Does euthyroid mean healthy? Effect of restoration of thyroid function on body composition, insulin resistance and visfatin concentrations in women with hypo- and hyperthyroidism.

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Abstract

Background

We aimed to investigate the effect of restoration of euthyroidism on serum visfatin in severe thyroid dysfunction, and its associations with insulin resistance and body composition.

Methods

This was an observational study with consecutive enrollment. We included females newly diagnosed with overt hypo- or hyperthyroidism caused by autoimmune thyroid diseases. Laboratory parameters and body composition analysis were assessed before and after the therapy.

Results

Initially, 105 females were enrolled: 49 hyperthyroid (median age of 34 years) and 44 hypothyroid (median age of 46) completed the study. In the hyperthyroid group, visfatin levels increased (< 0.0001), while glucose levels decreased (< 0.0001). Total body mass and fat mass in the trunk and limbs significantly increased during the treatment. In the hypothyroid group, significant weight loss resulted from decrease of fat and muscle masses in trunk and limbs. Visfatin serum concentrations positively correlated with total fat mass($r = 0.19, p = 0.01$) and insulin levels($r = 0.17, p = 0.0.18$).

Conclusions

We may conclude that restoration of thyroid function is not associated with beneficial changes in body composition, especially among hyperthyroid females, reflected by the significant increase of fat mass followed by the increase of circulating visfatin concentrations.

Background

The adipose tissue is a well-established source of multiple circulating peptides that are responsible for various metabolic effects (1). Visfatin, cytokine secreted mainly by adipose tissue, has been extensively investigated within the past decade in different pathologies including metabolic disorders, neoplasms, and inflammatory conditions. Thyroid hormones also profoundly affect thermogenesis, metabolic rate, food intake and energy expenditure. Thus, both hypo- and hyperthyroidism significantly alter these processes, resulting in body composition changes reflected by clinical signs and symptoms (2, 3). Moreover, concomitant chronic inflammation causing thyroid disorders, independently of thyroid hormones, may have systemic effects (4, 5).

We have recently found visfatin/NAMPT overexpression in thyroid cancers and in thyroid glands of patients with Graves' orbitopathy, as well as in their leukocytes, supporting anti-apoptotic and proinflammatory properties of this adipocytokine (6–8). However, previous studies on changes in visfatin serum levels in different thyroid dysfunctions brought inconclusive results, what might be partially explained by the heterogenous etiology of thyroid disorders (9–13). We already reported that visfatin serum concentration in hypothyroidism is associated with free thyroid hormones and antithyroperoxidase antibodies, while in hyperthyroidism visfatin mainly correlates with fat content with minor effect of thyroid autoimmunity (14, 15) .

Therefore, we aimed to investigate the effect of restoration of euthyroidism on serum visfatin in severe thyroid dysfunction, and its associations with insulin resistance and body composition. To limit the interference of individual factors, we have also analysed changes in three different thyrometabolic states in the same patients.

Patients And Methods

Study design and patient enrollment

This was an observational study with consecutive enrollment. We included females newly diagnosed with overt hypo- or hyperthyroidism caused by autoimmune thyroid diseases (Hashimoto's disease or Graves' disease, respectively). The diagnoses of hyper- and hypothyroidism, as well as Graves' or Hashimoto's disease were made according to current recommendations, and were based on physical and biochemical examination. All patients were subsequently treated according to guideline-based therapy: patients with hyperthyroidism received methimazole and some of them were treated with radioiodine (RAI). These females who developed hypothyroidism following RAI administration and patients with Hashimoto's disease became euthyroid on levothyroxine substitution. Exclusion criteria were: other acute or chronic diseases including autoimmune diseases and/or infections and any other medications taken on regular basis (potentially affecting body composition or visfatin concentrations). The study was approved by the local Ethical Committee and all patients signed an informed consent.

