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INVESTIGATIVE REPORT

# Co-existence of Chronic Urticaria and Metabolic Syndrome: Clinical Implications

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**A systemic pro-inflammatory and pro-coagulating state occurs in subjects who have both chronic urticaria and metabolic syndrome. To investigate the prevalence and clinical impact of metabolic syndrome in Korean patients with chronic urticaria, a hospital-based cross-sectional study of 131 patients was performed. Metabolic syndrome was assessed by the criteria of the National Cholesterol Education Program's Adult Treatment Panel III. Urticaria disease activity was assessed by total urticaria activity score (range 0–15). Thirty-nine patients (29.8%) had metabolic syndrome compared to 17.8% in a matched control group ($p=0.001$). Patients with chronic urticaria and metabolic syndrome were older, had a higher mean urticaria activity score and serum levels of eosinophil cationic protein, tumour necrosis factor-α, and complements, and showed a higher rate of negative autologous serum skin tests compared with those without metabolic syndrome. Logistic regression analysis indicated that an urticaria activity score of ≥13 ($p=0.025$) and the presence of metabolic syndrome ($p=0.036$) were independent predictors of uncontrolled chronic urticaria. We conclude that patients with severe and uncontrolled chronic urticaria should be evaluated for metabolic syndrome in order to reduce cardiovascular risk and improve chronic urticaria outcomes.** ***Key words: chronic urticaria; metabolic syndrome; urticaria activity score; inflammation.***

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Chronic urticaria (CU) is a common skin disorder defined by persistent or recurrent wheals and pruritus of at least 6 weeks' duration. The wheals are thought to be due to activation of cutaneous mast cells, which release various inflammatory mediators including histamine, proteases, leukotrienes, and tumour necrosis factor-α (TNF-α). Circulating autoantibodies specific for the high-affinity immunoglobulin E (IgE) receptor (FcεRIα) and IgE, complement proteins, and activated eosinophils and T lymphocytes induce mast cell degranulation and cytokine production (1). Thyroid dysfunction, anti-thyroid antibodies and aggravation of urticarial symptoms due to physical stimuli are commonly recognized in patients with CU, but the exact mechanism by which anti-thyroid antibodies and physical stimuli lead to activation of mast cells is unclear. CU is a chronic inflammatory skin disease characterized by infiltrating T cells, eosinophils and neutrophils. Studies have demonstrated that circulating levels of C-reactive protein (CRP) and pro-inflammatory cytokines, such as interleukin (IL)-6, TNF-α, and matrix metalloproteinase 9 (MMP-9), which stimulate the production of CRP in the liver, are increased in patients with CU (2–4). Furthermore, these inflammatory markers associated with acute phase response appear to correlate well with clinical activity score and severity of urticaria (2–5).

Metabolic syndrome (MetS) is a combination of central obesity, dyslipidaemia, glucose intolerance, and elevated blood pressure (6). A systemic pro-inflammatory and pro-coagulating state, characterized by increased levels of inflammatory markers such as IL-1, IL-6, TNF and CRP, occurs in subjects with MetS (7). The presence of MetS frequently increases the risk of cardiovascular diseases. Associations between MetS and inflammatory diseases, for example systemic lupus erythematosus and rheumatoid arthritis, and psoriasis, have been reported (8, 9). Although a considerable proportion of patients with CU have autoimmunity and systemic inflammation, there have been no reports of associations between MetS and CU. The aim of the present study was to investigate the prevalence and clinical impact of MetS in patients with CU.

## METHODS

### *Subjects*

A hospital-based cross-sectional study was performed on 131 patients with CU (49 males and 82 females, age range 20–71 years, mean age 40.5 years, ethnic Koreans) who were followed in the Outpatient Allergy Clinic of Ajou University Hospital, South Korea, from July 2010 to June 2011. Inclusion criteria were age ≥ 20 years and almost daily urticaria symptoms (such as wheals and itching) for at least 6 weeks. Patients with other chronic skin diseases were excluded. None of the subjects had a history of occurrence of acute infectious disease in the previous month. All subjects submitted a written informed consent form at the time of their enrolment and the study was approved by the institutional review board.

