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Treatment of severe thyroid function disorders and changes in body composition

Zmiany w składzie tkankowym obserwowane w trakcie terapii ciężkich zaburzeń funkcji tarczycy

Adam Stangierski[1], Marek Ruchała[1], Tomasz Krauze[2], Jerzy Moczko[3], Przemysław Guzik[2]

[1]*Department of Endocrinology, Metabolism, and Internal Medicine, Poznan University of Medical Sciences*
[2]*Department of Cardiology Intensive Care Therapy and Internal Medicine, Poznan University of Medical Sciences*
[3]*Department of Computer Science and Statistics, Poznan University of Medical Sciences*

Abstract

Introduction: Hyper- and hypothyroidism are accompanied by altered metabolic rate, thermogenesis, and body weight. The aim of this study was to estimate the relation between treatment-induced changes in thyroid function, and the accompanying body composition in patients with either severe hypo- or hyperthyroidism.

Material and methods: Body composition analysis and hormonal assessment were measured at the initial diagnosis of thyroid disorder, after three-month treatment, and finally after complete recovery from hyperthyroidism (n = 18) or hypothyroidism (n = 27). Nonparametric Spearman correlation was used to analyse the relation between thyroid hormones and body composition as well as their respective changes.

Results: In hypothyroid patients applied treatment significantly reduced ($p < 0.05$) total body weight, mainly due to a decrease in fat mass, whereas in hyperthyroid patients it caused a weight gain, with a simultaneous increase in muscle, water and fat mass. Total body weight and fat mass were significantly correlated with thyroid hormones' concentrations in all patients. Changes of fat, water, or muscle mass were strongly correlated with the changes in the patients' hormonal status.

Conclusions: Body composition is related to the concentration of thyroid hormones in thyroid dysfunction. Treatment-induced changes in thyroid hormones concentrations are correlated with the magnitude of the change of body weight, including muscle, water, and fat amount. **(Endokrynol Pol 2016; 67 (4): 359–366)**

Key words: *body composition; hyperthyroidism; hypothyroidism; body mass*

Streszczenie

Wstęp: Zarówno nadczynność, jak i niedoczynność tarczycy charakteryzują się zaburzeniami podstawowej przemiany materii, termogenezy oraz masy ciała. Celem pracy była ocena związku między zmianami funkcji tarczycy oraz zmianami składu tkankowego ciała u pacjentów w trakcie terapii ciężkich zaburzeń funkcji tarczycy.

Materiał i metody: Badanie składu ciała oraz badanie biochemicznych wykładników funkcji tarczycy przeprowadzono u 18 chorych z pełnoobjawową nadczynnością tarczycy oraz u 27 chorych z niedoczynnością tarczycy, w okresie rozpoznania choroby, po około trzech miesiącach leczenia oraz po całkowitym wyrównaniu funkcji tarczycy, w okresie eutyreozy. Ponadto przeprowadzono analizę związku między zmianami funkcji tarczycy oraz zmianami w składzie ciała przeprowadzono nieparametryczną analizę Spearmana.

Wyniki: W grupie chorych leczonych z powodu niedoczynności tarczycy zaobserwowano statystycznie istotny spadek masy, głównie kosztem masy tkanki tłuszczowej ($p < 0,05$), podczas gdy w grupie chorych z pierwotnie rozpoznaną nadczynnością tarczycy stwierdzono istotny wzrost masy tkanki tłuszczowej, mięśniowej oraz wody całkowitej ($p < 0,05$). W obu grupach zaobserwowano ponadto istotne korelacje między stężeniem hormonów tarczycy a masą tkanki tłuszczowej na wszystkich etapach leczenia ($p < 0,05$). Jednocześnie zmiany wszystkich parametrów składu tkankowego ciała (Δ) silnie korelowały ze zmianami biochemicznych wykładników funkcji tarczycy(Δ) ($p < 0,05$).