Laboratory measurements

Serum concentrations of visfatin, TSH, FT4, FT3, anti-thyroperoxidase antibodies (TPOAbs), fasting glucose and insulin were measured in a consecutive manner in each patient before and after restoration of thyroid function. Thyrotropin receptor antibodies (TRAbs) were assessed in the hyperthyroid group before the onset of therapy and when the euthyroidism was anticipated. ELISA Assay Kit from Phoenix Pharmaceuticals was used to assess visfatin levels. Electrochemiluminescence technique was applied for estimation of TSH, FT4, FT3 concentrations (normal ranges: TSH 0.27–4.2 mU/l; FT4 11.5–21.0 pmol/l; FT3 3.9–6.7 pmol/l). TRAb titers were measured with the use of radioimmunoassay TRAK Human Brahms (normal < 2 IU/l). TPOAb was assessed by radioimmunoassay (normal ranges: <34 IU/ml). Glucose levels were estimated using Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics) and insulin concentration was assessed using ELISA kit from Phoenix Pharmaceuticals.

HOMA-IR was calculated to estimate insulin resistance. All patients were assessed before and after the therapy. In addition, hyperthyroid females who received RAI were assessed in hypothyroid state.

Body composition analysis

Body composition measurements were performed with the total body bioimpedance analyzer Tanita MC 180 MA II (Tanita, Japan) in all patients before and after restoration of thyroid function. Similar to laboratory assessment, body composition in hyperthyroid females treated with RAI was also performed in hypothyroid state.

Statistical analysis

Statistical analysis was performed with MedCalc Statistical Software version 18.10 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Normality was analyzed by the D'Agostino-Pearson test. Since data did not follow normal distribution, comparison of the analyzed parameters within groups before and after restoration of thyroid function was performed using the nonparametric Wilcoxon test for paired data. Changes of analyzed parameters in the hyperthyroid, hypothyroid and euthyroid state were investigated with the non-parametric Friedman test with the post hoc multiple comparison tests. Comparison of results between hyper- and hypothyroid women was performed with the Mann-Whitney test. Spearman rank test was applied to find correlations between analyzed parameters. P value < 0.05 was considered statistically significant.

Results

Initially, 105 females were enrolled into the study: fifty two with newly diagnosed hyperthyroidism in a course of Graves' disease and fifty three with naïve hypothyroidism caused by Hashimoto thyroiditis. Twelve women were lost to follow-up. Forty nine hyperthyroid females with a median age of 34 years (25th -75th percentile: 25–48 years) and forty four hypothyroid females with a median age of 46 years (25th -75th percentile: 33–52 years) achieved euthyroidism and completed the study. A median observation time was 9 months (25th -75th percentile: 8–10 months) in hyperthyroid group, and 6 months (25th -75th percentile: 5–7 months) in hypothyroid group. Fifteen hyperthyroid women developed hypothyroidism after RAI therapy, and underwent additional analysis in hypothyroid state.

Effects of therapy on hormonal and metabolic status

Hormonal and metabolic parameters are compared in Table 1.

Hyperthyroid women

TSH concentrations significantly increased and free thyroid hormones levels decreased after the therapy. The lowering of glucose levels after restoration of thyroid function was noted, while insulin concentrations remained unaltered. Visfatin concentrations increased when euthyroidism was achieved. We have not observed any associations between visfatin and other biochemical parameters.

Hypothyroid women

TSH and TPOAbs concentrations decreased, while free thyroid hormones increased significantly after the therapy. Glucose and insulin levels, as well as visfatin did not change. Visfatin serum concentrations positively correlated with TPOAbs in both hypo- and euthyroid subjects (r = 0.535, p = 0.0002; r = 0.0026, p = 0.0026, respectively). In euthyroid patients, visfatin negatively correlated with FT3 (r=-0.372; p = 0.0141).