To estimate the prevalence of MetS in the general population, we obtained health data from 1,285 age- and gender-matched controls who took part in medical examinations at Ajou University Hospital Health Promotion Center in 2009.

*Assessment of urticaria activity scores and urticaria control*

CU disease activity was assessed using the urticaria activity score (UAS), which scores wheals according to quantity (0, no wheals; 1, < 10 wheals; 2, 10–50 wheals; 3, > 50 wheals), distribution range (0, none; 1, < 25% of the body surface area (BSA); 2, 25–50% of the BSA; 3, > 50% of the BSA), mean diameter (0, no wheals; 1, < 1 cm; 2, 1–3 cm; 3, > 3 cm), and duration (0, no wheals; 1, < 4 h; 2, 4–12 h; 3, > 12 h), and pruritus according to intensity (0, no pruritus; 1, mild; 2, moderate; 3, severe) within the last week for outpatient clinic visits, yielding a total score of 0–15 (10).

The urticaria control state during the 3 months of treatment was classified into 3 categories according to published guidelines: remission, well-controlled, and uncontrolled (11). Remission was defined as the absence of urticaria symptoms for at least 4 weeks without any medication. Patients who had no wheals or itching when taking medication, but whose symptoms returned when they stopping taking their medication, were deemed to have well-controlled CU. Patients whose disease could not be controlled with medication were deemed to have uncontrolled CU.

*Assessment of metabolic syndrome*

Relevant data collected included age, gender, weight, height, body mass index (BMI), waist circumference, blood pressure, and smoking habits. BMI was calculated as weight (kg)/height $(m)^2$. MetS was diagnosed by the presence of 3 or more of the following National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III 2001) criteria: waist circumference ≥ 90 cm in men or ≥ 80 cm in women; hypertriglyceridaemia (triglyceride level ≥ 150 mg/dl); high-density lipoprotein (HDL) cholesterol level < 40 mg/dl in men or < 50 mg/dl in women; blood pressure ≥ 130/85 mmHg; and fasting plasma glucose level ≥ 100 mg/dl.

Venous samples were taken after an overnight fast. Venous blood was drawn following an 8-h overnight fast and abstinence from vigorous activity for 24 h. Fasting glucose, total cholesterol, HDL cholesterol, and triglyceride levels were measured by an enzymatic colorimetric method using a TBA-200FR analyser (Toshiba, Tokyo, Japan).

*Assessment of atopy and measurement of total IgE, anti-nuclear antibody, and anti-thyroid antibody levels*

Atopy was defined by a positive skin test response to at least 1 of 55 common inhalant allergens or elevated serum levels of IgE specific to *Dermatophagoides farina*, *D. pteronyssinus* or common inhalant allergens in our environment.

Levels of total IgE and eosinophil cationic protein (ECP) were measured using the ImmunoCAP system (Pharmacia Diagnostics, Uppsala, Sweden) according to the manufacturer's instructions. ANA was detected using HEp-2 cells by an indirect fluorescent antibody technique (Fluoro HEPANA test; Medical & Biological Laboratories, Nagoya, Japan). Anti-thyroglobulin and thyroid microsomal antibodies were detected by radioimmunoassay (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany).

*Autologous serum skin test and assay of inflammatory markers*

Antihistamines and corticosteroids were withdrawn at least 5 days before blood sampling. An intradermal autologous serum skin test (ASST) was performed according to the method described in the EAACI/GA²LEN task force consensus report (11). A positive result was defined as a serum-induced wheal with a diameter at 30 min at least 1.5 mm greater than that induced by saline. Serum concentrations of CRP (IBL-America, Minneapolis, USA) and TNF-α (R&D systems, Minneapolis, USA) were measured by enzyme-linked immunoassay (ELISA) using commercially available reagents.