Wnioski: W zaburzeniach funkcji tarczycy obserwuje się silne zależności między składem tkankowym ciała a stężeniem hormonów tarczycy. Zmiany w składzie tkankowym ciała są jednocześnie silnie skorelowane ze zmianami stężenia hormonów tarczycy obserwowanymi w trakcie terapii. **(Endokrynol Pol 2016; 67 (4): 359–366)**

Słowa kluczowe: *skład tkankowy ciała; nadczynność tarczycy; niedoczynność tarczycy; masa ciała*

Introduction

Thyroid hormones regulate the metabolism of the whole human body — triiodothyronine (T3) is necessary to maintain the energy requirements of various cells and tissues, to balance their anabolism and catabolism, and regulate body weight [1–4]. An abnormal amount of T3 disturbs a number of metabolic processes [2]: shortage of T3 in hypothyroidism reduces basic metabolic rate and thermogenesis, inhibits catabolism and gains total body weight [5]; excess of T3 in hyperthyroidism reverses these processes [6].

Marek Ruchała M.D., Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland, e-mail: mruchala@ump.edu.pl

Specific therapy of hypo- [7, 8] and hyperthyroidism [9–11] restores proper body mass. Only a few studies have evaluated changes in body composition, *i.e.* muscle, water, and fat masses induced by thyroid diseases. It appears, however, that the relation between body composition and thyroid hormones, and particularly their respective treatment-induced changes, has not been studied so far. We hypothesise that: 1) body composition is related to the current status of thyroid hormones, and 2) the change in body composition is strictly related to the change of thyroid hormones concentration caused by specific treatment of hypo- and hyperthyroidism.

The aim of this study was to:
— estimate body muscle, water, and fat mass in patients with hypo-and hyperthyroidism before and during the therapy of thyroid diseases, and after restoring euthyroidism;
— analyse the relation between the concentration of free-triiodothyronine (fT3), thyroxine (fT4), and thyroid stimulating hormone (TSH), and different components of body mass;
— investigate the association between the changes in T3, T4, and TSH, and the changes in the muscle, water, and fat mass at different stages of the therapy of thyroid diseases.

Material and methods

This observational pilot study included 70 consecutive adult patients from our outpatient clinic with an initial diagnosis of a naïve hypo- or hyperthyroid disorder. The Poznan University of Medical Sciences Ethical Committee in Poznan, Poland approved the study protocol (nr of declaration 161/11; 2011-Feb-11). All patients provided their informed written consent for participation before entering the study. Only the most contemporary guideline-based therapy of thyroid diseases according to the recommendations of the American Thyroid Association (ATA*)* was applied. No experimental treatment was allowed.

The main inclusion criteria were based on the current recommendations of the ATA [12–14], *i.e.* the presence of symptoms characteristic for thyroid function disease:
— a newly diagnosed hypothyroidism with free T3 (fT3) < 3.95 pmol/L, free T4 (fT4) <11pmol/L and TSH > 4.5 μU/mL) or
— hyperthyroidism with fT3 > 6.80 pmol/L, fT4 > 21.5 pmol/L and TSH < 0.27 μU/mL.

Additional requirements were:
— completing all visits during the follow-up;
— a restoration of euthyreosis no later than during the third follow-up visit. The following patients were excluded from the study:

