

Circulating resistin levels are lower in hypothyroid women but independent from thyroid hormones concentrations

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Abstract

OBJECTIVES. Although resistin is involved in metabolism, its role in humans is unclear. Since thyroid status influences metabolism, and since only few studies have evaluated the associations between resistin and thyroid status with inconclusive results, we investigated serum resistin levels and their correlations with TSH, FT4 and FT3 in hypothyroid and euthyroid women.

DESIGN AND METHODS. Study group consisted of 22 women with a history of total thyroidectomy and radioiodine ablation performed for thyroid cancer. Controls were 22 healthy euthyroid women matched for age and BMI. After six-weeks of thyroxine withdrawal, subjects were admitted to the Department of Endocrinology of the Poznan University of Medical Sciences to perform this study.

RESULTS. Serum resistin concentrations were lower in hypothyroid patients, 12.40 ± 5.197 vs. 18.01 ± 7.31 , $p=0.0065$. In hypothyroid subjects, correlations were as follows: r of -0.2636 and p of 0.248 , r of 0.0336 and p of 0.885 , and r of 0.3080 and P of 0.174 for resistin and FT4, resistin and FT3, and resistin and TSH, respectively. In controls: r of 0.0311 and p of 0.8908 , r of -0.0986 and p of 0.6625 , and r of 0.1605 and p of 0.4754 for resistin and FT4, resistin and FT3, and resistin and TSH, respectively.

CONCLUSIONS. Short-term profound hypothyroidism decreased resistin levels. However, no significant correlations between the levels of circulating resistin and thyroid hormones and TSH were shown.

INTRODUCTION

The thyroid gland has always been understood as an important regulator of metabolism. In contrast, historically, adipose tissue was thought to be an inert tissue that stores energy and insulates the body from temperature and trauma. However, it is now evident that the adipose tissue is an active endocrine organ secreting many kinds of adipo-

cytokines, such as adiponectin (Acrp30/adipoQ), leptin, IL-6, and TNF α that may affect metabolism (Spiegelman and Flier, 1996; Friedman and Halaas, 1998; Prins, 2002; Steppan and Lazar, 2002) and, consequently, interfere with thyroid-regulated metabolic processes. Resistin (FIZZ3/ADSF) is another adipocyte-derived peptide. It belongs to the family of cysteine-rich resistin-like molecules (RELM) (Steppan et al., 2001b), together with

RELM-alfa and RELM-beta. Serum concentrations of resistin are markedly increased in obese mice and are decreased by treatment with thiazolidinediones. Moreover, administration of an antiresistin antibody increases insulin-stimulated glucose uptake in obese mice whereas treatment of normal mice with recombinant resistin impairs insulin action (Steppan et al., 2001a). Thus, resistin might link obesity with insulin resistance and diabetes in mice models. However, other studies in rodent models have questioned the role of resistin in obesity and insulin resistance (Juan et al., 2001; Le Lay et al., 2001; Way et al., 2001). The situation in humans is even more controversial. In contrast to mice, human resistin is barely detectable in adipose tissue (Nagaev et al., 2001; Savage et al., 2001), and no correlation was found between resistin expression of isolated adipocytes and obesity or type 2 diabetes (Nagaev et al., 2001; Savage et al., 2001; Janke et al., 2002). Resistin serum levels were found to be related to body mass index (BMI) in human subjects by some authors (Azuma et al., 2003; Degawa-Yamauchi et al., 2003; Fujinami et al., 2004), whereas other studies did not reveal a correlation between body mass and resistin levels in blood (McTernan et al., 2003; Heilbronn et al., 2004; Youn et al., 2004).

