Original Article

DOI: 10.4274/haseki.galenos.2022.8399
Med Bull Haseki 2022;60:263-269

Abdominal Obesity and Metabolic Parameters in Chronic Spontaneous Urticaria

Nida Oztop*, Sengul Beyaz**, Cihan Orcen***

*Basaksehir Cam and Sakura City Hospital, Clinic of Adult Immunology and Allergic Diseases, Istanbul, Turkey

**Ankara City Hospital, Clinic of Adult Immunology and Allergic Diseases, Ankara, Turkey

***University of Health Sciences Turkey, Derince Training and Research Hospital, Clinic of Adult Immunology and Allergic Diseases, Kocaeli, Turkey

Abstract

Aim: Abdominal obesity (AO) can affect some disease developments such as diabetes, cardiovascular diseases, or thyroid autoimmunity. To date, there is no data on the anthropometric parameters' impact on the development of refractory chronic spontaneous urticaria (CSU). We evaluated the impact of AO on the course of the presence of refractory CSU and to determine the possible associated risk factors for having refractory CSU.

Methods: This study was designed as a retrospective study and data was collected from January 2021 to April 2022. For determining AO, the waist-to-height ratio (WHtR) was used and calculated by the physicians, retrospectively. WHtR>0.5 was considered AO. Patients were divided into two groups [Group 1= refractory CSU (n=87) and Group 2= non-refractory CSU (n=83)]. Demographics, clinical characteristics of patients, and laboratory test findings were recorded from patients' medical files, retrospectively.

Results: A hundred and seventy CSU patients were included in the study. The mean age of the patients was 38.95±13.08 years. The number of patients accompanying angioedema was significantly higher in refractory CSU than in non-refractory CSU [65 (74.7%) vs 45 (54.2%), p=0.005]. Exacerbation of urticaria plaques with stress was more common in refractory CSU than in non-refractory CSU (p=0.030). WHtRs were similar in both groups. Baseline C-reactive protein (CRP) and blood neutrophil count were significantly higher in refractory CSU (p=0.008 and p=0.024, respectively).

Conclusion: High baseline CRP levels, baseline blood neutrophil count, stress and angioedema accompanying CSU are the associated risk factors of refractory CSU in the Turkish population. Furthermore, AO may not have an impact on the development of antihistamine refractory CSU.

Keywords: Refractory urticaria, abdominal obesity, angioedema, stress, autoimmunity

Introduction

Urticaria is characterized by transient pruritic wheals with or without angioedema, and if urticaria plaques persist for more than six weeks, it is defined as chronic urticaria (CU) (1). Although CU symptoms are related to activated skin mast cell mediators such as histamine, the underlying mechanism of mast cell activation is still unknown (1). CU is more common in females than in males. Usually, CU can be self-limited. However, it can persist for years in 20% of patients (2). More than 50 million patients could have been affected by CU in their lifetime and it deteriorates patients' quality of life (QoL) and social activities (3). According to the International EAACI/GA2LEN/WAO, CU is divided into two groups: (a) chronic spontaneous urticaria (CSU), which has no identified eliciting factors, and (b) chronic inducible urticaria, which has a specific stimulation to occur, such as cold, heat, pressure, or vibration (1). Although CSU has no trigger for the symptoms, some specific factors can exacerbate the urticaria plaques like drugs (e.g. non-steroidal anti-inflammatory drugs), infections, emotional stress, or some foods (e.g. species) (1,4). In the recent urticaria guidelines, CSU is classified as type 1 [autoallergic, related to immunoglobulin E (IgE) to

Address for Correspondence: Nida Oztop,
Basaksehir Cam and Sakura City Hospital, Clinic of Adult Immunology and Allergic Diseases, Istanbul, Turkey
Phone: +90 212 909 60 00 E-mail: nida_oztop@hotmail.com ORCID: orcid.org/0000-0003-2607-3833
Received: 14.04.2022 **Accepted:** 15.05.2022

self-antigens] and type IIb (autoimmune, related to mast-cell activating autoantibodies) (1).