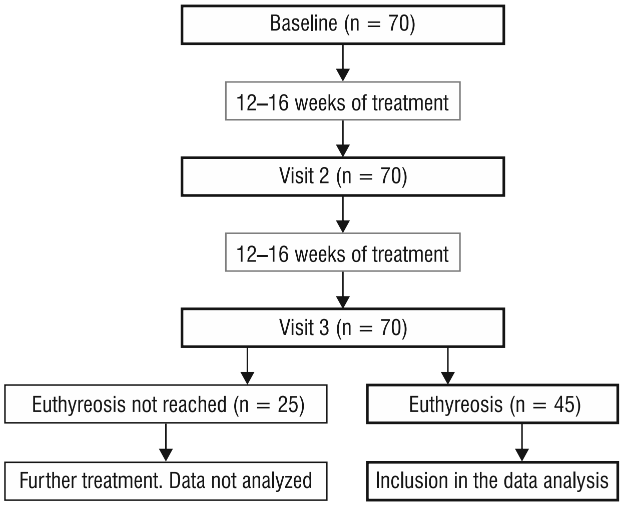

Figure 1. *Study protocol and flow*
Rycina 1. *Protokół i przebieg badania*

— those with any chronic condition requiring additional pharmacological treatment potentially altering body composition (*e.g.* diuretics, beta-blockers, hypoglycaemic agents, or steroids);
— those with thyroid cancer;
— those with any inflammation potentially affecting body composition (based on the clinical evaluation and measurement of C-reactive protein [CRP] concentration).

Study protocol and flow

The study protocol involved hormonal assessment and body composition analysis at the initial visit before the onset of therapy (Visit 1), after 12–16 weeks (Visit 2), and 24–32 weeks (Visit 3), when the euthyroidism was anticipated. Study protocol and flow are presented in Figure 1.

Body composition analysis

A detailed body composition analysis was performed with the use of a total body bioimpedance analyser Tanita MC 180 MA II (Tanita, Japan) for the measurement of total body weight, as well as the estimation of mass of muscles, water, and fat. All body composition measurements were made at each study stage.

Biochemical analysis

A sample of 10 mL of venous blood was collected from fasting patients in the morning hours during each visit. All patients were asked to refrain from smoking and drinking tea or coffee for at least 12 hours, and from drinking any alcohol for at least 24 hours before blood sampling. The concentrations of TSH, fT3, and fT4 were assessed with the use of the

Table I. ***Results of hormonal assessment in patients with hyperthyroidism during the whole study***
Tabela I. ***Wyniki badań hormonalnych u pacjentów leczonych z powodu nadczynności tarczycy***

	Visit 1		Visit 2		Visit 3	
	Median	25th–75th percentile	Median	25th–75th percentile	Median	25th–75th percentile
TSH (normal values: 0.28–4.4) [μIU/mL]	0.01	0.01–0.01	0.09*	0.01–17.1	2.6*	1–4.2
fT3 (normal values: 3.95–6.8) [pmol/L]	24.4	19.1–29.2	5.8*	3.9- 8.5	4.7*	4.3–5.7
fT4 (normal values: 11–21.5) [pmol/L]	50.1	39.9–90	9.6*	6.6–20.6	16.1*	13.4–17.4

*p < 0.005 for all comparisons between Visit 2 *vs.* Visit 1 or Visit 3 *vs.* Visit 1 for all hormones

electrochemiluminescence method (Hitachi COBAS e 600, Japan). CRP determination was performed with immunoturbidimetry (Roche Diagnostics, Mannheim, Germany)

Statistical analysis

Finally, 45 patients, *i.e.* 18 patients with hyperthyroidism and 27 with hypothyroidism, were included in the analysis. The Shapiro-Wilk test showed that the majority of continuous data presented non-normal distribution. Therefore, all data are described as median and the 25th and 75th percentile — the interquartile range (IQR). Only results for Visit 2 and 3 were compared with the results of Visit 1 with the nonparametric Wilcoxon test for paired data. For the comparison between patients with hyperthyroid and hypothyroid disease the nonparametric Mann-Whitney test was applied. The nonparametric Spearman rank test was used to analyse the correlations: (1) between the concentrations of fT3, fT4, and TSH with components of body mass for pooled data (total n = 135 — 3 visits times 45 patients); and (2) between the changes in hormone concentrations and body composition measured between Visit 1 and 2 (n = 45), and Visit 2 and 3 (another n = 45) for pooled data (total n = 90); $p < 0.05$ was considered statistically significant. Statistical analyses were made with the use of Medcalc softwere (version 13.0.4.0) (Medcalc, Belgium).

