Correction of Hypothyroidism Leads to Change in Lean Body Mass without Altering Insulin Resistance

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Key Words

Body composition · Hypothyroidism · Thyroxine · Lean body mass · Insulin resistance

Abstract

Background: Hypothyroidism is associated with insulin resistance, dyslipidemia, and abnormal body composition. This study assessed changes in body composition and insulin resistance after thyroxine (T₄) replacement in overt hypothyroidism. **Methods:** In this prospective longitudinal study carried out in a tertiary care center, adult nondiabetic patients with overt hypothyroidism were rendered euthyroid on T₄. Anthropometry including skinfold thickness (SFT) at the triceps and subscapularis was recorded. Patients underwent testing for fasting plasma glucose, creatinine, serum insulin, T₄, thyrotropin (TSH) and body composition analysis by dual-energy X-ray absorptiometry (DEXA) both before and at 2 months after restoration to the euthyroid state. **Results:** Twenty-seven patients (20 female and 7 male) aged 35.3 ± 11.0 years (min–max: 17–59 years) with overt hypothyroidism were recruited. Serum T₄ at the time of recruitment was 48.9 ± 24.6 nmol/l (normal range = 64.4–

142 nmol/l). All patients had TSH ≥ 50 μIU/l. Following treatment, there was a mean body weight reduction of 1.7 kg (p = 0.01). Waist circumference as well as triceps and subscapularis SFT decreased significantly (p < 0.001). There was no change in fat mass (FM), percentage of fat (%FM) or bone mineral content in any of the specified regions or in the body as a whole. In contrast, mean lean body mass (LBM) decreased significantly by 0.8 kg (p < 0.01) in the trunk and 1.3 kg (p < 0.01) in the whole body. Insulin resistance and level of glycemia were not affected by treatment with T₄. **Conclusion:** LBM decreases significantly without affecting FM after correction of hypothyroidism. Insulin resistance was not influenced by T₄ treatment.

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Introduction

Hypothyroidism, either subclinical or overt, has been associated with increased risk of coronary artery disease [1–3]. It is also known to be associated with insulin resistance [4] and dyslipidemia [5] characterized by elevated

low-density lipoproteins and triglycerides [5]. Adequate treatment with thyroxine (T_4) is reported to improve both the insulin resistance as well as the dyslipidemia [5, 6]. Abnormal body composition in the form of an increase in the percentage of body fat [7] and truncal distribution of fat has been reported in hypothyroidism in comparison to matched euthyroid controls [8, 9]. Such a body composition is also known to be associated with the metabolic syndrome [10], which in turn is a major risk factor for diabetes mellitus, hypertension, and coronary artery disease [11]. Metabolic syndrome increases the relative risk for cardiovascular disease by 1.65 (95% CI: 1.38–1.99) [11].

It is not known whether all the effects of hypothyroidism on glucose and lipid metabolism are due to a deficiency of T_4 or whether some of these could also be due to the abnormal body composition inherent in hypothyroidism. There is a dearth of studies in the literature that simultaneously assessed changes in glucose metabolism and insulin resistance along with changes in the body composition following the initiation of adequate thyroid replacement in hypothyroidism. We aimed to study the changes in weight and body composition in hypothyroid patients after their restoration to euthyroidism. We also attempted to assess the impact of these changes as well as that of T_4 levels themselves on metabolic parameters that are known to be influenced by weight and body composition, namely, insulin resistance and levels of glycemia.

Materials and Methods

Study Design

The present study was a prospective study conducted in the Department of Endocrinology and Metabolism at the Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India. The study period was from June 2013 to December 2014. Patients with overt hypothyroidism (thyrotropin, TSH, >50 mIU/l and T_4 , <64.4 nmol/l) were recruited. Those with diabetes mellitus or chronic kidney disease (glomerular filtration rate <60 ml/min/1.73 m²) were excluded. Written informed consent was obtained from all study participants. The study was approved by the institutional Ethics Committee.