Table 1
Changes of biochemical parameters in the study groups before and after restoration of thyroid function

HYPERTHYROIDISM				**HYPOTHYROIDISM**		
Median (25%-75%)	Before	After	P	Before	After	p
TSH [μIU/mL]	0.01 (0.0-0.1)	1.45 (0.98–2.4)	< 0.0001	81.6 (55.8–100)	1.6 (1-2.3)	< 0.0001
FT4 [pmol/L]	60.6 (35.4–86.6)	16.7 (14.9–18.9)	< 0.0001	2.33 (1.5–3.8)	16.7 (15.3–19.7)	< 0.0001
FT3 [pmol/L]	24.4 (16-32.4)	4.4 (4-5.1)	< 0.0001	0.94 (0.7–1.6)	5.0 (4.2–5.8)	< 0.0001
glucose [mg/dl]	**97 (90–101)**	**88 (86–95)**	**< 0.0001**	89 (83–97)	90 (85–96)	0.60
Insulin [mU/ml]	9.3 (5.8–15.7)	9.3 (8.6–11.5)	0.60	6.7 (4.6–8.9)	6.8 (5.3–8.7)	0.47
HOMA-IR	2.3 (1.4–4.1)	2.0 (1.7–2.7)	0.13	1.42 (1–2)	1.5 (1.1–1.9)	0.64
Visfatin [ng/ml]	**9.1 (7.9–11.4)**	**12.3 (9.9–13.6)**	**< 0.0001**	9.32 (8.50–0.86)	9.1 (8.13–11.21)	0.93

TSH thyroid stimulating hormone; FT4 free thyroxine; FT3 free triiodothyronine

Effects of therapy on body composition

Results of body composition analyses are presented in Tables 2 and 3.

Hyperthyroid women

Total body mass and fat mass significantly increased during the treatment. No significant change in total muscle mass was observed, while trunk muscle mass increased. Fat tissue increased in the trunk and limbs.

Hypothyroid women

Restoration of euthyroidism was associated with significant weight loss as a result of decrease of fat and muscle masses in trunk and limbs.

Table 2
Changes of body composition in hypo- and hyperthyroid females before and after restoration of thyroid function

HYPERTHYROIDISM				HYPOTHYROIDISM		
Median (25%-75%)	Before	After	P	Before	After	P
Body weight [kg]	58.5 (52.1–68.5)	63.4 (58.5–77.1)	< 0.0001	68.4 (55.4–69.6)	64.7 (59.2–74.6)	< 0.0001
FC [%]	24.6 (19.4–28.8)	28.9 (24.4–34.2)	< 0.0001	28.9 (25.4–32)	27 (23.7–30.8)	0.0001
FM [kg]	14.7 (9.8–21.6)	18.6 (14.9–27.7)	< 0.0001	19.2 (15.7–23.2)	16.4 (13.9–21.1)	< 0.0001
FFM [kg]	43.9 (40.5–48.9)	44.8 (39.9–49)	0.065	47.3 (43.5–52.9)	46.5 (42.5–50.4)	< 0.0001
MM [kg]	42.3 (39.3–46.8)	43.3 (39.8–47.9)	0.19	44.6 (41.3–50.2)	43.5 (39.8–47.8)	< 0.0001

FC fat content; FM fat mass; FFM free fat mass; MM muscle mass

Table 3
Changes of fat and muscle distribution in hypo- and hyperthyroid females before and after restoration of thyroid function

HYPERTHYROIDISM				HYPOTHYROIDISM		
Median (25%-75%)	Before	After	P	Before	After	P
MM trunk [kg]	23.9 (22-26.9)	25.6 (23.4–28.9)	0.007	26.4 (24-29.7)	25.7 (22.6–27.9)	0.0001
MM limbs [kg]	18.0 (16.6–20.7)	18.1 (14.7–20.4)	0.02	18.3 (16.6–20.9)	17.5 (15.9–19.5)	0.0012
FM trunk [kg]	6.8 (4.8–12.5)	9.2 (7.1–15.3)	< 0.0001	9.7 (7.3–12.2)	9.0 (5.5–11)	0.0001
FM limbs [kg]	7.5 (5.2–10.1)	9.4 (7-11.9)	< 0.0001	8.8 (7.6–11.9)	8.5 (6.8–11.3)	0.0003
VFI	3 (1–6)	4 (2–6)	< 0.0001	5 (3–6)	4 (2–6)	< 0.0001

FM fat mass; MM muscle mass; VFI visceral fat index

Hyperthyroid females had significantly lower body weight ($p = 0.0034$) and fat mass ($p = 0.015$) than hypothyroid females before the therapy was started, while muscle mass was similar at this time. When euthyroidism was reached, both groups did not differ with body weight, fat and muscle masses.