Results

Preliminary, there were six male and 22 female patients with hyperthyroid disease, with a median age of 36.5 years (25th–75th percentile: 31–53 years) with an initial diagnosis of Graves disease or toxic nodular goitre. Methimazole (Thyrozol; Merck, Germany) in a dose of 60–80 mg/daily was initially induced during the first visit and, based on clinical hormonal evaluation, this dose was gradually and individually titrated for each patient during control Visit 2. There were also 9 male and 33 female patients with hypothyroid disease with a median age of 45 years (25th–75th percentile: 31–75 years old) with chronic and advanced autoimmune thyroiditis (Hashimoto disease) or individuals with post-ablative 131-iodine induced hypothyroidism. During the initial visit, treatment with levothyroxine (LT4) (1.5–2 μg/kg) was started. Depending on the clinical state and hormonal assessment during Visit 2, the initial dose of LT4 was adequately modified.

The concentration of CRP was 1.9 mg/L (25th–75th percentile: 1.1–2.9 mg/L) in hyperthyroid patients and 1.4 mg/L (25th–75th percentile: 0.0–2.4 mg/L) in hypothyroid individuals at the time of Visit 1.

Euthyroidism was confirmed during the third visit (V3) in 18 patients with hyperthyroidism and in 27 patients with hypothyroidism.

Effects of therapy on hormonal status and body composition

Hyperthyroid group

TSH concentration was significantly lower during Visit 1 than during Visit 2 and 3 ($p < 0.005$ for all comparisons). The concentrations of fT3 and fT4 were significantly higher during Visit 1 than during Visit 2 and 3 ($p < 0.005$ for all comparisons) (Table I).

Total body mass and fat mass significantly increased after the early phase of treatment, while muscle mass and total body water were higher compared to the baseline values after euthyroidism was restored (Table II).

Hypothyroidism group

TSH concentration was significantly higher during Visit 1 than during Visit 2 and 3 ($p < 0.0001$ for all comparisons). The concentrations of fT3 and fT4 were significantly lower during Visit 1 than during Visit 2 and 3 ($p < 0.0001$ for all comparisons) (Table III).

Total body mass and fat mass significantly decreased after the early phase of treatment. There was no significant change in the muscle mass and total body water during the treatment (Table IV).

Analysis of hormonal profiles revealed that patients with hyperthyroid disease, in comparison with hypothyroid individuals, had significantly lower concentrations of TSH at Visit 1 ($p < 0.0001$) and 2 ($p = 0.026$), and signifi-

Table II. *Changes in body composition during treatment of hyperthyroidism*
Tabela II. *Zmiany w składzie tkankowym ciała w trakcie terapii nadczynności tarczycy*

	Visit 1		Visit 2		Visit 3	
	Median	25th–75th percentile	Median	25th–75th percentile	Median	25th–75th percentile
Total body mass [kg]	61.6	56.7–77.7	65.9*	58.1–79	65.2	59.4–83.5
Body fat mass [kg]	13.4	9.1–18.6	15.3*	10.2–21.2	16.7	10.9–24.6
Muscle mass [kg]	44.1	41.2–52.9	44.7	42.7–54.2	46.2***	43–55.2
Total body water [kg]	33.1	31.1–40.6	33.9	31.9–40.9	34.7***	32.5–42.1

*p < 0.0005 Visit 2 *vs.* Visit 1; **p < 0.005 Visit 2 *vs.* Visit 1; ***p < 0.05 Visit 3 *vs.* Visit 1

Table III. *Results of hormonal assessment in patients with hypothyroidism*
Tabela III. *Wyniki badań hormonalnych u pacjentów leczonych z powodu niedoczynności tarczycy*

