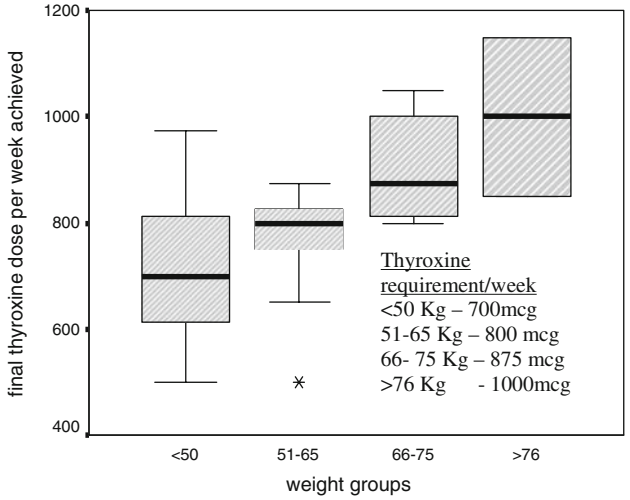

Fig. 1 Age groups and weight correlation

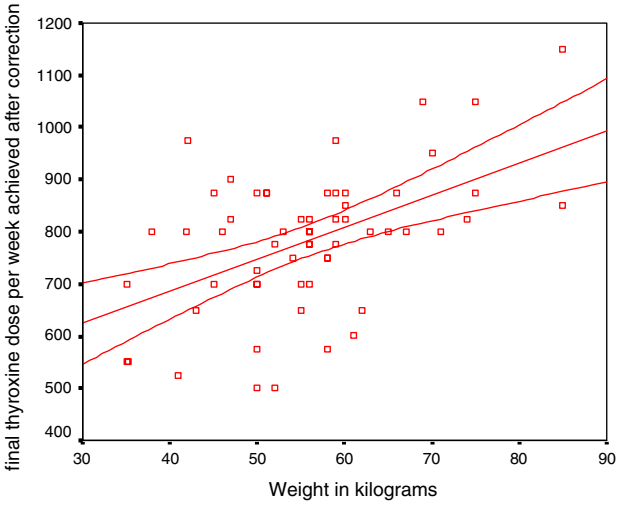

Fig. 2 Body weight and final thyroxine dose correlation (mean with 95% confidence intervals)

Table 3 Multivariate analysis (for the whole group)

Parameter	Mean ± SD	*p* Value
Age	41.53 ± 11.76	0.966
Weight	55.78 ± 10.95	0.004
BSA	1.54 ± 0.167	<0.001
BMI	22.67 ± 3.697	0.163

BSA Body surface area; *BMI* body mass index

Table 4 Correlation of parameters significant on multivariate testing and final thyroxine dose achieved

Parameter	Correlation	*p* Value
Weight	0.506	<0.001
BSA	0.570	<0.001

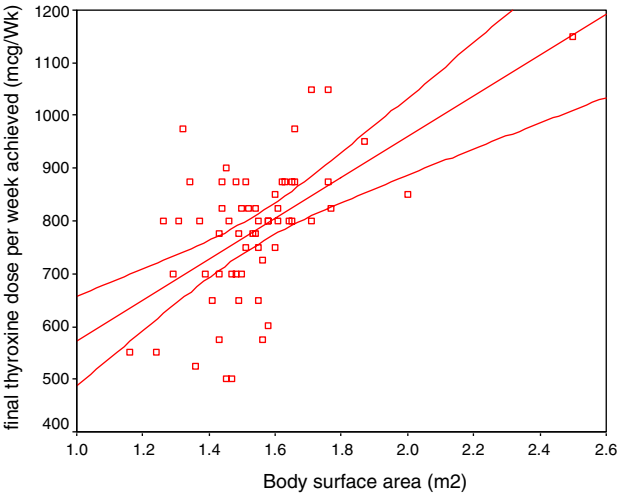

Fig. 3 Body surface area and final thyroxine dose correlation (mean with 95% confidence intervals)

On multivariate analysis we found that the thyroxine requirement strongly correlated with body surface area (BSA) and with body weight (Table 3). On subsequent correlation testing, we found that BSA was more strongly associated than weight with the thyroxine requirement (Table 4).

The thyroxine requirement, when analyzed for the whole group, was 2.04 mcg/kg body weight per day (Fig. 2) and was 75.2 mcg/m^2 BSA per day (Fig. 3).

Discussion

Thyroxine supplementation is becoming an essential part of management of benign thyroid disorders as the surgical preference shifts toward total thyroidectomy in the treatment of benign thyroid disorders [3]. It is essential to replace thyroxine in appropriate amounts as under-replacement may lead to clinically overt hypothyroidism with features like weight gain, lethargy, and excessive somnolence, etc. Hypothyroidism has detrimental effects such as decreased endothelial function and adverse lipid metabolism predisposing to cardiovascular events even in the subclinical setting [4–6]. In fact, prolonged hypothyroidism may cause dysfunction of the myocardium, predisposing the patient to heart failure. In patients with Graves' ophthalmopathy, prolonged hypothyroidism may cause worsening of symptoms [7]. At the same time, excessive thyroxine replacement may cause overt symptoms of decreased bone mineral density

and can also predispose patients to cardiac arrhythmias [8–10].

