MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

© Med Sci Monit, 2013; 19: 210-215
DOI: 10.12659/MSM.883847

Received: 2012.02.09
Accepted: 2012.09.26
Published: 2013.03.22

Serum resistin and high sensitive CRP levels in patients with subclinical hypothyroidism before and after L-thyroxine therapy

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Source of support: Departmental sources

Background: Subclinical hypothyroidism (SH) is defined by increased thyrotropin (TSH) and normal free thyroxine (fT4) and free triiodothyronine (fT3) levels. Resistin is secreted from adipose tissue and is reported to be associated with insulin resistance and/or inflammation. High sensitive CRP (hs-CRP) is a reliable marker of inflammation. Data related to levels of resistin and hs-CRP in SH and the effect of L-thyroxine treatment on those is limited. We aimed to determine the levels of resistin and hs-CRP in women with SH, and potential effects of L-thyroxine therapy on those levels.

Material/Methods: Thirty-six patients with SH and 27 age- and BMI-matched healthy control women were included. Waist circumference (Wc), waist-to-hip ratio (WHR), resting energy expenditure (REE), fat mass (FM) and lean mass (LM), TSH, free T4 (fT4), free T3 (fT3), total cholesterol (TC), triglycerides (TG), and HDL- and LDL-cholesterol were determined in all participants. Patients received L-thyroxine treatment for 6 months, after which all measurements were repeated. Resistin and hs-CRP levels were studied from frozen samples after the completion of the study.

Results: The 2 groups had similar values for Wc, WHR, FM, LM, TC, TG, HDL-C, LDL-C, resistin, and hs-CRP at the beginning. fT4 were higher, whereas TSH was lower in the control group. Resistin and hs-CRP levels did not change after treatment. hs-CRP correlated with BMI and FM before and after treatment.

Conclusions: Our results suggest that achievement of euthyroid status by replacement therapy did not change resistin or hs-CRP levels in women with SH. hs-CRP correlated with parameters of obesity, which emphasizes the role of body weight in inflammation.

Key words: resistin • high-sensitive-CRP • subclinical hypothyroidism

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Background

Subclinical hypothyroidism (SH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine. It is common, with a prevalence of 3–8% in the population [1]. Regarding the clinical importance of the disease, there is no clinical evidence related to the adverse effects or the benefits of L-thyroxine therapy for these patients. Patients with thyroid dysfunction frequently show changes in metabolic parameters [2].

Hypothyroidism is associated with lower oxygen expenditure, heat production, and basal metabolic rate. Adipose tissue is a hormonally active system that produces and releases different bioactive substances. Resistin is a peptide hormone synthesized by RSTN gene, belonging to the RELM family. During its discovery, due to its resistance to insulin it has been described as (Resist+in-sulin) [3,4]. Resistin is secreted from adipocytes, muscle, and pancreas cells, but mainly from mononuclear cells [5]. In animal models, resistin has been reported to be associated with insulin resistance and diabetes mellitus, but the exact function in humans is not clear. In obese patients no correlation was present between resistin and insulin sensitivity, but resistin correlated with insulin sensitivity index in obstructive sleep apnea [6–8]. Resistin has proinflammatory cytokine properties and its role in inflammatory diseases independent of insulin resistance had been reported [9]. Resistin is reported to be an independent and strong predictor of major cardio- and cerebrovascular events [10].

C-reactive protein (CRP), named after its ability to precipitate somatic c-polysaccharide of *Streptococcus pneumonia*, is a reliable marker systemic inflammation and tissue damage. Due to its wide reference range, high-sensitive measurement methods were developed for screening properties. It is used as an strong marker in inflammatory, cardiovascular, and infectious diseases [11]. Results of studies that investigated changes in CRP and resistin in thyroid dysfunction are contradictory. In hypo- and hyperthyroidism, increase, decrease, or no change have been reported [12–14]. In SH with subtle thyroid dysfunction, studies of the effect of normalization of thyroid-stimulating hormone levels on resistin, CRP, and body composition are rare. We aimed to determine the levels of resistin and hs-CRP in women with SH, and potential effects of L-thyroxine therapy on those levels.