	Visit 1		Visit 2		Visit 3	
	Median	25th–75th percentile	Median	25th–75th percentile	Median	25th–75th percentile
TSH [μIU/mL]	100	60.6–100	9.6*	2.7–17.9	1.8*	0.6–3.5
fT3 [pmol/L]	2.4	1.8–3	4.5*	3.8–5.5	4.7*	4.2–5.4
fT4 [pmol/L]	3.9	3.2–6.2	16.9*	12.6–19.2	19.5*	16.5–21.2

*p < 0.0001 for all comparisons between Visit 2 *vs.* Visit 1 or Visit 3 *vs.* Visit 1 for all hormones

Table IV. *Changes in body composition observed during treatment of hypothyroidism*
Tabela IV. *Zmiany w składzie tkankowym ciała w trakcie terapii niedoczynności tarczycy*

	Visit 1		Visit 2		Visit 3	
	Median	25th–75th percentile	Median	25th–75th percentile	Median	25th–75th percentile
Total body mass [kg]	72.35	62.7–87.5	69.3*	60.4–85.6	68.9	60.5–83.7
Body fat mass [kg]	21.5	16.1–25.4	19.15*	14.7–24.1	20	15.7–25.7
Muscle mass [kg]	47.6	42.8–58.1	46.2	43.2–57.1	47.2	42.7–56.1
Total body water [kg]	35.3	31.4–44.1	34.4	31.7–43,1	35.2	31.5–43

*p < 0.0005 Visit 2 *vs.* Visit 1;**p < 0.005 Visit 2 *vs.* Visit 1

cantly higher concentration of fT3 at Visit 1 (p < 0.0001), and fT4 at Visit 1 (p < 0.0001). However, after reaching euthyroidism (Visit 3), hyperthyroid patients had significantly lower fT4 concentration (p = 0.003).

Hyperthyroid patients had significantly lower body weight (p = 0.0426) and fat mass (0.0132) than hypothyroid patients at Visit 1 before the treatment was started (Table II and IV). No significant differences were observed for the mass of muscles and total body water at this time. During Visit 2 and 3 there were no significant differences in the total body weight and masses of any analysed body compartments.

Correlations between hormone concentration and body composition

At each stage of treatment, whole body weight and masses of particular body compartments were correlated with corresponding values of TSH, fT3, and fT4 concentrations for pooled data of all patients and all measurements (total 135 pairs of different correlations).

TSH was significantly and positively correlated with body weight and fat mass but not with muscle mass and total body water. Both fT3 and fT4 were significantly and negatively correlated only with body weight and fat mass but not with muscle mass and total body water (Table V).

Correlations between changes in hormone concentration and body composition

Changes in fT3, fT4, and TSH were significantly correlated with changes in the body weight and all of its analysed contributions, *i.e.* fat, muscle, and body water mass. Changes in both fT3 and fT4 were negatively correlated with changes in body weight and fat, muscle, and water masses. Changes in TSH were positively correlated

Table V. *Correlations between the concentration of TSH and thyroid hormones, and body weight and masses of particular body compartments (pooled data, n = 135)*

Tabela V. *Korelacje między stężeniem TSH i hormonów tarczycy a masą poszczególnych tkanek (dane zbiorcze, n = 135)*

	fT3		fT4		TSH	
	rho	P value	rho	P value	rho	P value
Body weight	–0.17	*0.05*	–0.18	*0.03*	0.26	*0.0021*
Fat mass	–0.29	*0.0007*	–0.27	*0.0018*	0.34	*0.0001*
Muscle mass	–0.04	n.s.	–0.07	n.s.	0.13	n.s.
Total body water mass	–0.01	*n.s.*	–0.06	*n.s.*	0.11	*n.s.*

Table VI. *Correlations between the changes in body composition and changes in thyroid status (pooled data, n = 90)*

Tabela VI. *Korelacje między zmianami w składzie tkankowym organizmu a zmianami biochemicznych wykładników funkcji tarczycy (dane zbiorcze n = 90)*