In addition, alterations in thyroid hormone levels influence human metabolism and are frequently associated with changes in body weight. Thus, patients with hypothyroidism usually show an increase in body weight and a decreased rate of metabolism, whereas, on the contrary, hyperthyroid patients usually lose weight and their rate of metabolism is increased (Ingbar, 1985). Consequently, as thyroid secretion affects adipose tissue function, the secretion of adipocytokines and resistin might be impaired in thyroid dysfunctions. As resistin is a secretory protein (Steppan et al., 2001a), and as thyroid status reflects the general metabolic status of the body, it would be important to determine the circulating resistin concentrations and examine their re-

lations with thyroid metabolic status in human. This would provide a clue to the role of resistin in human, and its plausible relationships with the thyroid.

Only few studies have thoroughly evaluated the associations between resistin and thyroid status, and their results have been inconclusive (Iglesias et al., 2003; Cettour-Rose et al., 2005; Krassas et al., 2005; Botella-Carretero et al., 2006).

Therefore, the aim of this study was to investigate the associations between serum resistin levels and thyroid hormones in hypothyroid women.

MATERIALS AND METHODS

The study group consisted of 22 consecutive female hypothyroid patients and 22 age- and BMI-matched healthy euthyroid women as controls (mean age 49.9 ± 15.0 and 43.7 ± 10.1 yrs, respectively, $P=0.07$). Prior to this study, all hypothyroid subjects had undergone total thyroidectomy and radioiodine ablation for differentiated thyroid cancer. Then, they were admitted to the Department of Endocrinology for control search for tumor rests and this study was performed under these circumstances. In none of the subjects recurrence was demonstrated. Each subject ceased levothyroxine treatment six weeks prior to admission to enable radioiodine tests. None of the subjects or controls showed the features of the metabolic syndrome according to IDF criteria, or presented with diabetes mellitus. None had a history of alcohol overconsumption. None of the subjects was completely sedentary, or involved in athletics. All subjects were examined in the morning (at 08:00 a.m.) after an overnight fast.

All subjects were examined physically, and their body mass index (BMI) was measured with the formulation: body mass (kg) divided per square height (m). Physical signs confirming thyroid hypofunction included facial appearance, heart rate and rhythm, skin temperature

Table 1. Characteristics of hypothyroid subjects and euthyroid controls. All values are shown as mean \pm standard deviation, and median. Data were compared with Mann-Whitney test. $P<0.05$ denotes statistically significant. Abbreviations: BMI stands for body mass index, circumf. for circumference, FPG for fasting plasma glucose, FT4 for plasma free thyroxine, FT3 for plasma free triiodothyronine, TSH for plasma thyrotropin.

	Subjects	Controls	P
Sample size	22	22	-
Age (years)	49.86 \pm 15.03, 52.50	43.73 \pm 10.14, 44.00	0.0723
BMI	28.05 \pm 6.39, 26.95	25.00 \pm 5.30, 23.20	0.0671
Waist circumf. (cm)	86.64 \pm 13.44, 84.50	82.05 \pm 12.80, 77.50	0.1620
Hip circumf. (cm)	100.95 \pm 8.95, 100.50	101.23 \pm 9.61, 100.00	0.9531
FPG (mmol/L)	4.76 \pm 0.47, 4.55	4.99 \pm 0.80, 4.85	0.6380
FT4 (pmol/L)	2.65 \pm 2.19, 2.10	17.26 \pm 1.96, 17.10	0.0000
FT3 (pmol/L)	1.53 \pm 1.00, 1.43	4.57 \pm 0.61, 4.70	0.0000
TSH (μ U/mL)	91.66 \pm 58.59, 81.35	1.75 \pm 0.84, 1.68	0.0000
Resistin (ng/mL)	12.40 \pm 5.197, 11.96	18.01 \pm 7.31, 16.87	0.0065