With these concerns, this study was undertaken to identify an optimal method of replacing thyroxine after total thyroidectomy for benign thyroid disorders. The conventional practice has been to replace thyroxine at empirical doses without taking body weight/surface area of the patient in to consideration. We feel that this may not be the optimal method. We have therefore compared two other methods of replacement of thyroxine with the empirical dosing method: the per/kg body weight of the patient (PBM) method and the per/kg LBM method. Because the literature for thyroxine replacement requirement after total thyroidectomy is sparse, we resorted to replacing thyroxine in the PBM group at 1.6 mcg/kg per day, the reported requirement in patients with primary hypothyroidism [2]. Fat cells are metabolically less active than other cells, and therefore may not require thyroxine for metabolic activity. In contrast, muscle tissue is metabolically active and takes part in the uptake of thyroxine for metabolic processes. Kidney and liver, too, utilize thyroxine for metabolism; hence it was thought that fat and bone free mass may be directly correlated with thyroxine requirement. There is only one study suggesting thyroxine replacement according to LBM after total thyroidectomy, that by Ombuwale and Chadwick [11]. These authors suggest that LBM calculated purely on anthropometric measurements may not be an ideal basis for thyroxine replacement. They did not find any correlation between LBM and daily thyroxine requirements and suggested for more accurate measurement methods like body impedance [12, 13]. The only way we could make an objective assessment of LBM was with the help of a Dexa machine; hence, we used this technique for assessment of lean mass. Cunningham and Barzel [14] found that in older subjects with primary hypothyroidism, thyroxine replacement based on per kg LBM is better than depending upon total body weight alone for assessing thyroxine replacement requirements. Banovac et al. [1] suggested thyroxine requirement may be between 2 and 3 mcg/kg of LBM per day in patients with primary hypothyroidism; hence, we chose a median of 2.5 mcg/kg per day replacement in our study.

We had tried to ensure that the patients in all groups adhered to the thyroxine replacement protocols by repeated counseling both at visits and by telephone. Though we kept TSH normalization as the end point of our study we also ensured that patients had normal free T4 levels and no clinical features suggestive of hypo-hyperthyroidism. We adopted a single preparation of thyroxine for patients in all groups to avoid differences in bioavailability of various preparations.

On analysis we found that there was no difference in the number of medical visits required prior to achieving euthyroidism when the LBM group and the EM group were compared. When the PBM group was compared with the EM and PBM groups, however, we found that the number of visits required was significantly high in the PBM group. This difference may be explained in part by the grossly inadequate starting replacement dose of thyroxine in the PBM group, which then required more visits than the other two groups to establish euthyroidism.

We found that the final thyroxine dose required was higher in the EM and PBM groups than in the LBM group, likely because of the statistically significantly higher TSH levels recorded in the LBM group patients. This difference led us to establish a narrower TSH range than we intended initially (0.4–2.5 μIU/l) [15], but we had to abandon this parameter as patient compliance became low because of the increased number of follow-up visits required. From an analysis of the LBM subgroup, we found that the thyroxine requirement was higher at 2.75 mcg/kg of LBM per day when compared with the 2.5 mcg/kg of LBM with which we had started thyroxine replacement in the LBM group.

Once the groups were analyzed separately, we did an analysis for the whole group of 60 patients to determine if there were any other factors influencing the final thyroxine replacement dose. On multivariate analysis the only independent factors found to correlate significantly with the final thyroxine dose requirement were dose per kilogram of body weight and the BSA. We found that the mean per kg body weight requirement of thyroxine is higher in our patients when compared to those reported from the West (2.04 mcg/kg per day vs. 1.69 mcg/kg day) [11]. Weight group analysis revealed a increased requirement of thyroxine with increasing weight and was found to be comparable with data reported in the literature [11] (Fig. 1). Another interesting finding in our study was a strong correlation between thyroxine requirement and BSA, more than the body mass alone. The calculated requirement was 75.2 mcg/m^2 per day. We could find studies with similar results only in the pediatric population [16]. Because body mass index (BMI) is a direct function of height and weight of the patient, it was expected that the final thyroxine dose may be a function of BMI, but in our study we did not find any such correlation. Nor did we find any statistical difference in the thyroxine requirement among various age groups in comparison with reduced thyroxine requirements with advancing age, as reported elsewhere [17].

In conclusion, patients undergoing total thyroidectomy may require higher doses of thyroxine to achieve euthyroidism when compared to patients with similar anthropometric parameters having primary hypothyroidism. The method of replacing thyroxine based on LBM is the ideal, but replacement based on fixed-dose regimens could be a good method if the body weight is taken into consideration.

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