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ORIGINAL ARTICLE

Irisin and Myostatin Levels in Patients with Graves' Disease

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Background and Aims. Skeletal muscle system, which is one of the primary targets for thyroid hormones, has an important role in energy metabolism. Some myokines such as irisin and myostatin have considerable effects on energy metabolism in addition to the musculoskeletal system. Our aim was to investigate circulating irisin and myostatin levels in patients with Graves' Disease (GD).

Methods. This study included 41 patients with GD who were in overt hyperthyroid status and 44 healthy subjects.

Results. Serum irisin levels were higher in patients with hyperthyroidism than in control group ($p = 0.003$). However, there was no statistical difference in myostatin levels between groups ($p = 0.21$). Irisin levels were positively correlated with free triiodothyronine (FT3), free thyroxine (FT4), thyrotropin receptor antibody (TRAb) ($p = 0.03$, $p = 0.02$, $p = 0.02$, respectively) and negatively correlated with thyroid-stimulating hormone (TSH) ($p = 0.006$) in both groups. In multiple regression analysis, the presence of GD was the only significant factor associated with serum irisin levels ($\beta = 0.29$, $p = 0.01$). Myostatin levels were positively correlated with age, body mass index (BMI), FT4, HOMA-IR ($p = 0.001$, $p = 0.04$, $p = 0.003$, $p = 0.03$, respectively) and negatively correlated with TSH ($p = 0.01$). Multiple regression analysis also revealed that age and FT4 were the significant factors associated with circulating myostatin levels ($\beta = 0.27$, $p = 0.02$; $\beta = 0.22$, $p = 0.04$, respectively).

Conclusion. Our results suggest that increased irisin levels might contribute to altered energy metabolism in hyperthyroidism. Further studies to determine whether myostatin is affected due to hyperthyroidism are needed.

Key Words: Irisin, Myostatin, Graves' disease, Hyperthyroidism.

Introduction

Graves' disease (GD) is an autoimmune disorder and is the most common cause of hyperthyroidism. It may also lead to ophthalmopathy and dermopathy (1,2). Due to the wide range of the effect of thyroid hormones, GD may also affect many other organ systems such as the musculoskeletal system (3). Muscle weakness, in addition to many other complaints, is a common finding in hyperthyroidism (4). It was shown that muscle mass and muscle strength were decreased in hyperthyroidism (5). Moreover, contraction and relaxation rates of muscles are increased (6). Also, thyroid hormones affect thermogenesis and substrate metabolism on the musculoskeletal system (6,7). Despite the increase of the energy intake, weight loss occurs in patients with hyperthyroidism (8). Increased energy expenditure in hyperthyroidism is suggested to occur by interactions of increased thyroid hormones on the muscle system (9).

Skeletal muscles play an important role in the regulation of energy metabolism and maintaining physical activity (10). Skeletal muscles synthesize and secrete substances that have autocrine, paracrine or endocrine effects (11). These bioactive substances such as irisin and myostatin secreted from muscles are called myokines.

Conflict of Interest: The authors report no conflict of interest.

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Irisin, which is processed proteolytically from fibronectin type III domain containing protein 5 (FDNC5) and peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1), is an inducer of FDNC5 in the muscle tissue (10). Irisin has a central role in energy metabolism (10). Irisin has been suggested to increase basal metabolic rate and energy expenditure resulting in weight loss. It has been hypothesized that irisin induces the browning of white adipose tissue, changing this tissue into beige fat cells (12).

Myostatin (growth and differentiation factor-8; GDF-8) is a member of the transforming growth factor-β family (11). Myostatin is involved in muscle growth and repair (10). Increased levels of myostatin have been found in conditions related with cachexia and sarcopenia (13,14). In addition to that, myostatin is associated with obesity and type 2 diabetes mellitus (13). In some animal studies, it was reported that myostatin null gene mutations lead to surprisingly high muscle mass, decreased adiposity, enhanced insulin sensitivity and resistance to obesity (11,15,16).