*Statistical analyses*

Data for continuous variables are shown as means ± standard deviations (SD). Prevalence rates are shown as percentages. Student's *t*-test and analysis of variance (ANOVA) were used for between-group comparisons of continuous variables. Categorical variables were compared using the Pearson's $\chi^2$ test. Spearman's rho test was applied for correlation analysis. Logistic regression was used to examine the effects of various factors on risk of MetS and uncontrolled CU. *p*-values < 0.05 were considered significant. All statistical analyses were performed using SPSS for Windows version 12 (SPSS, Chicago, IL, USA).

## RESULTS

### *Prevalence of metabolic syndrome*

In total, 131 patients with CU were enrolled. Patients comprised 49 men (37.4%) and 82 women (62.6%) with a mean age of 40.5 ± 10.6 years. BMI ranged from 16.9 to 32.0 kg/$m^2$. Nine patients (6.96%) had previously been diagnosed with diabetes and/or hypertension. Thirty-nine patients (29.8%) met the criteria for MetS, compared with 229 (17.8%) of the 1,285 age- and gender-matched controls. The difference in the prevalence of MetS between patients with CU and controls was statistically significant ($p = 0.001$). Comparison of individual MetS components between patients with CU and controls revealed that the prevalences of central obesity and high levels of glucose and triglycerides were significantly higher in patients with CU (Table I).

### *Association of clinical characteristics of chronic urticaria with metabolic syndrome*

As shown in Table II, patients with CU with MetS were significantly older (mean age 45.1 ± 9.9 vs. 38.5 ± 10.3 years, $p = 0.001$), and were more often males (53.8% vs. 30.4%, $p = 0.011$), compared with those without MetS.

Table I. *Prevalences of individual metabolic syndrome components in patients with chronic urticaria (CU) and normal controls (NCs)*

| | CU<br>*n* = 131<br>*n* (%) | NCs<br>*n* = 1,285<br>*n* (%) | *p*-value |
|---|---|---|---|
| Central obesity | 69 (52.7) | 499 (38.8) | 0.002 |
| Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg | 41 (31.3) | 371 (28.9) | 0.524 |
| Glucose ≥ 100 mg/dl or DM | 44 (33.6) | 228 (17.7) | < 0.001 |
| Triglycerides ≥ 150 mg/dl (or on lipid-lowering agents) | 42 (32.1) | 266 (20.7) | 0.001 |
| HDL ≤ 40 mg/dl for men or ≤ 50 mg/dl for women | 36 (27.5) | 311 (24.2) | 0.301 |

BP: blood pressure; DM: diabetes mellitus; HDL: high-density lipoprotein.

Table II. *Comparison of clinical characteristics of patients with chronic urticaria (CU) with and without metabolic syndrome (MetS)*

| | With MetS $n=39$ | Without MetS $n=92$ | $p$-value |
|---|---|---|---|
| Age, years, mean ± SD | 45.1 ± 9.9 | 38.5 ± 10.3 | 0.001 |
| Male, *n* (%) | 21 (53.8) | 28 (30.4) | 0.011 |
| BMI, kg/m², mean ± SD | 25.0 ± 2.8 | 22.1 ± 2.5 | <0.001 |
| Waist circumference, cm, mean ± SD | 90.4 ± 6.2 | 80.6 ± 6.7 | <0.001 |
| Systolic BP, mmHg, mean ± SD | 130.8 ± 13.1 | 115.8 ± 13.7 | <0.001 |
| Diastolic BP, mmHg, mean ± SD | 77.1 ± 15.0 | 70.5 ± 10.0 | 0.004 |
| Glucose, mg/dl, mean ± SD | 120.6 ± 52.3 | 94.8 ± 17.9 | 0.005 |
| Triglycerides, mean ± SD | 208.6 ± 124.6 | 92.2 ± 50.1 | <0.001 |
| HDL, mean ± SD | 45.9 ± 13.4 | 57.5 ± 11.6 | <0.001 |
| Duration of CU, months, mean ± SD | 36.0 ± 68.3 | 22.4 ± 37.9 | 0.249 |
| Log total IgE, KU/l, mean ± SD | 2.17 ± 0.51 | 2.04 ± 0.49 | 0.165 |
| Atopy, *n* (%) | 13 (33.3) | 35 (38.0) | 0.609 |
| Angioedema, *n* (%) | 8 (20.5) | 40 (43.5) | 0.017 |
| Anti-thyroid antibodies, *n* (%) | 9/37 (24.3) | 18/90 (20.0) | 0.548 |
| ANA, *n* (%) | 4/34 (11.8) | 12/90 (13.3) | 0.816 |
| ASST, *n* (%) | 5/35 (14.3) | 29/73 (39.7) | 0.008 |
| C3, mg/dl, mean ± SD | 142.7 ± 32.2 | 124.5 ± 31.1 | 0.003 |
| C4, mg/dl, mean ± SD | 33.9 ± 11.8 | 27.8 ± 8.0 | 0.005 |
| Log ECP, µg/l, mean ± SD | 1.38 ± 0.37 | 1.230 ± 0.38 | 0.047 |
| Log TNF-α, pg/ml, mean ± SD | –0.43 ± 1.33 | –1.09 ± 1.16 | 0.026 |
| Log CRP, µg/ml, mean ± SD | 0.074 ± 0.54 | –0.11 ± 0.62 | 0.198 |

