

Serum Ghrelin Levels in Patients with Chronic Urticaria and Atopic Dermatitis and Its Relationship with Metabolic Syndrome

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ABSTRACT

Objective: Chronic urticaria is a systemic inflammatory disease. Atopic dermatitis is a chronic immunological disease that is characterized by an increase in systemic inflammatory response. In several studies, chronic urticaria and atopic dermatitis were reported to be associated metabolic syndrome (MetS). In this study, we aimed to investigate the serum ghrelin levels in the patients with chronic urticaria and atopic dermatitis.

Methods: Thirty patients with chronic urticaria, 30 patients with atopic dermatitis and 30 control subjects participated in this study. Blood fasting glucose and serum lipids, insulin, C-peptide levels and thyroid function tests were measured. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to calculate insulin resistance. Ghrelin levels were determined by an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol.

Results: The mean serum ghrelin levels in the patients with chronic urticaria (54.13 ± 40.94 pg/mL) and atopic dermatitis (65.33 ± 93.54 pg/mL) were significantly higher than those of the controls (30.36 ± 17.13 pg/mL) ($p = 0.003$, $p = 0.04$, respectively).

Conclusion: We detected higher serum ghrelin levels in the patients with chronic urticaria and atopic dermatitis than the controls. However, we failed to find any association between serum ghrelin levels and insulin resistance or MetS. We think that the high levels of serum ghrelin in the patients with chronic urticaria and atopic dermatitis may be related to the mechanisms independent of insulin resistance.

Keywords: Atopic dermatitis, chronic urticaria, ghrelin

INTRODUCTION

Chronic urticaria is defined as urticaria or angioedema or both, persists for longer than six weeks. Numerous mediators such as histamine, leukotrienes, serin proteases, heparin, tryptase and proinflammatory cytokines trigger mast cell degranulation. Urticaria is related with atopic dermatitis and allergic rhinitis, especially in childhood (1). Atopic dermatitis is accepted as a chronic, systemic immunologic disease with a tendency to increase in inflammatory response. In atopic dermatitis, antigenic stimulation of Langerhans cells, mast cells and keratinocytes cause an increase in eosinophils, inflammatory dendritic cells and Th2 response (2).

Ghrelin is a peptide hormone mainly secreted by gastric mucosa (3). Ghrelin has many important functions such as stimulating growth, appetite, lipid storage and gluconeogenesis, controlling gastric motility and gastric acid secretion, regulating pancreatic exocrine and endocrine secretions, proliferation of neoplastic cells and regulating immune system (4, 5). Increased plasma ghrelin levels were observed in obese individuals in a number of studies and high plasma ghrelin level was considered to be a feature of metabolic syndrome (MetS) like hyperinsulinemia and insulin resistance (6, 7).

Recently, there have been some studies reporting the relation between chronic urticaria and MetS (8). Atopic

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dermatitis is considered to be a risk factor for MetS (9). The aim of this study is to evaluate serum ghrelin level and its relationship with MetS in the patients with chronic urticaria and atopic dermatitis.

SUBJECTS AND METHODS

The local ethics committee approved the study (no: 03 of February 21, 2013). An informed consent was obtained from all the participants. A total of 30 patients with chronic urticaria, 30 patients with atopic dermatitis and 30 healthy control subjects were enrolled into the study. The diagnosis of chronic urticaria and atopic dermatitis were based on the clinical findings and Hanifin-rajka diagnostic criteria, respectively (10).

The participants under the age of 18, having systemic diseases, having malignancy or infection, being pregnant or using systemic medications were excluded from the study. The patients with chronic urticaria and atopic dermatitis taking systemic corticosteroids or any immunosuppressive drug for the last three months were also excluded.

Body mass index (BMI) was calculated according to the formula of $BMI = \text{weight (kg)}/\text{height}^2 \text{ (m}^2\text{)}$: score 0: 18.5–24.9 kg/m², score 1: 25.0–29.9 kg/m², score 2: 30.0–39.9 kg/m², score 3: ≥ 40.0 kg/m². Body mass index (BMI) values over 30 were accepted as obese (11).

Serum-fasting glucose level, triglyceride, total cholesterol, LDL, VLDL and HDL cholesterol, insulin, C-peptide and thyroid function tests were measured. The diagnosis of MetS was based on the diagnostic criteria of International Diabetes Federation (IDF). The participants having two or more criteria below were accepted as MetS. The diagnostic criteria of IDF for MetS were: waist circumference ≥ 94 cm (male) or ≥ 80 cm (female), hypertriglyceridemia ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL (male) or < 50 mg/dL (female), arterial blood pressure $\geq 130/85$ mmHg, serum-fasting glucose level ≥ 100 mg/dL (12). Homeostasis model assessment for insulin resistance (HOMA-IR) index was used to measure insulin resistance ($\text{HOMA-IR} = \text{insulin [mU/L]} \times \text{glucose [mmol/L]}/22.5$) (13).

