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Can Body Mass Index and/or Waist Circumference Be the Risk Factors of Chronic Spontaneous Urticaria?: A Nationwide Population-Based Study

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Dear Editor:

Several studies have suggested an association between chronic spontaneous urticaria (CSU) and body mass index (BMI)[1-3] or metabolic syndrome[1,4]. In contrast, a French study reported that obesity was not associated with severe CSU[5]. There is little evidence that waist circumference (WC), another scale which correlates well with visceral obesity, is associated with CSU. We hypothesized that obesity could be associated with increased CSU risk. The aim of our study was to investigate the impact of BMI and/or WC on the risk for CSU in an adult Korean population using a nationwide database. The study was approved by the Institutional Review Board of The Catholic University of Korea (IRB no. KC16EISE0852).

The health check-up database, a sub-dataset of the Korean National Health Insurance Service (NHIS) database (2002～2015), was used for data collection. NHIS subscribers are advised to have biannual health check-ups including height,

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weight, WC, systolic and diastolic blood pressure, and laboratory examinations, which constitute the health check-up database. Data from all Korean subjects aged ≥20 years from January 1, 2002, to December 31, 2015, were extracted for analysis. Among them, subjects who had undergone at least one biannual health examination between 2009 and 2012 were followed up from the date of their health check-up until 2015 as the endpoint of the occurrence of CSU. For subjects with more than twice health check-ups, the first result was used. The incidence was calculated as the number of patients with newly diagnosed CSU divided by the total person-years at risk. Because a diagnostic code for CSU does not exist in the International Classification of Diseases (ICD)-10, a diagnosis of CSU was defined when one of the following two criteria were met: either 1) two outpatient diagnoses of L50.1 (idiopathic urticaria), L50.8 (other specified urticaria), or L50.9 (urticaria, unspecified) at least 6 weeks apart in one year; or 2) one outpatient diagnosis of L50.1, L50.8, or L50.9 plus one diagnosis of T78.3 (angioneurotic edema) at least 6 weeks apart in one year. This definition was validated in American study using ICD-9 based diagnostic code to have a positive predictive value of 90.4% and a sensitivity of 71.1%[6]. To ensure that only newly diagnosed subjects were included, at-risk subjects were defined as those who had not been diagnosed with CSU between 2002 and the date of the health check-up. The high BMI (general obesity) group was defined as subjects with BMI more than ≥25 kg/m^2, and the high WC (abdominal obesity) group was defined as subjects with WC more than 90 cm in men or 85 cm in women, according to the Korean definition for obesity[7]. Comorbidities were identified using the results of laboratory examinations or diagnostic codes and any associated medications prescribed during the study period. Cox proportional hazards regression analyses were conducted to calculate the multivariable hazard ratio (HR) and 95% confidence interval (CI) for the association of BMI and WC with the incidence of CSU after adjusting for demographic factors of age, gender, smoking status, alcohol consumption, and exercise, and comorbidities of diabetes mellitus, hypertension, and hyperlipidemia. Detailed histories of smoking status, alcohol consumption, and physical activity were obtained by questionnaire, and they were further classified into two categories each for smoking (no/past, and current), alcohol (≥30 g daily or no). Socioeconomic status was categorized into two groups based on income level (<20% or ≥20%).

Table 1. A comparison of the clinical characteristics of the study population according to the presence or absence of chronic spontaneous urticaria

	No CSU (%) (n=22,741,513)	CSU (%) (n=289,493)	*p*-value
Mean age (yr)	47.6±14.4	53.3±14.4	<0.0001
20~39	6,661,651 (29.3)	49,550 (17.1)	<0.0001
40~64	12,954,599 (57.0)	168,891 (58.3)	
≥65	3,125,263 (13.7)	71,052 (24.5)	
Gender (women)	11,176,012 (49.1)	159,480 (55.1)	<0.0001
Mean BMI	23.7±3.3	23.9±3.2	<0.0001
High WC	6,402,141 (28.2)	101,341 (35.0)	<0.0001
Current smoker	5,608,991 (24.7)	57,864 (20.0)	<0.0001
Heavy drinker	1,511,135 (6.6)	15,233 (5.3)	<0.0001
Income (≥20%)	16,671,929 (73.3)	209,663 (72.4)	<0.0001
DM	2,096,912 (9.2)	36,127 (12.5)	<0.0001
HTN	5,954,519 (26.2)	98,731 (34.1)	<0.0001
Hyperlipidemia	4,351,294 (19.1)	72,802 (25.1)	<0.0001
Mean SBP	122.2±15.2	123.3±15.4	<0.0001
Mean DBP	76.1±10.1	76.4±10.0	<0.0001
Mean glucose	97.5±23.4	98.9±24.4	<0.0001
Mean total cholesterol	194.6±36.9	196.9±37.9	<0.0001
Mean HDL	55.5±16.7	55.0±18.1	<0.0001
Mean LDL	113.4±33.6	115.2±34.6	<0.0001

Data are expressed as mean±standard deviation for continuous variables and numbers (percentages) for binary variables. CSU: chronic spontaneous urticarial, BMI: body mass index, WC: waist circumference, DM: diabetes mellitus, HTN: hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein. *p*-values represent the comparison of clinical characteristics between subjects who did and did not develop CSU using Student's t-tests for continuous variables and the chi-square test for categorical variables.

