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Adipocytokine correlations with thyroid function and autoimmunity in euthyroid sardinians

Alessandro P. Delitala[a,*], Maristella Steri[a], Edoardo Fiorillo[a], Michele Marongiu[a], Edward G. Lakatta[b], David Schlessinger[c], Francesco Cucca[a,d]

[a] Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Cagliari, Italy
[b] Laboratory Cardiovascular Sciences, Intramural Research Programme, National Insitute on Aging (NIA) – NIH, Baltimore, USA
[c] National Institute on Aging, NIH, DHHS, Baltimore, MD, USA
[d] Department of Biomedical Sciences, Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy

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ABSTRACT

Objective: Cytokines release by adipocytes could interact with TSH secretion. We evaluated the relationship between adipocytokines and TSH. We further tested for association of cytokines and thyroid autoimmunity.
Methods: We conducted a cross-sectional study in a community-based sample including 5385 individuals (2964 female) with TSH within the reference range. Subjects who reported taking thyroid medications or drugs that alter thyroid function were excluded. TSH, FT4, adiponectin, leptin, antibody against thyroperoxidase and against thyroglobulin were measured. Linear and logistic regression models were used to test for association.
Results: Females had higher adiponectin and leptin level and increased frequency of thyroid antibodies. In multiple regression analysis TSH was directly associated with leptin ($\beta = 0.003$, $p = 0.001$) and the presence of circulating antibody against thyroperoxidase ($\beta = 0.315$, $p < 0.001$), but negatively associated with age ($\beta = -0.012$, $p < 0.001$) and FT4 ($\beta = -0.359$, $p < 0.001$). Adiponectin, the presence of antibody against thyroglobulin and smoking habit were not associated with TSH levels ($p = 0.223$, $p = 0.174$ and $p = 0.788$, respectively). Logistic regression analysis revealed that higher adiponectin levels were associated with thyroid autoimmunity.
Conclusions: Leptin is positively associated with TSH levels in euthyroid individuals, suggesting an effect of the adipokine on TSH secretion. Our results support the hypothesis that the leptin and pituitary-thyroid axis might interact in the context of energy homeostasis. The effect of adiponectin on thyroid autoimmunity will require more studies.

1. Introduction

The past 20 years have witnessed revolutionary change in views of the roles of white adipose tissue (WAT) in the body. Whereas storage and release of lipids remain major functions of adipocytes, adipose tissue is now known to express and secrete a variety of specific lipid molecules for intracellular signalling and to secrete protein molecules ("adipokines"), that act both locally (paracrine, autocrine) and systemically (endocrine) to communicate with essentially every organ system [1]. In addition, adipose tissue is also a major site for the metabolism of sex steroids and glucocorticoids.

It is now well established that excess of adipose tissue, particularly in the viscera, is associated with insulin resistance, diabetes, hypertension, prothrombotic and proinflammatory states, and cardiovascular disease [2,3]. Thus, excess adipose tissue directly contributes to the pathogenesis of obesity-related disorders. Leptin, a 167 amino acid protein, is the best characterized adipocyte-derived hormone [3–5]. This adipokine exerts pleiotropic actions on glucose metabolism, stimulates bone formation [6], regulates immune cell function [7,8], and may promote atherosclerosis and cardiac remodeling [7,9,10]. Adipocytes secrete leptin in proportion to adipose tissue mass as well as nutritional status, and secretion is greater from subcutaneous than visceral adipose tissue [11]. Moreover, this adipokine acts as an afferent satiety signal at a central hypothalamic level.

Leptin also elicits regulatory effects that include interactions with thyroid axis function. In murine fasting models, leptin administration raises thyrotropin (TSH) levels, probably through the stimulation of thyrotropin-releasing hormone (TRH), in the paraventricular nucleus of

* Corresponding author at: Azienda Ospedaliero-Universitaria di Sassari, U.O.C. di Medicina Interna 2, Viale San Pietro 8, 07100 Sassari, Italy.
E-mail address: aledelitala@tiscali.it (A.P. Delitala).

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Table 1
Summary characteristics of the sample.

	Female (n = 2964)	Male (n = 2421)	Total (n = 5385)
Age, yrs.	40.4 (28.6–55.8)	42.2 (29.4–57.8)	41.4 (28.8–56.5)*
BMI. kg/m^2	23.6 (20.8–27.1)	25.9 (23.3–28.6)	24.7 (21.8–28.0)**
TSH, mUI/ml	1.69 (1.13–2.34)	1.46 (1.01–2.03)	1.59 (1.06–2.20)**
FT4, ng/dl	1.28 (1.17–1.40)	1.29 (1.18–1.42)	1.29 (1.18–1.41)*
Adiponectin, mg/dl	2.78 (1.94–3.91)	1.81 (1.27–2.68)	2.33 (1.52–3.42)**
Leptin, ng/ml	7.86 (3.61–13.70)	3.22 (1.33–6.07)	5.14 (2.11–10.60)**
TPOAb, n (%)	393 (13.3%)	155 (6.4%)	548 (10.2%)**
TGAb, n (%)	390 (13.2%)	132 (5.5%)	522 (9.7%)**
TGAb or TPOAb, n (%)	593 (20.0%)	227 (9.4%)	820 (15.2%)**
Smokers, n (%)	446 (15.1%)	666 (27.5%)	1112 (20.7%)**