	∆fT3		∆fT4		∆TSH	
	rho	P value	rho	P value	rho	P value
∆body weight	–0.67	*< 0.0001*	–0.73	*< 0.0001*	0.76	*< 0.0001*
∆fat mass	–0.54	*< 0.0001*	–0.61	*< 0.0001*	0.63	*< 0.0001*
∆muscle mass	–0.4	*0.0001*	–0.41	*0.0001*	0.48	*< 0.0001*
∆total body water mass	–0.37	0.0012	–0.35	0.0008	0.4	0.0001

∆ — change

with changes in body weight and fat, muscle, and water masses. The strongest correlations were observed for the relation of changes in hormonal concentrations and body weight or fat mass, whereas the weakest was with the total water mass (Table VI, Figure 2).

Discussion

In this study we found that in patients with hyperthyroid disease, the applied treatment caused a significant increase in total body weight as well as the masses of fat, muscles, and body water. In subjects with hypothyroid disease, the treatment significantly reduced total body weight and body fat mass but showed no influence on muscle and body water mass. Furthermore, patients with hyperthyroid disease had significantly lower body weight and fat mass than individuals with hypothyroid disease, but only before an appropriate treatment had been started. During the treatment and when euthyroidism was obtained, there were no statistical differences in body weight and the masses of muscles, fat, and water between both studied groups. The novelty of this study is the analysis of the link between concentration of fT3, fT4, and TSH and body composition as well as between the changes in the hormonal concentrations and the changes of body composition. In more detail, there were significant correlations between thyroid hormonal profile and body weight and fat mass, but not with muscle or body water mass. However, the changes in body weight and all analysed body compartments, *i.e.* fat, muscle, and water mass, were all significantly correlated with the changes in fT3, fT4, and TSH observed during the treatment. For these associations, changes in hormones were most strongly related to the changes in total body weight and fat mass.

Most previous studies on this topic compared body composition between patients with thyroid function disorders and healthy individuals [15–17], which does not allow avoidance of the individual metabolic differences between the subjects, thusly blinding the results. In contrast, we compared body composition and its change within the same patients, at different stages of thyroid disease: in severe thyroid dysfunction, during treatment, and after restoring euthyroidism. Few similar studies in hyperthyroid patients showed an increase of total body weight after 3–24 months of treatment [6, 9–11, 18–20], but no details on body compartments such as fat, muscle, or water mass were assessed. Few other studies in hypothyroid patients revealed either a loss or no significant change of total body mass during the LT4 replacement therapy [7–9].

It is unknown whether the weight loss in overt hyperthyroidism results from decrease in body fat or muscle mass. Greenlund et al. [16] and Brunova et al.