Table 2. Multivariate Cox proportional-hazards regression analysis of the association between either the BMI or the waist circumference and the CSU incidence rate

Group	Number	CSU	Incidence rate*	Model 1	Model 2
BMI (kg/m^2)					
<18.5	935,423	10,004	2.019	1 (reference)	1 (reference)
18.5≤BMI<23	9,162,223	107,997	2.192	1.02 (1.00~1.04)	1.02 (1.00~1.04)
23≤BMI<25	5,567,473	72,891	2.410	1.06 (1.04~1.08)	1.05 (1.03~1.07)
25≤BMI<30	6,512,383	87,546	2.484	1.09 (1.06~1.11)	1.06 (1.04~1.09)
≥30	853,504	11,055	2.452	1.12 (1.09~1.15)	1.08 (1.05~1.11)
WC (cm)					
<80	8,600,674	91,438	1.986	1 (reference)	1 (reference)
80≤WC<85	5,308,064	65,337	2.268	1.04 (1.03~1.05)	1.03 (1.02~1.04)
85≤WC<90	4,488,788	61,711	2.531	1.09 (1.07~1.10)	1.07 (1.06~1.08)
90≤WC<95	2,682,123	39,811	2.740	1.13 (1.12~1.15)	1.11 (1.10~1.13)
95≤WC<100	1,238,068	19,717	2.958	1.18 (1.16~1.20)	1.15 (1.13~1.17)
100≤WC<105	476,348	7,726	3.039	1.20 (1.17~1.23)	1.17 (1.14~1.19)
105≤WC<110	161,007	2,541	2.991	1.18 (1.14~1.23)	1.14 (1.10~1.19)
≥110	75,934	1,212	3.084	1.28 (1.21~1.35)	1.23 (1.16~1.30)

Values are presented as hazard ratio (95% confidence interval). Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, smoking status, alcohol status, exercise status, household income, and the presence of diabetes mellitus, hypertension and hyperlipidemia. BMI: body mass index, CSU: chronic spontaneous urticarial, WC: waist circumference. *Per 1,000 person-years.

In total, 23,031,006 subjects were followed for a mean duration of 5.4±1.1 years, and 289,493 cases of CSU were identified during the follow-up period. The clinical characteristics of the study population classified according to the development of CSU were summarized (Table 1). Those who developed CSU were more likely to be elderly and women and also to have a higher BMI, WC, and more comorbidities than subjects who did not ($p<0.0001$). Table 2 displays the results of the adjusted HR of CSU stratified by BMI and WC after accounting for demographic factors and comorbidities. The adjusted HR for CSU was the lowest in subjects with a BMI <18.5 kg/m^2 (HR, 1; reference) and a WC <80 cm (HR, 1; reference), whereas the highest rates were seen for those with a BMI >30 kg/m^2 (HR, 1.08; 95% CI, 1.05~1.11) and a WC >110 (HR, 1.23; 95% CI, 1.16~1.30), respectively. Overall, higher BMIs and WCs were weakly associated with an increasing tendency for an adjusted HR of CSU.

Population-based study from Italy found a significantly increased risk of CSU in subjects with obesity defined by BMI in the study population including subjects from a primary care clinic only[2]. Our study provided possible evidence that obesity could have a role in the development of CSU. Furthermore, we found that abdominal obesity had a greater impact on the risk of CSU than general obesity These results are in line with a large body of evidence indicating that abdominal obesity has greater impact on obesity-related health risks than general obesity[8]. Although the precise mechanism linking obesity and CSU remains unknown, systemic inflammatory cytokines are associated with both obesity and CSU presence or disease activity[9,10]. The systemic inflammatory response resulting from obesity is thought to be involved in the pathogenesis of CSU[3,4,9,10]. Further studies are needed to elucidate any causal relationship for the obesity-CSU link.

The major strength of our study was a long-term retrospective cohort study design using nationwide database. Moreover, both BMI and WC were measured using a consistent method in real-world clinical practice, validating the results. Limitation was the possibility of false diagnoses. The effects of unidentified confounding factors could not be adjusted. To overcome the limitations, we used a validated definition of CSU and adjusted for possible confounding factors, although the validation study has not been done in Korea. We excluded the patients who did not undergo the health examination, which makes it difficult to generalize the results. In conclusion, our nationwide, population-based study demonstrated that both higher BMI and higher WC were weakly associated with an increased risk of CSU after adjusting for demographic factors and comorbidities. The proposed obesity-CSU link could expand our understanding of the pathogenesis and comorbidities of CSU.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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