For pooled data of all women and all measurements, we found weak positive correlation between TSH concentrations and total body weight, as well as fat mass ($r = 0.19$, $p = 0.01$; $r = 0.2$, $p = 0.006$, respectively). There was also inverse correlation between FT4 and FT3 and total body weight ($r=-0.246$, $p = 0.0008$; $r=-0.17$, $p = 0.022$, respectively) and fat mass ($r=-0.16$, $p = 0.026$; $r=-0.18$, $p = 0.018$, respectively). Muscle mass was associated neither with TSH nor thyroid hormones. Visfatin serum concentrations positively correlated with total fat mass ($r = 0.19$, $p = 0.01$) and insulin levels ($r = 0.17$, $p = 0.0.18$), while there were no associations with body weight, fat trunk limb masses, muscle mass or TSH and free thyroid hormones.

Changes in visfatin concentration and body composition in three different thyrometabolic functional states in the same patients

We observed considerable increase in total body weight and visfatin concentrations in each patient, with the individual differences between hyperthyroidism, hypothyrodism, and euthyroidism ($p < 0.0001$) (Fig. 1a). The lowest fat mass was observed in hyperthyroid state ($p < 0.0001$) and it increased during the study (Fig. 1b). Although fat mass tended to decrease when females achieved euthyroidism, we did not find significant difference between hypothyroid and euthyroid states. In hypothyroidism, muscle mass decreased.

Discussion

We performed prospective study in women with severe thyroid dysfunctions of autoimmune origin, and we found that restoration of euthyroidism is associated with alterations in body composition. Hyperthyroid women gained weight, mainly due to increase of fat mass in trunk and limbs, while muscle mass remained unaltered. Significant increase of fat mass in hyperthyroid females was followed by the increase of visfatin concentration after the treatment. There is limited number of studies evaluating the changes in body composition during anti-thyroid therapy, especially taking into account an estimation of regional body mass distribution with a subdivision to limbs and trunk. Significant increase in fat mass during restoration of thyroid function was reported also by other authors (2). However, in contrast to our findings some studies described increase in muscle mass when euthyroidism was achieved (2, 16). What more, clinical improvement of muscle strength has been noted after restoration of thyroid function in subclinical and overt hyperthyroidism (16). Observed muscle weakness in hyperthyroid patients mainly results from changes in skeletal muscle metabolism with no muscle cells destruction, therefore post-therapeutic muscle mass might remain similar (17). We have performed a study solely among women, and similar influence of normalization of thyroid function on body composition parameters, including fat and muscle masses in Graves' hyperthyroidism has been recently reported by other authors (18). Weight loss in hypothyroid females in current study is a result of the decrease in both fat and muscle masses.

Similar reduction of adiposity have been observed by other authors (2, 19). Interestingly, one study reported that the decrease of body weight was caused mainly by the decrease of lean mass, while fat mass remained unaltered during the therapy (20). One may suggest, that differences in physical activity during the therapy might explain observed differences. Observed metabolic and anthropometric changes after the restoration of thyroid function in both hyper- and hypothyroid patients might not be accompanied by normalization of energy expenditure. Levothyroxine-replacement therapy causing decrease of FT3 levels has been proved to be associated with lowering of FT3-dependent resting energy expenditure in contrast to healthy controls (21). Recent systemic review and meta-analysis found that normalization of TSH in levothyroxine-treated patients does not lead to sufficient decrease of low dose lipoprotein and total cholesterol levels (22). These effects might be clinically significant not only for patients primarily treated with levothyroxine because of hypothyroidism, but also for initially hyperthyroid subjects who needed radical therapy with radioiodine or thyroidectomy followed by necessity of levothyroxine substitution. Therefore, prevention of unfavourable anthropometric changes observed during the therapy of thyroid dysfunctions could have beneficial metabolic effects.