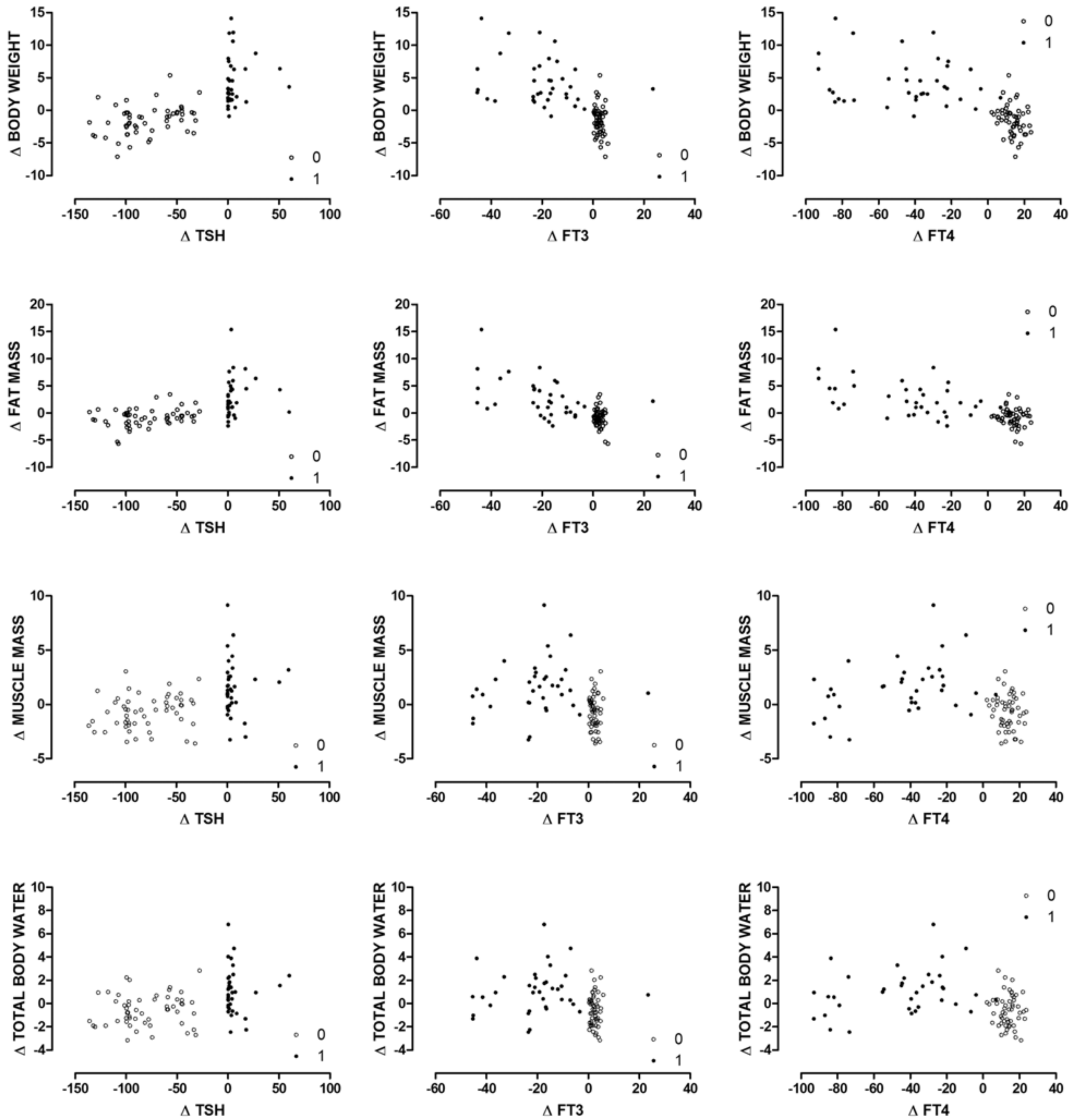

Figure 2. *Correlations between changes in hormone concentration and changes in body weight, fat mass, muscle mass, and total body water in all analysed groups of patients. Pooled data (n = 90) (0 — hyperthyroid group, 1 — hypothyroid group)*

Rycina 2. *Korelacje między zmianami w składzie tkankowym ciała a stężeniem hormonów tarczycy u wszystkich analizowanych pacjentów. Analiza zbiorcza (n = 90) (0 — nadczynność tarczycy, 1 — niedoczynność tarczycy)*

[9] reported that overproduction of T3 leads to a similar decrease of both fat and free fat mass (FFM). Miyakawa et al. pointed out that hyperthyroidism in men mainly causes loss of body fat [21]. Thyroid hormones, together with growth hormone, catecholamines, glucagon, insulin, and others, regulate the metabolism of muscular cells [22–24]. Hyperthyroidism increases protein turnover leading to the loss of muscle mass [25], accelerates thermogenesis, and induces gluconeogenesis and lipolysis [25–28] by metabolising amino acids from muscles and free fatty acids from adipose tissue. These metabolic changes result from a constant production of energy at an increased level.