SD: standard deviation; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; ANA: anti-nuclear antibody; ASST: autologous serum skin test; ECP: eosinophilic cationic protein; CRP: C-reactive protein; C: complement.

Mean total serum IgE levels, atopy rates, and prevalences of serum autoantibodies, such as ANA and anti-thyroid antibodies, did not differ between CU patients with and without MetS. The prevalence of angioedema and the positive ASST rate were significantly higher in patients without MetS than in those with MetS (43.5% vs. 20.5%, $p=0.017$ for angioedema, and 39.7% vs. 14.3%, $p=0.008$ for ASST, respectively).

Among systemic inflammatory markers, serum levels of complement component 3 (C3), C4, ECP and TNF-α were significantly higher in patients with MetS than in those without MetS (Table II). However, serum CRP levels and peripheral neutrophil counts did not differ significantly according to the presence or not of MetS. Among the 5 components of the UAS, wheal duration (UAS3) was significantly correlated with levels of C3 ($r=0.196$, $p=0.027$), C4 ($r=0.247$, $p=0.005$) and CRP ($r=0.243$, $p=0.032$), while total UAS and the other 4 components of the UAS did not show any correlations with inflammatory markers.

### *Association of MetS with clinical outcomes in CU*

Mean UAS in patients with CU and MetS was significantly higher than that in patients without MetS (Table III). Among 5 components of the UAS, wheal duration was significantly different between the 2 groups. The proportion of patients with a UAS of ≥13 was significantly higher in those with MetS (50%) compared with those without MetS (20.6%).

The requirements for antihistamines and systemic steroids were not different between the 2 groups. However, the proportion of patients whose urticaria remained uncontrolled after 3 months of treatment was significantly greater for those with MetS (Table III). Uncontrolled urticaria was found in 35.9% of patients with MetS and only 13.0% of those without MetS (odds ratio (OR), 3.73, 95% confidence interval (CI), 1.53–9.11; $p=0.003$). Remission rates for the 3-month treatment period were not significantly different between the 2 groups.

### *Predictors of metabolic syndrome and uncontrolled chronic urticaria*

Table IV summarizes the independent predictors of MetS in the study subjects. Uncontrolled CU, negative ASST results, and a UAS of ≥13 independently predicted MetS (after adjustment for confounders including age and gender). Furthermore, logistic regression analysis indicated that a UAS of ≥13 ($p=0.030$) and presence of MetS ($p=0.039$) were significant and independent predictors of uncontrolled CU.

There were significant positive correlations between uncontrolled CU and levels of both TNF-α ($r=0.265$ and $p=0.019$) and ECP ($r=0.222$ and $p=0.012$).