Similar to hyperthyroidism, irisin is suggested to stimulate energy expenditure (12). Few studies have investigated irisin levels in patients with hyperthyroidism. The results of these studies suggest that irisin levels might be affected as a result of thyroid dysfunction (17,18). To the best of the authors' knowledge, there is no study investigating myostatin levels in patients with hyperthyroidism. However, expression of myostatin was found to be increased in hypothyroid rats, but its expression was not changed in thyrotoxic rats due to levothyroxine (LT4) overtreatment (19). In addition, myostatin gene expression from extraocular muscles was found to be down-regulated in T3-treated rats (20).

There is insufficient data about myokines such as irisin and myostatin in hyperthyroidism, which has a variety of significant effects on the muscular system. Addressing this possibly significant interaction between irisin, myostatin and thyroid hormones, the aim of the present study was to investigate serum levels of irisin and myostatin in patients with GD and their relationship with glucose and lipid metabolism.

Materials and Methods

Forty-one patients with GD who were in overt hyperthyroid status and 44 healthy subjects who were matched with the patient group in terms of age, gender and body mass index (BMI) were enrolled in the study. Subjects were recruited from hospital endocrinology outpatient clinics. Patients with GD were selected according to their history, physical examination, and laboratory tests. The latter included increased free triiodothyronine (fT3) level and/or increased free thyroxine (fT4) level, suppressed thyroid-stimulating hormone (TSH) level, positively detected thyrotropin receptor antibody (TRAb), increased radioactive iodine (RAI) uptake in patients without thyroid nodules and/or diffuse involvement in thyroid scintigraphy. Exclusion criteria of the study were diseases that may affect endocrine hormones (Cushing's syndrome, acromegaly, gastrointestinal diseases, etc.), chronic diseases (diabetes mellitus, kidney failure, liver disease, etc.), neurologic diseases, rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.), established cardiovascular diseases, psychiatric disorders (anorexia nervosa, depression, psychosis, etc.), pregnancy, being in postpartum period and using corticosteroid or thyroid hormone replacement therapy in the last year. In addition to that, healthy control subjects with any thyroid disorder in their medical history were excluded from the study. The study protocol was approved by the institutional ethics committee and informed consent was obtained from all subjects.

All analyses were performed in patients with GD before treatment of hyperthyroidism such as antithyroid therapy or radioactive iodine therapy. Body weight (kg) and height (cm) were measured with a professional scale (DESIS Professional Weighing Centrum ELW) during fasting state. BMI (kg/m^2) of the subjects was calculated.

Biochemical Assessment

Blood samples of the subjects were taken early in the morning after a 10- to 12-h fast. Serum and plasma samples were collected and stored at −80° C until analysis of irisin and myostatin levels.

Serum irisin levels were measured with the enzyme-linked immunosorbent assay (ELISA) method using an available kit (Biovendor ELISA kit, Czech Republic). The assay has a sensitivity of 1 ng/ml, intra-assay variation of 4.86–6.74%, and inter-assay variation of 9.67–9.71%. Serum myostatin analysis was performed with the ELISA method using an available kit (Cloud-Clone Corp., Houston, TX). The minimum detectable level of the assay was 31 pg/mL. Intra-assay variation was $<10\%$ and inter-assay variation was $<12\%$. Creatine kinase (CK) levels were measured by photometry method (Cobas 8000, Roche Diagnostics, Switzerland).

Fasting blood glucose (FBG) levels were measured using standard enzymatic methods. Serum insulin levels were measured by electrochemiluminescence immunoassay (ECLIA) using Roche COBAS 8000 system. Insulin resistance was calculated using the HOMA-IR index formula (21). Total cholesterol (mg/dL), triglycerides (mg/dL), and high-density lipoprotein (HDL) (mg/dL) were measured using the enzymatic-spectrophotometric methods (Beckman, Olympus AU2700 Plus). Low-density lipoprotein (LDL) levels were calculated using the Friedewald formula. Apolipoprotein (Apo) AI (mg/dL), apo B (mg/dL) and lipoprotein-a (mg/dL) levels were measured by a nephelometer (Siemens, Bn Prospec model, Germany). TSH (IU/mL), fT4 (ng/dl), and fT3 (pg/mL) analyses were performed with chemiluminescence method using an autoanalyzer (Abbott,