Clinical Evaluation

The patients were weighed on a beam balance, while height was measured on a stadiometer with the head in the Frankfurt plain. Body mass index (BMI) was calculated using the formula: BMI = weight (kg)/[height (m)]². Waist circumference (WC) was measured in an erect posture, at the end of expiration, by a measuring tape just above the iliac crest. Skinfold thickness (SFT) was measured at the triceps and subscapularis areas by a Harpenden skinfold caliper; model CE 0120 (Baty International Ltd., Burgess

Hill, UK). Triceps SFT was taken on a vertical fold on the posterior midline of the upper arm, over the triceps muscle, halfway between the acromion process and the olecranon process after extending the elbow and relaxing the arm. Subscapular SFT was likewise measured on a vertical fold 1–2 cm below the inferior angle of the scapula. The average of three consecutive readings was taken.

Dual-energy X-ray absorptiometry (DEXA) was performed using a QDR X-Ray bone densitometer (Hologic Inc., Bedford, Mass., USA). Fat mass (FM), fat percentage (%FM), bone mineral content (BMC), lean body mass (LBM) and total mass were obtained using software that was developed using the ICE 60601-1-4 system. Data were reported separately for each upper limb, each lower limb, the trunk, head, subtotal (whole body minus the head), and whole body.

Blood samples of the enrolled patients were obtained in the morning between 08:00 and 09:00 h after an overnight fast for the estimation of plasma glucose, T_4 , TSH, creatinine, and serum insulin levels. Insulin resistance was estimated by homeostasis model assessment [12] using the formula:

$$\text{HOMA-IR} = \frac{\text{fasting insulin (mIU/l)} \times \text{fasting glucose (mmol/l)}}{22.5}$$

Patients were then started on T_4 supplements. The dose of the drug was increased periodically (every 4–6 weeks) stepwise based on TSH estimations until the patients were rendered euthyroid, that is, had TSH between 0.5 and 5 mIU/l. Once the patients had been restored to the euthyroid state, they were allowed to continue the same dose of T_4 and recalled after 2 months. After 2 months of initial documentation of euthyroidism, anthropometric measurements, body composition analysis by DEXA, and fasting biochemistry were repeated as before. T_4 , TSH, and insulin were measured by the chemiluminescence method on the Beckman Coulter Access immunoassay system (Beckman Coulter Ireland, Inc., Galway, Ireland). The minimum and maximum detectable limits for serum T_4 were 0.6 and 167.3 nmol/l, respectively. The normal range of T_4 for this assay in a healthy population is 64.4–142 nmol/l. The upper and lower detection limits for serum TSH were 0.01 and 100 mIU/l, respectively, while the expected values in a normal healthy population are 0.34–5.6 μ U/ml. The minimum and maximum detection limits for serum insulin ranged from 0.03 to 300 mIU/l (expected values in a normal healthy population range from 1.9 to 23.0 μ U/ml). Plasma glucose and creatinine were measured on a Beckman Synchron CX5 autoanalyser (Beckman Coulter, Brea, Calif., USA) using compatible commercially available kits.

Statistical Analysis

Data were recorded on a predesigned proforma and managed using Microsoft Excel 2007 (Microsoft Corp., Redmond, Wash., USA). All the entries were double checked for any possible error. Means and standard deviations of anthropometric parameters (height, weight, BMI, WC, SFT), fasting plasma glucose (FPG), fasting insulin, HOMA-IR (relative insulin resistance by homeostatic model assessment), and body composition analysis were calculated at baseline and at 2 months after the restoration of euthyroidism. A comparison of means between two points in time was done by the paired t test. A p value <0.05 was taken as significant. Correlation studies between baseline T_4 and various parameters

like weight, insulin resistance, and body composition were performed by calculating the Pearson coefficient of correlation. Statistical software SPSS version 15 (SSPS Inc., Chicago, Ill., USA) was used for statistical analysis.

Results

A total of 35 consecutive patients with confirmed overt hypothyroidism were recruited for the study over a period of 1.5 years. One of the patients conceived and had to be excluded to avoid unnecessary radiation exposure to the fetus, 1 patient was excluded due to a technical difficulty in the performance of DEXA body composition assessment, while 3 patients did not become euthyroid even at their consecutive follow-up visits; 3 other patients were lost to follow-up. The remaining 27 patients had completed 2 months of follow-up after achieving the euthyroid state on T_4 treatment and were available for repeat evaluation. None of the patients had undergone thyroid surgery; 1 patient out of 27 had received radioactive iodine ablation as ablative therapy for Graves approximately 4 months previously. The remaining 26 patients had spontaneously developing hypothyroidism.