Material and Methods

Thirty-six women with SH and 27 age- and BMI-matched healthy control women were included. Body weight, waist circumference (Wc), waist-to-hip ratio (WHR), fat mass (FM) and lean mass (LM) quantified by bioelectrical impedance analysis, TSH, fT4, fT3, total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, fasting glucose and insulin, levels were determined in all participants. Patients with SH who offered treatment received L-thyroxine treatment for 6 months in a prospective design after which all measurements were repeated. Resistin and hs-CRP levels were measured from frozen samples after the completion of the study.

Thyroid function tests are measured using electro chemiluminescent immunoassay (Roche Diagnostics Indianapolis, IN, USA). The functional sensitivity of the TSH assay was 0.014 µIU/ml (range 0.005–100 µIU/ml). Normal range of thyroid tests were TSH – 0.27–4.2 mIU/mL, and free T4 – 12–22 pmol/L). Patients with TSH levels between 4.2 to 10 mIU/mL with normal FT4 values are accepted to have SH.

Serum lipids are measured by enzymatic calorimetric method. LDL-C is calculated with the Friedwald formula. Plasma glucose is measured with a spectrometric analyzer with glucose oxidase method and insulin levels are measured with immunoradiometric assay Immunotech IRMA, Czech Republic) [Intraassay coefficient of variation (CV) 4.3%, interassay CV 3.4%]. Insulin sensitivity HOMA (homeostasis model assessment) is calculated as [fasting plasma glucose (mmol/l)x fasting plasma insulin]/ 22.5 [15].

Body composition is measured after an overnight fast with bioimpedance analysis using TANITA (Tanita, BC-418 MA type segmental body analysis monitor, Japan). Total body fat and truncal fat percentage, fat and lean mass (kg) were recorded.

Resistin is measured with ELISA from frozen samples (Biovendor, Human Resistin Elisa, Biovendor Laboratorni Medicina, Czech Republic) (Sensitivity 0.033 ng/ml, test limit 50 ng/ml, intra-assay variation 2.8–3.4%, inter- assay variation 5.1–6.9%).

hs-CRP is measured with the highly sensitive near infrared particle immunoassay rate- method (Immage®Immunochemistry Systems CRPH test, Beckman-Coulter Galway, Ireland). Ninety-five percent of population levels were less than 0.744 mg/dl. Interassay variation was ≤0.011 mg/dl, with 20% functional sensitivity.

All statistical analyses were performed using SPSS 13.0 (SPSS, Chicago, IL, USA). All data are presented as mean ±SD. Student t test and paired-sample t test, Mann Whitney and Wilcoxon tests were used to compare groups where appropriate. $P<0.05$ was considered significant.

Results

Thirty-six women with SH and 27 healthy sex- and-age matched controls were included in the study. All anthropometric, clinical

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Table 1. Anthropometric, clinical and laboratory findings of patients with SH and healthy controls.

	Women with SH (n=36)	Control group (n=27)
Age	34.9±10.2	33.6±9.8
Height (cm)	160±5.6	158.7±6.5
Weight (Kg)	65.6±11.3	67.8±10.4
BMI (kg/m^2)	25.7±5.2	27.2±4.8
Waist (cm)	82.8±14.1	89.2±14.7
WHR	0.8±0.08	0.8±0.2
FM (%)	30.6±7.0	32.24±5.86
FM (Kg)	20.75±7.82	22.08±6.21
FFM (Kg)	44.8±4.6	45.7±6.2
Total cholesterol (mg/dl)	175.6±37.5	176.4±43.5
Triglycerides (mg/dl)	103.5±55.3	110.8±61.6
HDL (mg/dl)	59.1±16.1	55±11.8
LDL (mg/dl)	105.3±32.4	107.7±33.3
FPG(mg/dl)	83.9±9.8	87±13.5
HOMA	1.76±1.11	2.13±1.17

Data Mean ±SD; BMI – Body mass index; WHR – Waist to hip ratio; FM – Fat mass; FFM – Fat free mass; HDL – high density lipoprotein; LDL – Low density lipoprotein; FPG – fasting plasma glucose; HOMA – Homeostatic model of assessment

Table 2. TSH, fT4, hs-CRP and resistin levels of women with SH and healthy controls before treatment.