Our study shows what happens during restoration of the euthyroid state; there is a significant increase of all major contributors to the total body mass, *i.e.* of the fat, muscle, and water. In some other studies, the main increase of muscle mass during antithyroid therapy was also documented [28]. All these data suggest that the anti-hyperthyroid treatment stops further loss of energy and restores its potential sources in adipose tissue and muscles. In our study, the anti-hyperthyroid therapy resulted also in an increase in total body water. Thyroid hormones do not influence water and electrolyte balance directly. However, the accompanying increased activity of aldosterone, atrial natriuretic factor [29], and adrenergic activation are found in hyperthyroid patients. There is also some shift of fluids from extravascular space into the circulation, resulting in an increased cardiac output [30] that is typical for hyperthyroidism. All these changes result in actual body dehydration. Antithyroid therapy reverses these processes and corrects hydration. This may explain our findings. For patients with hypothyroid disease, body composition changes seem to go in another direction.

Seppel et al. postulate that hypothyroidism induces weight gain mainly by increasing adiposity [31] — this is in concordance with our findings. Regarding the LT4 replacement therapy, Sanchez et al. and Lonn et al. noted a significant decrease of fat mass and free fatty mass (FFM) after 4–10 months and 3–12 months of such treatment, respectively [8, 20]. Karmisholt et al. observed a significant decrease in FFM with an unaltered fat mass one year after LT4 treatment induction [7]. In our study, weight reduction observed during LT4 therapy (only during the first control visit) was an effect mainly of decreased body adiposity. It is probable that that LT4 inhibited lipogenesis and enhanced lipolysis due to an increased body energy demands and faster metabolism.

Most of the studies describing correlations of thyroid hormones with masses of particular body compartments were performed in euthyroid subjects and usually presented contradictory conclusions. While some authors did not reveal any relations between thyroid status and body composition [31–32], the others found strong positive associations between total body mass and TSH/thyroid hormones concentrations [33–35]. To our knowledge, this is the first study showing both changes in thyroid hormone concentrations and body composition in time. We included patients in the symptomatic stage of thyroid disease, during the applied treatment, and after restoring euthyroidism. Strong associations between hormone concentrations and body compartments were shown, and these findings indirectly confirm a significant influence of thyroid hormones on fat and muscular metabolism. Our results also support the hypothesis that the actual thyroid status is an indicator of current body adiposity and FFM [33, 36, 37]. The limitations of our study must be recognised. First, the number of studied patients is not large. However, this was a pilot study and its promising results convinced us to plan new and more advanced future studies in much bigger groups. Second, the finally analysed groups were quite homogenous — all of the subjects had no other accompanying diseases, had completed the whole treatment of their disease, and had obtained euthyroid state. Another limitation is the evaluation of body composition with the use of bioimpedance. Although this method may not be as precise as gold standard methods such as Dual-energy X-ray Absorptiometry (DXA) [38, 39] or magnetic resonance imaging (MRI); however, bioimpedance assessment is completely noninvasive (*i.e.* no X-ray), harmless, and very cheap. The accuracy of bioimpedance has been shown in many clinical and population studies, including patients with thyroid dysfunction [40, 41]. Finally, we used pooled data of all patients and measurements, regardless the type of thyroid disease (hyper-and hypothyroidism) and its stage, *i.e.* before treatment, during treatment, and after recovery of normal thyroid function. This approach was deliberate for at least two reasons: first the statistical power of the analysed group has been increased, and second, we might analyse different correlations for much wider range of thyroid hormones concentrations and their changes from very low to very high with results of body composition analysis. A similar study for selected patients like hyperthyroid or hypothyroid disease or separately for different phases of the treatment might result in missing some important information and overlooking some general trends.

In conclusion, treatment of severe thyroid function disorders significantly changes total body weight and body composition. Furthermore, total body weight and fat mass are correlated with thyroid hormones and TSH. Additionally, the changes in thyroid hormones concentration are also strongly linked to the change in body composition/weight.

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