Ghrelin is sensitive to proteases because of its peptide structure. Therefore, aprotinin (500 kallikrein unite/mL) was added into the blood collection tubes before the blood samples were collected from the patients to prevent proteolysis. The blood samples were collected between 09:00 am and 10:00 am after an overnight fast of at least 8 hours. The blood samples (5 mL) were centrifuged at 3000 rpm. The serum samples were transferred into microcentrifuge tubes and stored at -80°C .

Serum ghrelin levels were determined with an enzyme-linked immunosorbent assay (ELISA kits cat. no: SPI BIO-A05106).

The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 22. Continuous data are expressed as the mean \pm SD. Comparisons between the groups were assessed using the student's *t*-test and Mann–Whitney *U* test; *p*-values less than 0.05 were considered statistically significant.

RESULTS

The ages of urticaria patients were between 18 and 67 years, the atopic dermatitis patients were 18–52 years, the controls patients were 18–45 years. The mean age of the urticaria patients, atopic dermatitis patients and the control group patients were 34.43 ± 12.9 , 29.70 ± 11.4 , 30.90 ± 8.5 , respectively. There was no significant difference between the groups in terms of mean age, gender and BMI ($p > 0.05$) (Table 1).

Table 1: Clinical features of the patients and the controls

	Urticaria	Atopic dermatitis	Control	<i>p</i> -value
Number	30	30	30	
Gender (M/F)	15/15	15/15	15/15	$p > 0.05$
Age* (year)	34.43 ± 12.9	29.70 ± 11.4	30.90 ± 8.5	$p > 0.05$
BMI* (kg/m ²)	26.08 ± 6.31	24.21 ± 5.50	23.71 ± 3.25	$p > 0.05$
BMI score*	2.63 ± 1.03	2.48 ± 1.05	2.30 ± 0.79	$p > 0.05$
Waist circumference* (cm)	76.43 ± 11.76	78.70 ± 21.45	78.90 ± 7.44	$p > 0.05$

*(mean \pm SD).

The mean serum ghrelin levels were significantly higher in the chronic urticaria patients (54.13 ± 40.94 , $p = 0.003$) and in the atopic dermatitis patients (65.33 ± 93.54 , $p = 0.04$) than in the controls patients (30.36 ± 17.13). There was no significant difference between the mean serum ghrelin levels of the chronic urticaria and atopic dermatitis patients ($p > 0.05$). The laboratory findings of the patient and control groups are shown in Table 2 and Figure 1.

An increased insulin resistance was detected in 11 (36.7%) of the chronic urticaria patients, in six (20%) of the atopic dermatitis patients and in eight (26.7%) of the controls. Although the mean serum ghrelin levels of the chronic urticaria patients with insulin resistance (73.67 ± 52.49 pg/mL) were higher than the chronic urticaria patients without insulin resistance (42.81 ± 28.32 pg/mL), the difference was not statistically significant ($p > 0.05$). The mean serum ghrelin levels of the atopic dermatitis

Table 2: Laboratory results of the patient and the control groups

	Urticaria	Atopic dermatitis	Control	<i>p</i> -value
Glucose* (mg/dL)	100.76 ± 32.07	92.73 ± 11.41	89.80 ± 9.71	<i>p</i> > 0.05
Triglyceride* (mg/dL)	114.30 ± 50.41	89.76 ± 43.78	115.13 ± 80.08	<i>p</i> > 0.05
LDL-cholesterol* (mg/dL)	96.58 ± 36.12	98.44 ± 31.20	92.60 ± 30.42	<i>p</i> > 0.05
HDL-cholesterol* (mg/dL)	50.60 ± 13.20	51.80 ± 11.09	49.15 ± 13.06	<i>p</i> > 0.05
Total cholesterol* (mg/dL)	167.53 ± 44.04	167.40 ± 37.51	168.90 ± 24.04	<i>p</i> > 0.05
Insulin* (μIU/mL)	8.40 ± 3.05	8.90 ± 3.62	10.77 ± 5.74	<i>p</i> > 0.05
C-peptide* (ng/mL)	0.90 ± 0.59	1.15 ± 0.58	2.07 ± 0.78	<i>p</i> > 0.05
HOMA-IR*	2.17 ± 1.54	2.05 ± 0.92	2.35 ± 1.27	<i>p</i> > 0.05
Ghrelin* (pg/mL)	54.13 ± 40.94 ^a	65.33 ± 93.54 ^b	30.36 ± 17.13 ^{a,b}	^a <i>p</i> = 0.003 ^b <i>p</i> = 0.04

*(mean ± SD).