Baseline Clinical Features

The mean age of the patients ($n = 27$) was 35.3 ± 11.0 years (min–max: 17–59 years); 20 patients (74.1%) were female and 7 (25.9%) were male, giving a female/male ratio of 3.5:1. Serum T_4 at the time of recruitment was 48.9 ± 24.6 nmol/l (normal range = 64.4–142 nmol/l). All patients had TSH ≥ 50 mIU/l (normal range = 0.5–5 mIU/l). Baseline FPG, insulin, %FM, and the truncal FM/total FM ratio did not correlate with T_4 .

Changes in Body Composition after T_4 Replacement Therapy

The patients were reevaluated 2 months after restoration to the euthyroid state. The mean duration for restoration to the euthyroid state after the initiation of T_4 was 3.5 ± 1.3 months. Serum levels of T_4 and TSH were normalized after treatment to 145.4 ± 37.3 nmol/l and 2.0 ± 1.9 mIU/l, respectively. The recorded changes in various anthropometric parameters following correction of T_4 and TSH are given in table 1. There was a significant loss of weight ($p = 0.01$). The reduction in mean body weight was 1.7 kg and that in mean BMI was 0.7. WC as well as triceps and subscapularis SFT decreased ($p < 0.001$) after the achievement of euthyroid state.

The total body weight obtained by the summation of total body lean mass, FM, and BMC as reported on DEXA at baseline was 59.2 ± 16.3 kg, and this fell to 57.8 ± 15.9 kg after treatment ($p = 0.01$). There was an excellent correlation ($r = 0.995$, $p = 0.01$) between weight at baseline obtained by direct weighing (gravimetric weight) and that obtained by the above calculation based on the summation of DEXA compartmentalized measurements.

FM did not change significantly in absolute terms (kilograms) in the whole body or in any specified region ($p > 0.05$). There were no changes in the %FM or in the BMC in any of the specified regions or in the body as a whole. However, the truncal FM/total FM ratio was significantly reduced from 0.42 ± 0.07 at baseline to 0.41 ± 0.07 after treatment ($p = 0.03$).

In contrast to the above, there was significant decrease in LBM overall as well in all the regions measured except in the head region (table 1). There was a decrease of mean LBM by 0.8 kg and 1.3 kg ($p < 0.01$) in the trunk and whole body, respectively. There was no change in FPG, serum insulin, or insulin resistance after treatment (table 1).

Changes in body weight and BMI after correction of hypothyroidism correlated negatively with changes in serum T_4 on treatment ($r = -0.456$, $p = 0.02$ and $r = -0.441$, $p = 0.02$, respectively). However, changes in WC and SFT (both at the subscapularis and triceps) did not show any correlation with the changes in the T_4 levels after treatment. Likewise, changes in LBM after treatment showed a significant negative correlation with changes in T_4 ($r = -0.447$, $p = 0.02$). The changes in truncal FM/total FM ratio, FM, and %FM did not show any correlation with changes in T_4 .

Discussion

At baseline, our study showed no correlation of T_4 with FPG, insulin, or insulin resistance (HOMA-IR). A loss of approximately 1.7 kg body weight was noted from baseline following correction of hypothyroidism ($p = 0.012$). Further, the changes in body weight and BMI correlated negatively with changes in the serum T_4 after treatment. This was in accordance with other studies, all of which consistently showed a similar decrease in body weight after correction of hypothyroid status. There was a mean decrease in body weight of 2.8 and 4.3 kg in studies done by Sanchez et al. [13] and Karmisholt et al. [14], respectively. In another study by Cerit et al. [15], the mean body weight fell by 1.2 kg in 28 hypothyroid patients after thyroid hormone replacement. Stangierski et

Table 1. Changes in anthropometric indices, LBM, and insulin resistance after T₄ therapy