Total body adiposity was the major determinant of visfatin concentrations in females with thyroid dysfunctions of autoimmune origin, but jet fat trunk or visceral fat index did not correlate with its concentration. This observation is in line with other studies suggesting that subcutaneous fat tissue contributes well to circulating visfatin level (23, 24). Our findings might also explain contradictory results of other studies applying traditional methods for anthropometric assessment (i.e. body mass index, waist-to-hip ratio, or skin fold) (25, 26). We have confirmed our previous findings that serum visfatin correlates with TPOAbs in hypothyroid patients, which has been recently also reported in children (27). Likewise, Caixas at al. observed that in hyperthyroid patients fat mass increases during the therapy with concomitant increase of visfatin (9). The design of our study limits our possibilities to conclude whether observed visfatin changes during recovery in hyperthyroid females simply reflect increase of adiposity or is a compensatory response involved in glucose regulation. On the other hand, since TSH receptor is expressed in adipocytes, observed changes might result from TSH receptor stimulation in fat tissue potentially leading to release of visfatin (28). In contrast to other authors, visfatin remained unchanged after recovery in hypothyroid women (9). Visfatin has been suggested to act as a myokine, and in some studies levothyroxine substitution lead to increment of muscle mass (29). We have noticed significant decrease of muscle mass during the therapy, and this difference might explain contradictory results.

The main objective and novelty of our study is the prospective analysis of the link between visfatin, thyroid-related hormones and antithyroid antibodies levels, as well as body composition parameters, including fat content and muscle mass in trunk and limbs. What is more, to the best of our knowledge, this is the first study investigating serum visfatin changes in three different thyrometabolic states in the same individuals. The main limitation of our study is the use of bioimpedance method for body composition analysis, which is not as precise as Dual-energy X-ray absorptiometry (DXA). However, accuracy of bioimpedance has been already proved in several studies, also among patients with thyroid dysfunctions (30). What is more, we applied strict inclusion and exclusion criteria, which allowed us to

provide more accurate results. Finally, we followed the same patients during the therapy, which limited the influence of individual factors.

Conclusion And Future Perspectives

We may conclude that restoration of thyroid function is not associated with beneficial changes in body composition, especially among hyperthyroid females, reflected by the significant increase of fat mass followed by the increase of circulating visfatin concentrations. In hypothyroid women, restoration of thyroid function was associated with decrease of fat and muscle masses. All observed alteration of body composition might have negative influence on the eventual energy expenditure in patients after restoration of euthyroidism. This complex interplay between thyroid-related hormones and adipose tissue secreting pro-inflammatory adipocytokines should be considered during the therapy of thyroid dysfunctions. Our findings might be also placed in a broader context of increased long-term cardiovascular risk unrelated to hormonal status in patients with thyroid disorders (31). Based on our results, we could speculate that some additional clinical parameters, such as body weight and fat mass should be incorporated into the current recommended thyroid dysfunction therapy goal along with targeted hormonal values. What is more, it would be valuable to investigate the effect of physical activity on body composition changes during the therapy of severe thyroid dysfunctions in the future interventional, prospective studies on a large group of subjects.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Poznan University of Medical Sciences (decision No 351/14) and each participant signed informed written consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

NSG conceptualization, funding acquisition, data collection and analysis, writing; AZK data collection and analysis, manuscript review and editing; MK data collection and analysis, manuscript review and editing; ACz data collection and analysis, manuscript review and editing; PZ data collection and analysis, manuscript review and editing; DMW data collection and analysis, manuscript review and editing; JS data collection and analysis, manuscript review and editing; MR data collection and

analysis, manuscript review and editing, supervision.