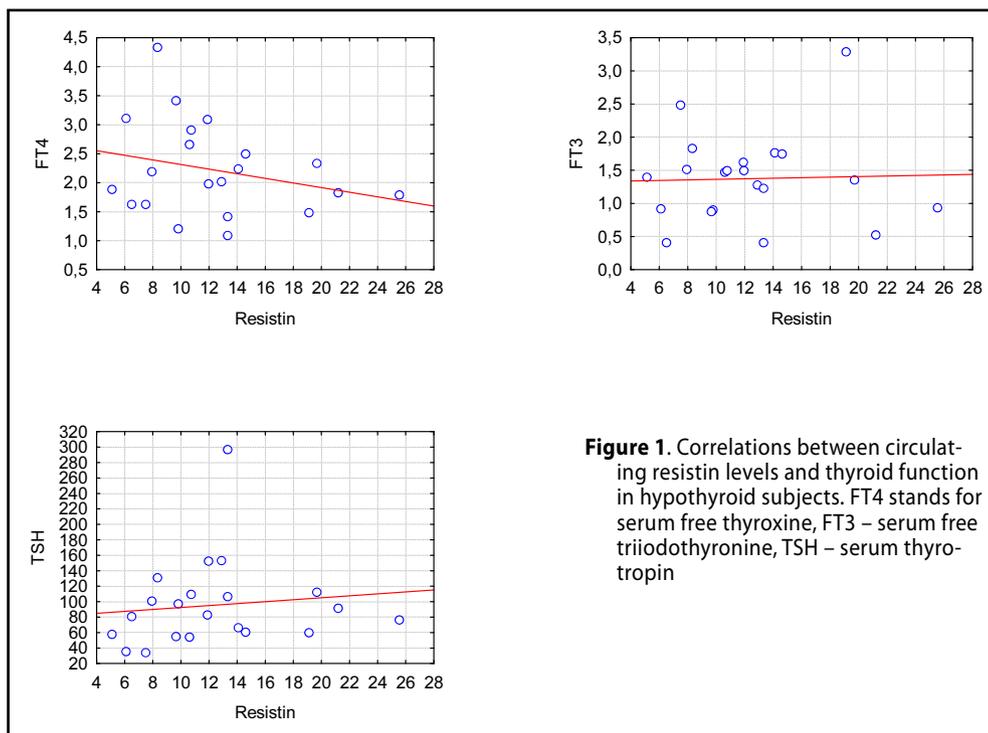


Figure 1. Correlations between circulating resistin levels and thyroid function in hypothyroid subjects. FT4 stands for serum free thyroxine, FT3 – serum free triiodothyronine, TSH – serum thyrotropin

and texture of the skin and hair, as well as a scar on the neck related to previous thyroidectomy, and lack of the thyroid gland in ultrasound examination. Hypothyroidism was diagnosed on the basis of history of thyroid ablation, clinical symptoms and laboratory evaluation: in each case the serum thyrotropin (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were measured and confirmed the diagnosis. All the hormonal assays were performed with an ELISA method, and a routine hospital biochemical analyzer Modular E-170 by Roche was used for all the measurements, except resistin. Serum levels of resistin were determined in the Department of Clinical Biochemistry of the Poznań University of Medical Sciences using a commercial ELISA kit (R&D Systems Inc., MN, USA; microplate reader Sunrise Tekan, Switzerland), and were expressed as nanograms per milliliter. Resistin was measured according to the manufacturer's recommended protocol, with a sensitivity of 0.026 ng/mL. An intra-assay and inter-assay coefficients of variation were 5.25% and 6.47%, respectively.

Statistical analysis was performed with the STATISTICA software by Statsoft. All the parameters were compared between the groups with the Mann-Whitney test. The correlations between FT4, FT3, TSH and resistin levels were calculated with the Spearman's correlation test. The values are given as the mean \pm SD.

The study was conducted in accordance with the guidelines in The Declaration of Helsinki and was approved by the ethics committee of the Poznań University of Medical Sciences. All subjects gave informed consent to participate.

RESULTS

The clinical data of the hypothyroid and control subjects are shown in Table 1. The study groups were of similar age, and their body mass indices and waist and hip circumferences did not differ. However, as expected, the hypothyroid subjects showed higher levels of TSH and lower FT3 and FT4. Their plasma glucose did not differ. Serum resistin concentrations were lower in hypothyroid patients, $P=0.0065$.