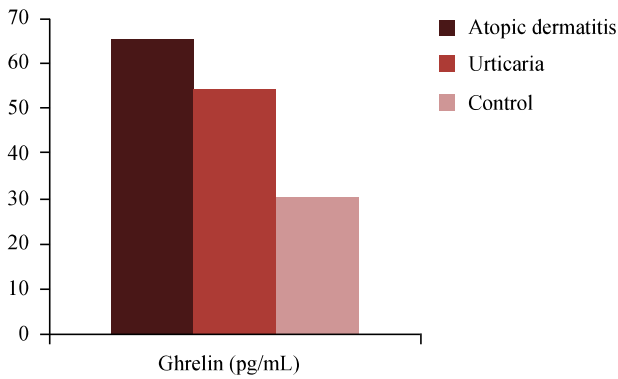


Figure 1: The laboratory findings of the patient and control groups.

patients with insulin resistance (50.47 ± 23.95 pg/mL) were lower than those of the atopic dermatitis patients without insulin resistance (69.04 ± 104.09 pg/mL); however, the difference was not statistically significant ($p > 0.05$). The mean serum ghrelin levels of two patient groups with insulin resistance (65.48 ± 45.07 pg/mL) were higher than those of the patients without insulin resistance (57.45 ± 80.37 pg/mL). The difference was not statistically significant ($p > 0.05$).

Metabolic syndrome (MetS) was found in five (16.7%) of the urticaria patients, in five (16.7%) of the atopic dermatitis patients and in one (3.3%) of the controls. The mean serum ghrelin level of all the patients with MetS (65.23 ± 42.67 pg/mL) and the mean level of the patients without MetS (57.18 ± 82.25 pg/mL) were similar ($p > 0.05$).

DISCUSSION

The secretion of ghrelin increases with fasting and decreases with fullness. It is known that ghrelin has regulatory effects on body weight (14). The blood ghrelin levels were found lower in obese people when compared

with non-obese individuals, and it is also reported that weight loss increases blood ghrelin levels. Ghrelin regulates body weight *via* insulin (4). Insulin has regulatory action on ghrelin levels. An increase in insulin levels suppresses ghrelin (15). It is shown that serum ghrelin levels decrease when insulin resistance increases in Type 2 diabetes patients and the patients with insulin resistance and *vice versa* (16).

Recently, in a study that evaluates the relationship between urticaria and MetS, serum glucose, triglyceride levels and the rates of central obesity were found higher significantly in recalcitrant chronic urticaria patients than the controls. The prevalence of MetS was also significantly higher in the urticaria group (8). Another study reported that hypertension, which is a component of MetS, prolongs the duration of the disease in urticaria patients (17).

Atopic dermatitis is accepted as an organ-specific manifestation of atopic complex, which consists of allergic skin changes, allergic rhinoconjunctivitis and asthma. Peripheral eosinophilia and high serum IgE levels may be associated with atopic dermatitis. Immune dysregulation in Th2 pathway and skin barrier dysfunction are considered in the pathogenesis of atopic dermatitis (2). There are studies reporting that atopic dermatitis may be a risk factor for MetS. Silverberg *et al* (9) reported that obesity in adults induced relapses in atopic dermatitis. It was demonstrated that obesity lasting more than two and a half year in early childhood was a risk factor for atopic dermatitis (18). There was a relation between obesity and asthma because pro-inflammatory mediators secreted from adipose tissue had some effect on mast cells. In addition, a positive correlation was demonstrated between the serum levels of total cholesterol, LDL cholesterol and atopy in school-age children (2). Ma *et al* (19) detected that insulin resistance did not induce

asthma attacks in atopic or non-atopic asthma patients and they reported that atopy and asthma had no relation with obesity and insulin resistance.

There is no study evaluating the serum ghrelin levels in chronic urticaria and atopic dermatitis patients in the literature. However, there are some studies reporting the relation between atopy, asthma, obesity and ghrelin. Cobanoglu *et al* (20) declared that there was no difference between the serum ghrelin levels of the children with asthma and the children without asthma. They also reported that there is no correlation between BMI and ghrelin. Okamatsu *et al* (21) reported that there was negative correlation between serum IgE and ghrelin levels in overweight children and there was no correlation between BMI and ghrelin.

The metabolic system and immune system are closely related to each other. Interactions between these systems increase, especially in stress and diseases to keep the balance of the organism (22). Ghrelin is a potent anti-inflammatory hormone. It suppresses the production of pro-inflammatory cytokines secreted from activated T-lymphocytes, monocytes, endothelial cells (23). In addition, ghrelin has been found to inhibit the proliferation of anti-CD3-activated T-lymphocytes. Th1 cytokines (IL-1 and IFN- γ) and Th2 cytokines (such as IL-4 and IL-10) which induce IgE synthesis in rodent spleen were inhibited by ghrelin (24).

Elevated serum ghrelin levels in atopic dermatitis may occur in order to suppress Th2 cell predominance, which is considered to be an important pathogenetic factor of the disease. It is reported that ghrelin induced the release of histamine from rat peritoneal mast cells (25). An increased ghrelin release may induce the secretion of histamine in chronic urticaria patients.

In conclusion, we have found significantly higher serum ghrelin levels in chronic urticaria and atopic dermatitis patients than the controls. We did not find any correlation between ghrelin levels and MetS, BMI and insulin resistance. Therefore, we thought that new studies are needed to disclose if ghrelin plays a role in urticaria pathogenesis.

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