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Figures

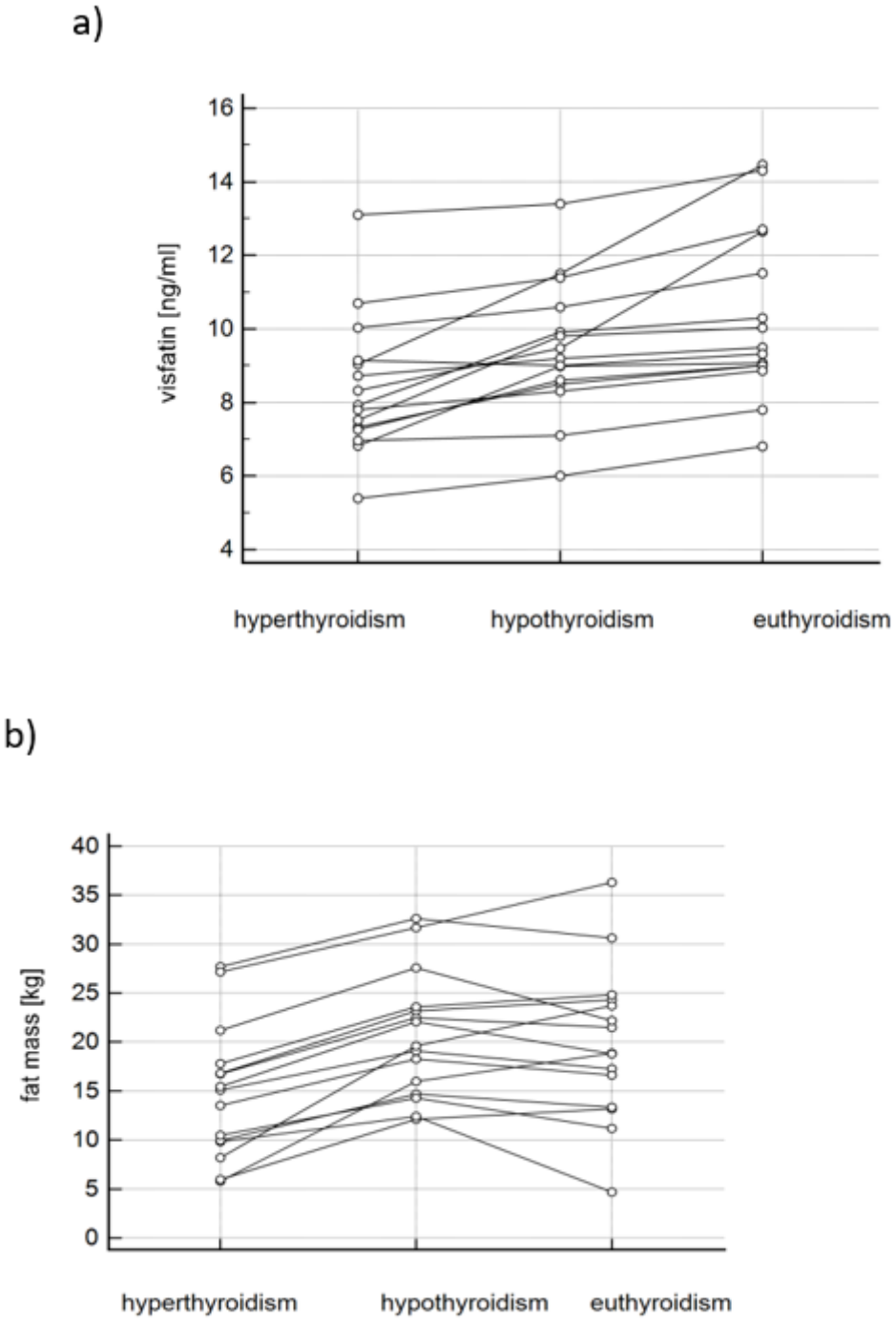

Figure 1

Individual visfatin (a) and fat mass (b) changes in each patient evaluated in hyperthyroidism, hypothyroidism, and euthyrodism.