To investigate the influence of thyroid status on the serum concentrations of resistin, correlations between resistin levels and FT3, FT4 and TSH were estimated separately in both study groups. In the hypothyroid subjects, those values did not correlate and the results for correlations were as follows: r of -0.2636 and p of 0.248 , r of 0.0336 and p of 0.885 , and r of 0.3080 and p of 0.174 for resistin and FT4, resistin and FT3, and resistin and TSH, respectively. The data are shown in Figure 1. Similarly, the following results were obtained in controls: r of 0.0311 and p of 0.8908 , r of -0.0986 and p of 0.6625 , and r of 0.1605 and p of 0.4754 for resistin and FT4, resistin and FT3, and resistin and TSH, respectively. These correlations are depicted in Figure 2.

DISCUSSION

Thyroid status markedly influences metabolism (Ingbär, 1985). Since resistin is one of adipocyte-derived peptides involved in metabolism, in this clinical study we analyzed the associations between plasma resistin levels and severe hypothyroidism in women *in vivo*. In

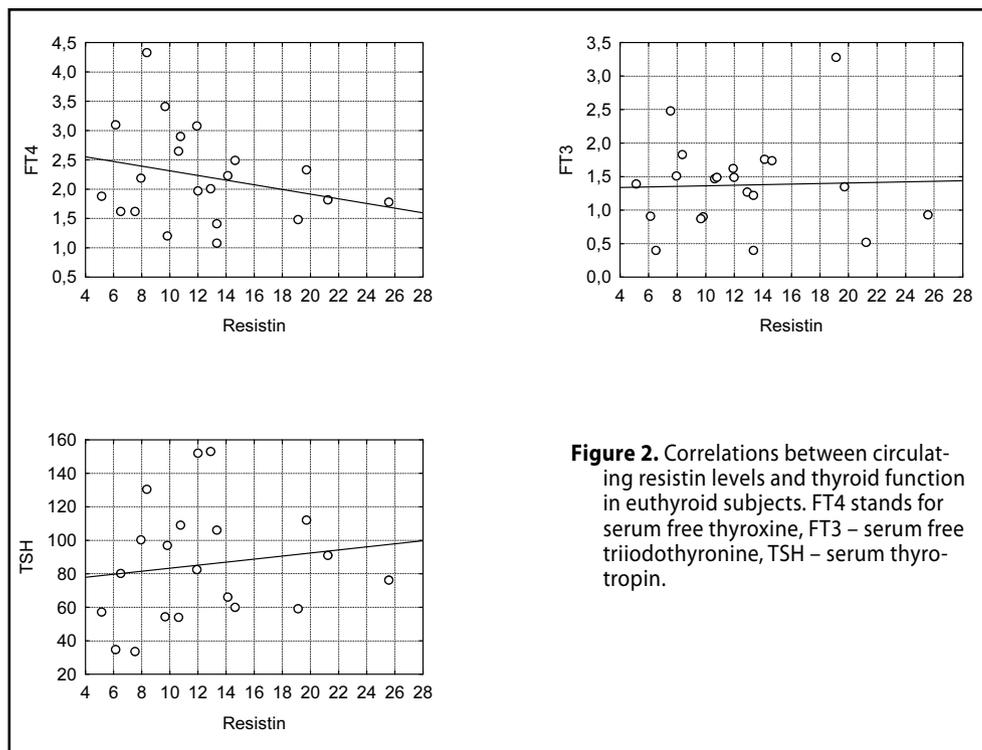


Figure 2. Correlations between circulating resistin levels and thyroid function in euthyroid subjects. FT4 stands for serum free thyroxine, FT3 – serum free triiodothyronine, TSH – serum thyrotropin.

all hypothyroid patients, the thyroid was removed completely by surgical means. As controls, the same number of healthy euthyroid female subjects participated. Both subjects and controls were age-matched and had similar anthropometric parameters. In this setting, we were able to compare two identical groups of women, in whom a complete lack of the thyroid was the only differentiating factor. As a consequence, we examined the influence of hypothyroidism on circulating plasma resistin levels *in vivo*.