Parameter	Before	After	p value
Gravimetric weight, kg	57.7±16.7	56.0±16.0	0.012
BMI	23.0±5.4	22.3±5.1	0.018
WC, cm	80.9±12.5	77.0±11.9	<0.001
Subscapularis SFT, mm	13.6±4.4	12.1±4.2	<0.001
Triceps SFT, mm	14.6±4.5	12.8±4.0	<0.001
Arms LBM, kg	4.5±1.7	4.3±1.6	0.002
Trunk LBM, kg	19.2±5.7	18.0±5.4	0.008
Legs LBM, kg	13.1±3.7	12.6±3.5	0.038
Subtotal LBM, kg	36.4±11.2	35.2±10.4	0.009
Whole body LBM, kg	39.2±11.6	37.9±10.8	0.008
Truncal/total FM ratio	0.42±0.01	0.41±0.01	0.03
FPG, mmol/l	4.6±0.4	4.9±0.5	0.07
Insulin, mIU/l	6.0±4.3	6.6±4.6	0.52
HOMA-IR	1.3±0.9	1.4±1.0	0.43

HOMA-IR = Relative insulin resistance by homeostatic model assessment.

al. [16] observed a reduction in median body mass from 72.35 to 69.3 kg following the treatment of hypothyroidism ($p < 0.0005$).

Likewise, reductions in WC and triceps and subscapularis SFT were noted in our study. However, these changes did not correlate with the changes in serum T₄ after treatment. The changes in WC and SFT in our study were also observed in other studies by Razvi et al. [17] in subclinical hypothyroidism and Wu et al. [18] in overt hypothyroidism, respectively. While reduced SFT in triceps and scapular areas normally represents a reduction in subcutaneous fat, however, in a situation of increased hyaluronic acid and other glycosaminoglycans in myxedema (which are hygroscopic and which tend to get reabsorbed after treatment, thereby releasing the water held), it would be premature to attribute these anthropometric changes to reduced subcutaneous adiposity. This only shows the fallacies of clinical anthropometry in conditions like hypothyroidism.

In our study, FM changed neither in the whole body nor in any part with T₄ treatment. The unaltered FM was in accordance with the studies done by Karmisholt et al. [14], Sanchez et al. [13], and Cerit et al. [15], where the population studied was similar to that in our study, namely, newly diagnosed primary hypothyroidism. In contrast to our finding, Wolf et al. [7] observed a decrease in FM (−0.95 kg) in their study. However, this study involved the treatment of relatively short-term hypothyroidism induced by the withdrawal of thyroid hormone replacement in thyroidectomized patients. In these circumstanc-

es the body composition responses to T₄ treatment may not be the same as seen in our study. A reduction in FM on treatment of hypothyroidism was also observed by Stangierski et al. [16]. However, they used a whole body bioimpedance analyzer for body composition analysis, whereas we used DEXA, which is generally considered to be more accurate.

We observed no change in the %FM either in the whole body or in any part thereof after the treatment of hypothyroidism. Wu et al. [18] also found no significant change in %FM after the treatment of short-duration hypothyroidism. Sanchez et al. [13], however, observed a rise in %FM in their study of hypothyroid patients from 45.2 ± 9.2 to $48.9 \pm 8.6\%$ 2 months after the restoration to the euthyroid state. This increase in %FM was possibly a consequence of a reduction in LBM without any change in FM, findings that are very similar to those in our study. It may be that the reduction in LBM in our study, though similar to that in Sanchez et al. [13], may not have been enough to raise the %FM appreciably.

Though neither the total FM nor the total %FM changed, there was a very minor, albeit significant, reduction in the truncal FM/total FM ratio from 0.42 ± 0.064 at baseline to 0.41 ± 0.064 after treatment ($p = 0.037$). Thus, T₄ may have some role in influencing the distribution of fat in the body, with low T₄ being associated with truncal adiposity.

While the FM, %FM, and total BMC remained unaltered, the LBM decreased significantly in our study in almost all areas except the head. There was a decrease in the mean LBM by 1.3 kg from 39.2 ± 11.6 to 37.9 ± 10.8 ($p =$

0.008), which accounts for the majority of the reduction in the body weight. Changes in FM and %FM after restoration to the euthyroid state did not correlate with the changes in T_4 . However, changes in LBM showed a negative correlation ($r = -0.50$; $p = 0.006$) with the changes in T_4 levels. Both Sanchez et al. [13] and Karmisholt et al. [14] as well as Cerit et al. [15] observed that the reduction in body weight in their patients resulted only from reductions in the LBM, without any change in the FM. The above observation is thus consistent across studies.