*Table III. Association of metabolic syndrome (MetS) with clinical outcomes in chronic urticaria (CU)*

| | With MetS $n=39$ | Without MetS $n=92$ | $p$-value |
|---|---|---|---|
| Mean UAS, mean ± SD | 11.6 ± 2.6 | 10.7 ± 2.1 | 0.024 |
| UAS1, wheal number, mean ± SD | 2.28 ± 1.0 | 2.20 ± 1.0 | 0.654 |
| UAS2, wheal distribution, mean ± SD | 2.64 ± 0.6 | 2.46 ± 0.7 | 0.130 |
| UAS3, wheal duration, mean ± SD | 2.13 ± 0.9 | 1.66 ± 0.8 | 0.005 |
| UAS4, wheal size, mean ± SD | 2.28 ± 0.8 | 2.15 ± 0.9 | 0.432 |
| UAS5, pruritus, mean ± SD | 2.36 ± 0.8 | 2.23 ± 0.8 | 0.412 |
| UAS ≥13, *n* (%) | 18 (46.2) | 20 (21.7) | 0.005 |
| H1RA requirement, loratidine mg/day, mean ± SD | 30.8 ± 16.6 | 27.6 ± 13.2 | 0.285 |
| Steroid requirement, prednisolone mg/month, mean ± SD | 28.7 ± 49.17 | 20.8 ± 58.1 | 0.457 |
| Control status after 3 months, *n* (%) | | | |
| Remission | 5 (12.8) | 13 (14.1) | 0.010 |
| Well-controlled disease | 20 (51.3) | 67 (72.8) | |
| Uncontrolled disease | 14 (35.9) | 12 (13.0) | |

SD: standard deviation; UAS: total urticaria activity score; H1RA: histamine receptor 1 antagonist.

Table IV. *Logistic regression: factors correlated with metabolic syndrome (MetS) and uncontrolled chronic urticaria (CU)*

| | | | 95% CI | |
|---|---|---|---|---|
| | *p*-value | Odds ratio | Lower | Upper |
| Model for MetS: $r^2=0.254$, $p<0.001$ | | | | |
| Negative ASST | 0.018 | 4.692 | 1.306 | 16.848 |
| UAS ≥13 | 0.020 | 3.498 | 1.215 | 10.076 |
| Uncontrolled CU | 0.030 | 3.782 | 1.136 | 12.589 |
| Total IgE, KU/l | 0.361 | 1.001 | 0.998 | 1.003 |
| Age, years | 0.179 | 1.034 | 0.985 | 1.085 |
| Gender | 0.219 | 1.868 | 0.690 | 5.061 |
| Model for uncontrolled CU: $r^2=0.145$, $p=0.010$ | | | | |
| UAS ≥13 | 0.025 | 3.554 | 1.176 | 10.744 |
| MetS | 0.036 | 3.652 | 1.087 | 12.274 |
| Negative ASST | 0.347 | 0.553 | 0.161 | 1.900 |
| Total IgE, KU/l | 0.691 | 1.000 | 0.998 | 1.003 |
| Age, years | 0.951 | 0.998 | 0.947 | 1.053 |
| Gende, male | 0.554 | 1.399 | 0.460 | 4.259 |

ASST: autologous serum skin test; UAS: urticaria activity score; CI: confidence interval.

## DISCUSSION

Approximately 30% of patients with CU in this study had MetS, and patients with MetS presented with poor clinical outcomes in CU, such as a higher mean UAS and a higher proportion of uncontrolled CU. Moreover, severe and uncontrolled urticaria was significantly comorbid with MetS in patients with CU. Thus, it appears that possible interplays between progression of urticaria and MetS may promote systemic inflammation in patients with CU. However, from the results of this cross-sectional study in Korean patients, we cannot elucidate whether the increased systemic inflammation is an epiphenomenon or plays a role in the pathogenesis of CU with MetS.

Asthma, atopic dermatitis, psoriasis, and rheumatoid arthritis have been reported to increase the risk of MetS (8, 9, 13–15). Although systemic inflammation and activated coagulation signalling are commonly found in patients with MetS and CU (1, 2, 5, 16, 17), no investigation has yet studied the prevalence and clinical features of MetS in patients with CU. We found that the prevalence of MetS was significantly higher among patients with CU than in healthy controls. The prevalence of MetS, as determined by the same criteria used for normal controls, was 17.8%, a similar figure to that reported in an epidemiological study in Korea (6).