	Women with SH (n=36)	Control group (n=27)	p
TSH (µIU/mL)	6.7950 (1.9675)	3.4600 (1.1500)	<0.001
fT4 (pmol/L)	13.2850 (2.8025)	15.8800 (4.000)	<0.001
hs-CRP (mg/dl)	0.1200 (0.2873)	0.1630 (0.344)	0.125
Resistin (ng/mL)	5.4550 (1.3825)	5.3900 (2.300)	0.851

Data: median(interquartile range); hs-CRP – high sensitive C-reactive protein.

and laboratory parameters were recorded (Table 1). Patients with SH had higher TSH and lower fT4 levels compared to the control group (Table 2). The rest of the parameters, including resistin and hs-CRP, were similar between groups.

Table 3. Clinical and laboratory findings of women with SH before and after LT4 treatment (n=34).

	Before treatment	After treatment	P
Weight (Kg)	65.7±11.5	65.4±11.5	0.540
BMI (kg/m^2)	25.8±5.3	25.6±5.3	0.547
Waist (cm)	81.6±13.3	80.5±11.2	0.409
WHR	0.8±0.08	0.78±0.07	0.169
FM (%)	31.05±7.03	30.2±6.75	0.319
FM (Kg)	21.2±7.8	20.49±7.3	0.458
FFM (Kg)	44.86±4.65	44.47±5.41	0.911
Total cholesterol (mg/dl)	176.7±38.5	175.8±23.9	0.845
Triglycerides (mg/dl)	97.9±45	96.1±45.1	0.845
HDL (mg/dl)	60.5±16.3	59±16.4	0.589
LDL (mg/dl)	103.6±32.5	101.1±22.6	0.549
FPG(mg/dl)	84.8±10.1	88.3±15.5	0.258
HOMA	1.8±1.2	2.2±1.6	0.082

Data Mean ±SD; BMI – Body mass index; WHR – Waist to hip ratio; FM – Fat mass; FFM – Fat free mass; HDL – high density lipoprotein; LDL – Low density lipoprotein; FPG – fasting plasma glucose; HOMA – Homeostatic model of assessment.

Table 4. hs-CRP and resistin levels of women with SH before and after treatment with LT4 (n=34).

	Before treatment	After treatment	p
hs-CRP (mg/dl)	0.1310(0.2785)	0.1610 (0.3153)	0.153
Resistin (ng/mL)	5.375 (1.370)	5.2900(2.800)	0.194

Data: median(interquartile range); hs-CRP – high sensitive C-reactive protein.

All women with SH were placed on L-thyroxine for 6 months. The results were available for 34 patients after they had reached euthyroid status. L-T4 treatment decreased TSH and increased fT4 significantly (p<0.0001 and p<0.0001, respectively), but did not change the rest of the parameters (Table 3). LT4 treatment did not change either resistin or hs-CRP levels (Table 4).

Resistin levels correlated positively with hs-CRP (p=0.034 and Rs=0.355) at the beginning of the study (p=0.012, Rs=–0.426; and p=0.028, and Rs=–0.382, respectively). Basal hs-CRP correlated positively with weight, BMI, waist, WHR, FM and TG (Table 5).

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Table 5. Correlations of hs-CRP at the beginning of the study.

	Rs	P
Weight	0.365	0.031
BMI (kg/m²)	0.424	0.011
Waist (cm)	0.444	0.010
WHR	0.425	0.015
FM (%)	0.355	0.036
FM (Kg)	0.378	0.025
TG (mg/dl)	0.395	0.017

Rs – Spearman correlation factor; FM – Fat mass; REE – resting energy expenditure; LM – lean mass.

Table 6. Correlations of hs-CRP at the end of the study.

	Rs	p
BMI (kg/m²)	0.512	0.005
WHR	0.474	0.011
FM (%)	0.380	0.042
FM (Kg)	0.405	0.029
TG (mg/dl)	0.437	0.016
HOMA	0.453	0.016

Rs – Spearman correlation factor; FM – Fat mass;
HOMA – Homeastasis model of assessment.

Resistin did not correlate with any of the parameters at the end of the study; on the other hand, hs-CRP correlated with BMI, WHR, FM, TG, and HOMA at the end of the study (Table 6).