As shown here, no interferences between the thyroid function and plasma resistin levels were found, although resistin concentrations were significantly lower in the hypothyroid women. However, the difference across the groups was not sufficient to yield significant statistical correlations. In this setting, the hypothyroid state resulted in lower resistin but no further correlation between the degree of hypothyroidism and resistin levels was found. Similarly, no correlations between thyroid parameters and resistin in euthyroid controls was present, either. Under these circumstances, not the degree of thyroid hypofunction but the lack of the thyroid *per se* seemed to influence resistin levels. One may argue about the causes of this condition. Presumably, hypometabolic condition of the human body measured with thyroid function may lead to a decreased resistin production in all resistin secreting cells. Hypothetically, the decreased resistin production would be triggered off by a given level of thyroid hypofunction. Then, independently from further deterioration of hypothyroidism, the production of resistin would stay constant. The same independence from thyroxine, triiodothyronine

and TSH concentrations is found in the healthy subjects examined, which supports our hypothesis. The fact that resistin levels in both groups differed but correlations were found in none, was only in accordance with this idea. Certainly, this theoretical explanation merits further research studies in various fields of biology and medicine and our clinical paper neither investigates, nor proves it. Still, we decided to present this theory to provoke scientific debate and, at least hypothetically, to try to explain the discrepancy which appeared in our study.

Although circulating resistin has been thoroughly studied in various clinical conditions, and though a lot of extensive data on its function in human or animal metabolism exist, so far studies of serum resistin during abnormal thyroid function have been scarce and have shown conflicting results. In one study by Botella-Carretero et al. (2006) performed in a similar group of 22 women with differentiated thyroid cancer, thyroxine withdrawal resulted in an increase in serum resistin. One may argue, however, that this group was not compared with healthy euthyroid subjects, and resistin increase was a result of previous hyperthyroidism. In contrast, other studies showed higher resistin in hyperthyroidism (Iglesias et al., 2003; Yaturu et al., 2004; Krassas et al., 2005), and a positive correlation between resistin and FT4 and FT3, and a negative correlation between resistin and TSH. In hypothyroidism, some studies showed no influence (Krassas et al., 2006) and some, reduced resistin levels (Iglesias et al., 2003). Undoubtedly, these data are scarce and inconclusive. The margin of their uncertainty is all increased by the fact that

the role of resistin in human metabolism is still under debate. Historical studies suggested that resistin may be involved in the pathogenesis of obesity and insulin resistance in animal models (Steppan et al., 2001a), but their results were not completely confirmed in humans: the expression of resistin in adipocytes does not differ among normal, insulin-resistant, and type 2 diabetic individuals (Nagaev et al., 2001; Savage et al., 2001; Janke et al., 2002; Arner, 2005). In addition, in contrast to several research groups (Silha et al., 2003; Bajaj et al., 2004), a considerable number of studies failed to detect an association between resistin concentration and markers for insulin sensitivity in humans (Lee et al., 2003; McTernan et al., 2003; Heilbronn et al., 2004; Vozarowa de Courten et al., 2004; Youn et al., 2004). Difficult confirmation of these early findings in human populations may be due to the fact that resistin appears to be derived from different sources in humans and rodents. Adipocyte is the sole source of resistin in mice (Kim et al., 2001; Steppan et al., 2001a), whereas investigations in humans suggest that very little resistin is expressed in adipocytes, but rather, monocytes and macrophages produce large quantities of resistin (Savage et al., 2001; Patel et al., 2003). Moreover, a lack of homology between the human and mouse resistin genes might also suggest a divergence in function (Yang et al., 2003).

Therefore, we conclude that resistin levels are lower in women with short-term profound hypothyroidism. However, no correlations between the levels of circulating resistin and thyroid hormones and TSH were shown in our paper. The lack of these correlations should be seen in view of an unclear role of resistin in humans, already investigated in a considerable number of previous studies presented above. This fact merits further research on resistin in clinical and experimental medicine.

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