MetS defines a cluster of interconnected metabolic abnormalities with central obesity and insulin resistance as the central characteristics. There is growing evidence that obesity is characterized by chronic low-grade inflammation. Indeed, circulating levels of inflammatory markers, including pro-inflammatory cytokines, acute-phase proteins, and anti-inflammatory cytokines, are increased in obese individuals (18). Several investigations have detected circulating levels of TNF-α, IL-1, IL-6 and CRP in most patients with CU with both positive and negative ASST results (2, 3). Although the ASST results were not associated with TNF-α or CRP levels in our study, the prevalence of MetS was significantly higher in patients with negative ASST results. A previous report revealed that both IL-10 mRNA expression in peripheral blood mononuclear cells and IL-10 secretion in response to a T-cell stimulus were significantly decreased in patients with CU with negative ASST results compared with both healthy controls and patients with CU with positive ASST results (3). IL-10 reduces the production of pro-inflammatory cytokines by various immune cells, including monocytes, B cells, and Th1 cells (19). Our finding that positive ASST results were an important protective predictor of MetS in patients with CU might reflect altered IL-10 secretion.

TNF-α, a powerful regulator of the synthesis of IL-6, and CRP and complement proteins have been identified as key risk factors for insulin resistance and MetS (7). We confirmed that levels of TNF-α and C3 were significantly higher in patients with CU with MetS, and were directly correlated with a higher UAS and uncontrolled CU. This is in agreement with previous studies, which showed that circulating levels of TNF-α and associated markers such as IL-6 and CRP were significantly correlated with clinical activity in patients with CU (2, 20). However, we did not find direct correlations between CRP levels and TNF-α, MetS, or CU outcomes in this study. Taken together, these results suggest that C3 and TNF-α can be considered central mediators in the interaction between MetS and CU. However, we cannot overlook the role of CRP in sustaining low-grade inflammation in patients with CU.

With regard to the associations between obesity and atopy or total IgE levels or chronic inflammatory skin diseases, some studies have reported similar associations (8, 13–15, 21). Obesity results in decreased immunological tolerance to antigens, and slanting of the immune system towards a Th2 profile. However, no study has yet determined whether obesity or other metabolic abnormalities are associated with CU. We found that waist circumference was significantly correlated with not only triglyceride and TNF-α levels, but also Th2 profiles, as defined by serum total IgE and ECP levels, among patients with CU. Furthermore, triglyceride levels were associated with urticaria severity and control status. Therefore, obesity may be associated with increased disease activity in CU, as has been shown for other chronic inflammatory skin diseases (15, 20).

As several histological studies have identified eosinophils as the main source of elevated levels of vascular endothelial growth factor (VEGF) and tissue factor in CU lesional skin, activation of eosinophils has been suggested to be a relevant event in the pathogenesis of CU (17, 22). A previous study demonstrated that activated eosinophils were more persistently involved in patients with CU without autoantibodies (23). We also found that patients with CU with uncontrolled disease or with MetS have higher serum levels of ECP and frequently produce negative ASST results. Clinical manifestations including

angioedema and cold and dermographic urticaria have been reported to be positively associated with serum ECP levels in patients with CU (24). In the present study, the ECP level did not vary according to the presence of angioedema, although it was significantly correlated with waist circumference and serum levels of C3 and total IgE. Thus, elevated serum ECP levels may also play a role in the interaction between CU and MetS.

The results of logistic regression analyses showed that UAS $\geq$13, uncontrolled disease activity and MetS were inter-dependent risk factors in patients with CU. We conclude that patients with severe and uncontrolled CU should be evaluated for the presence of MetS to reduce cardiovascular risk factors, as well as to improve CU outcomes. In addition, regardless of disease activity, patients with negative ASST results should be examined for MetS.

In conclusion, both MetS and CU may share chronic low-grade inflammation involving TNF-α, ECP and C3, and may be mutually triggered or exacerbated. However, further studies are needed to validate the association between MetS and CU and to investigate the risk of cardiovascular diseases and diabetes among patients with CU. Whether strategies to alleviate central obesity and dyslipidaemia will be helpful in controlling CU remains to be determined.

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