Discussion

Our results suggest that women with SH have similar resistin and hs-CRP levels in comparison with age- and BMI-matched healthy women. Achievement of euthyroid status by replacement therapy did not change any of these parameters.

SH is a unique disease because it is presented with a sole increase in TSH, but normal free thyroid hormone levels. CRP has been studied previously in SH [12,13,16–22]. Some studies reported an increase in SH [13,18], but the rest of them could not find any change compared to control groups [17,19,21–23]. We could not demonstrate a difference in hs-CRP levels in women with SH compared to the control group, and treatment with LT4 did not have any effect on these parameters. In spite of the absence of any difference between the control group and patients with SH, hs-CRP correlated with weight-related parameters. Adipose tissue is more frequently mentioned in the pathogenesis of inflammation [24]. CRP levels are closely associated with parameters of adiposity, insulin resistance, and metabolic syndrome [25–27]. Presence of inflammatory cells in the adipose tissue may be the cause of changes, even if we were not able to demonstrate any difference in amount of the adipose tissue [28,29]. The interactions between the metabolic pathways and inflammation occurring through an activation of the adipose tissue still remains mysterious.

Adipokines (leptin and adiponectin) had been studied in SH and controversial results had been reported. There is only limited data available related to resistin, a unique molecule regarding its role in insulin sensitivity and inflammation in thyroid disorders. As a product of adipose tissue, resistin has some role beyond that of other adipokines [30–35]. Resistin plays an important role in the pathogenesis of obesity-related insulin resistance and type 2 diabetes mellitus in animal models, but its precise role in humans is debatable [3,36–38]. Resistin has some proinflammatory cytokine properties and plays an important role in inflammatory diseases irrespective of its role in insulin resistance. It has been suggested that resistin modulates molecular pathways that maintain cross-talk between inflammation and metabolic markers [9]. Thyroid hormone abnormalities and resistin interference has been studied in different diseases [14,29,39–41]. Botella-Carretero et al. demonstrated an increase in resistin and TSH in thyroid cancer patients during withdrawal of thyroid hormones for iodine scan, but this increase was not different from the control group [39]. Krassas et al could not demonstrate a relationship between resistin and thyroid hormone status [42]. High doses of triiodothyronine did not have any effect on resistin, whereas diminished leptin and adiponectin gene expression in calorie-restricted obese rats [43]. Contrary to this, a positive correlation between resistin, fT3, and fT4 had been documented by Yaturu et al. [14]. In a study including 43 hyperthyroid and 23 control patients, resistin levels were higher in hyperthyroid patients and decreased after restoration of the thyroid hormone levels [40]. This was supported by results of a recent study [44]. Bossowski et al. showed similar results in untreated Graves' patients in whom resistin levels were higher compared to simple goiter and Hashimoto disease patients [45]. Iglesias et al also documented higher resistin in hyperthyroidism, which was explained by an increase insulin resistance in hyperthyroidism [46]. Kaplan et al. showed short-term thyroidectomy-induced hypothyroidism did not affect adipokines [47]. Our inability to document a correlation between insulin sensitivity parameters and resistin suggests the presence of alternative pathways through which resistin plays a role.

Our study is a prospective study in which the same patients with SH were evaluated after they became euthyroid. The group was

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homogenous in terms of metabolic and adipose tissue functions because all patients were premenopausal women, although the possibility of extrapolation of this data to men is not clear. The small sample size is another weak point of this study.

Conclusions

When hypothyroidism is present, changes occur in body temperature, food consumption, all parameters in glucose and lipid consumption, and energy metabolism. Approximately 40% of genes expressed in adipose tissue are novel and 20–30% of them can synthesize proteins. The changes in energy metabolism, even in SH status, may affect adipokine levels. The TRH-TSH pathway affects fat metabolism through a complex interaction between hypothalamus, hypophysis, thyroid, and adipose tissue [48–50]. With the presently available data it is impossible to form conclusions about changes in adipocytokines according to thyroid status. Gender and patient characteristics, degree and duration of thyroid dysfunction, antibody concentrations, metabolic effects of other hormones, and possible effects of intermediate metabolism may all be responsible for the conflicting results related to the relationship between thyroid and adipocytokine.

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