The measurement of LBM by DEXA is mainly dependent on the assumption of a constant hydration of lean tissue. Thus fluid retention may lead to its overestimation [19, 20]. Ultrastructural studies have shown a decrease in type I mean fiber area after treatment of hypothyroidism [21]. This, along with loss of fluid and glycosaminoglycans (myxedema), is probably the anatomical basis of the decrease in lean mass after the achievement of euthyroidism that was observed in our study and as documented by others previously.

BMC showed no significant change after treatment with T_4 in our study. Bone mass was also unchanged after thyroid replacement to hypothyroid patients in studies by Karmisholt et al. [14] and Sanchez et al. [13]. There is evidence that T_4 is catabolic to the bone [22]. A recent meta-analysis of studies on TSH suppressive therapy, which evaluated 41 controlled cross-sectional studies involving 1,250 patients, confirms this conclusion [22]. Suppressive therapy is associated with a decrease in bone mineral density in the lumbar spine, the hip, and all other sites in postmenopausal (but not in premenopausal) women [22]. The same meta-analysis showed that long-term T_4 replacement therapy causes bone loss at the hip and spine in premenopausal (but not in postmenopausal) women [22]. It is indeed reassuring to observe that appropriate thyroid hormone replacement to hypothyroid patients, maintaining the TSH in the normal range, was not deleterious to the bone – at least in the short term. Our study did not involve a significant number of postmenopausal women; hence it would not be possible to comment on effects of T_4 replacement on BMC in this population.

Following restoration to the euthyroid state, the plasma glucose values, insulin, and HOMA-IR remained unaltered (table 1), despite a significant reduction in the mean weight by 1.7 kg ($p = 0.012$). These findings are similar to those observed by Handisurya et al. [23], Kim et al. [24], and Anantarapu et al. [25], who showed that there were no changes observed in plasma glucose following the correction of hypothyroidism. No difference was observed between fasting glucose and insulin between hy-

pothyroid patients with autoimmune thyroid disease ($n = 12$) and euthyroid participants ($n = 12$) in the study by Zybek-Kocik et al. [26]. This could be because the overall balance of glucose homeostasis is maintained in hypothyroidism due to various contrasting effects of T_4 on glucose metabolism. Hypothyroidism is associated with a reduction in the disposition of glucose to skeletal muscle and adipose tissue [27, 28]. At the same time hypothyroidism is also associated with reduced gluconeogenesis as well as reduced degradation of insulin. The net effect of these mutually nullifying influences is that there is no discernable effect of hypothyroidism on serum glucose levels. Moreover, while insulin resistance is mainly related to FM and %FM in the body, in most studies including ours, though the body weight and BMI decreased significantly after treatment, there was no change in the FM or %FM. Hence, the indices of HOMA-IR also were found to be unchanged after the restoration of euthyroid status.

Strengths and Limitations

We enrolled newly diagnosed patients with overt hypothyroidism so that any effects of T_4 replacement would be more easily observed. Indeed, all our patients had baseline TSH >50 mIU/l, suggestive of overt hypothyroidism. Only nondiabetic patients were included to minimize the confounding effects of any medication or lifestyle modifications that would have to be instituted for the management of diabetes. Patients were evaluated before and at 2 months after the restoration of euthyroid state. The reason for choosing 2 months was to allow sufficient time for changes to take place in the body composition.

The main limitation of the study was the small numbers recruited and the limited duration of follow-up. This may have limited the power to detect slight changes in insulin sensitivity and glycemia, whereas the changes in body composition were readily detected. However, similar results were observed by other authors as well [23–25].

Treatment of hypothyroidism results in a significant reduction in weight, WC, and SFT. A reduction in LBM was responsible for much of the weight lost. Total body FM, total %FM, and total BMC remained unaltered. However, thyroid replacement may result in a more favorable redistribution of fat from the truncal to peripheral areas.

Contrary to expectations, the weight loss and the observed changes in body composition after thyroid hormone replacement therapy as well as the normalization of the serum T_4 levels were not observed to have any effect on insulin sensitivity or on fasting glycemia.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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