Data are expressed as median (25–75°); n, absolute number.
Abbreviations: BMI, body mass index; FT4, free thyroxine; TSH, thyrotropin; TPOAb, antibodies against thyroperoxidase; TGAb, antibodies against thyroglobulin.
* Female vs. male, $p < 0.05$.
** Female vs. male, $p < 0.001$.

the hypothalamus [12]. Some studies also suggest that leptin may regulate TSH secretion in humans [13]. Thyroid dysfunction observed in patients with leptin deficiency or leptin receptor abnormality strongly suggests that leptin and the hypothalamic-pituitary-thyroid axis are interacting [14], and leptin may play a role in the peripheral metabolism of thyroid hormones [15]. TSH receptors have also been identified in human adipose tissue, and a direct effect of TSH on leptin secretion by adipose tissue has been reported [3,16,17]. Taken together, the data support the view that leptin may represent a link between thyroid function and adipose tissue mass.

The adipose-specific glycoprotein adiponectin is the most abundant cytokine in adipose tissue and circulates in high concentration, being inversely correlated with visceral obesity and insulin resistance. In contrast to most adipokines, adiponectin is distinguished by its insulin-sensitizing functions. Visceral obesity and type 2 diabetes are associated with low levels of adiponectin [18]. It also displays anti-inflammatory and anti-atherogenic properties [19–22], regulates bone metabolism [23], and protects the heart from ischemia [24].

The relationship between adiponectin and thyroid function, however, is not clearly defined, and only a few studies in humans have been documented. Most studies have been done in hyperthyroid or hypothyroid patients, assuming that the findings were representative of direct effects of thyroid hormones on this adipokine. However, indirect effects have not been excluded, and conclusions have been tentative and even disputed [25,26]. In general, the results do consistently suggest that adiponectin may be upregulated in the hyperthyroid state, but is not modified in hypothyroid subjects.

The aim of our study was to assess whether the relationship between leptin and adiponectin and the thyroid axis in euthyroid individuals. We also tested whether the adipocytokines could be correlated with thyroid autoimmunity

2. Subjects and methods

The cohort is from the SardiNIA study, a population-based survey that investigates several hundreds of phenotypic traits in a longitudinal manner aiming to define the genetic components and the ageing effects involved in their regulation [27–29]. From the initial sample of 6148 individuals, subjects who reported taking thyroid medications (thyroid hormone replacement or thyrostatics) or drugs that alter thyroid function tests (amiodarone, lithium, and corticosteroids) were excluded. For the purpose of the present study, we included only subjects with TSH within the reference range, yielding a final sample of 5385 (aged 14–102 years).

Each participant signed an Informed Consent. All study methods were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the governing Ethics Committee, ASL4.

2.1. Biochemical and hormone assays

Blood venous samples were drawn between 7 and 8 a.m. after an overnight fast and stored at -80 °C until use. Serum samples were assayed for TSH, free thyroxine (FT4), and antibodies against thyroperoxidase (TPOAb) and against thyroglobulin (TGAb) using an automated assay system (Immulite 2000, Siemens, Germany). The method is a two-site, solid-phase chemiluminescent immunometric assay. Normal values were TSH, 0.4–4.0 μIU/ml; FT4, 0.89–1.76 ng/dl; TPOAb, < 35 IU/ml; TGAb, < 40 IU/ml [30].

Leptin and adiponectin (human serum adipokine – panel B; Lincoplex kit: Cat. # HADK2-61 K-B) were measured with a multiplex testing Luminex Model no. Luminex 200 IS Serial No. LX10006265401.

2.2. Statistical analysis

Data are presented as median and interquartile range unless otherwise specified. Multivariable linear regression analysis for continuous variables was conducted to detect associations between TSH and the covariates age, sex, FT4, smoking status, TPOAb and TGAb. Logistic regression models were used to test which of the above variables were predictive of thyroid autoantibodies positivity. A two-sided p value < 0.05 indicated statistical significance in STATA 12.0.

3. Results

Major characteristics of the population sample are described in Table 1. Overall, females were somewhat younger than males and were characterized by lower BMI, higher TSH, and reduced FT4 levels. Females had higher concentration of leptin and adiponectin than males. Table 2 shows the result of multiple regression analysis. TSH had a negative association with age ($\beta = -0.012$, $p < 0.001$) and with FT4 ($\beta = -0.359$, $p < 0.001$). Female sex, the presence of TPOAb, and leptin were positively associated with TSH level ($\beta = 0.150$, $p < 0.001$; $\beta = 0.315$, $p < 0.001$; $\beta = 0.003$, $p = 0.001$, respectively). By contrast, BMI, the presence of TGAb, and smoking habits were not associated with TSH ($p = 0.146$, $p = 0.174$ and $p = 0.788$, respectively).

Logistic regression analysis for the presence of TPOAb showed that age, female sex, TSH, and adiponectin were predictors of antibody positivity (respectively: OR 1.01, 95% CI = 1.00–1.01, $p = 0.011$, OR 1.89, 95% CI = 1.51–2.35, $p < 0.001$; OR 1.66, 95% CI = 1.49–1.86, $p < 0.001$; OR 1.09, 95% CI = 1.05–1.14, $p < 0.001$). BMI, FT4, smoke, and leptin were not associated with the presence of circulating TPOAb ($p = 0.099$ or higher) (Fig. 1, panel A).