Using a standard dose of second-generation H1 antihistamines is suggested as the first-line therapy for CSU (1,4). Up-dosing to fourfold antihistamine can be used as a second-line therapy if CSU persists in the patients (1,4). Nevertheless, if the CSU persists under the four-dose H1 antihistamine therapy, omalizumab treatment, which is an anti-IgE monoclonal antibody, could be suggested to control refractory CSU (1,4). However, it is still unclear to predict in which patients do not respond to antihistamine therapy.

Although it is well known that patients' diets, conditions, and abdominal obesity (AO), which is related to anthropometric parameters including body mass index (BMI), waist circumference (WC), or hip circumference, can affect some disease development such as diabetes, cardiovascular diseases, or thyroid autoimmunity (5-8). In the literature, there is no data on the anthropometric parameters' impact on the development of refractory CSU. Additionally, to date, there is limited data on which patients with CSU could have refractory disease and are unresponsive to antihistamine therapy. Therefore, in this study, we aimed to evaluate the impact of AO on the course of the presence of refractory CSU. Additionally, we aimed to determine the possible risk factors for having refractory CSU.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital's Ethics Committee (date: 12.05.2022, approval number: 2022-40) and written informed consent was obtained from all included patients.

Patient Selection and Study Design

This study was designed as a retrospective study, and data was collected from January 2021 to April 2022. A hundred and seventy CSU patients who were more than 18 years old and were followed at the Adult Immunology and Allergic Diseases outpatient clinic were included in this retrospective study. CSU was diagnosed according to the International EAACI/GA2LEN/WAO and Turkish National Society Urticaria guidelines, and refractory CSU was defined as patients who did not respond to four-fold antihistamine therapy for one month (1,4). Patients with known autoimmune diseases, accompanying physical urticaria, and those using omalizumab treatment were excluded from the study. To determine the differences between refractory or non-refractory CSU, patients were divided into two main groups as Group 1, which had refractory CSU under four-fold antihistamine treatment for one month (n=87, 51.2%), and Group 2, which had well-controlled CSU under the antihistamine treatment for one month (n=83, 48.8%).

Clinical Data Collection

Demographics and clinical features of the patients, including age, gender, smoking and alcohol habits, disease duration time, presence of angioedema accompanying CSU or other disease history, triggers (food, drugs, infection or stress) for CSU, and used antihistamine doses were collected from the patients records. To evaluate the AO impact on the development of refractory CSU, anthropometric measurements including weight, height, BMI, and WC were collected from patients' records, retrospectively. To determine the AO, the waist-to-height ratio (WHtR) was used (9), and it was calculated by the physicians, retrospectively. According to the literature, a WHtR>0.5 was considered as having AO (9).

Data for the standard diagnostic evaluation of the patients, baseline laboratory testing including neutrophil, lymphocyte, basophil, eosinophil count, fasting blood glucose, LDL cholesterol, triglyceride, anti-thyroid peroxidase, and C-reactive protein (CRP) were recorded from patients' medical files. The neutrophil/lymphocyte ratio (N/Lr) was calculated retrospectively. Turkish validated seven-day urticaria activity score (UAS7) was used for evaluating the disease activity before and 1 month after the antihistamine treatment (1). Accordingly, the UAS7=28-42, UAS7=16-27, UAS7s=7-15, and UAS7≤6 are considered as severe, moderate, mild, and well-controlled, respectively (1). Stress level was collected from patients' records which was evaluated with visual analogue scale (VAS)" if VAS was >5, it was considered as having high stress level (3).

Statistical Analysis

The Statistical Package for Social Sciences version 25.0 (SPSS Inc., Armonk, NY, USA) was used to analyze the data, and GraphPad Prism software (San Diego, CA, USA) was used for graphics.The patients' descriptive characteristics are presented as mean standard deviation, median, and interquartile range (IQR) percentile of 25-75. A Kolmogorov-Smirnov test was conducted to evaluate the normality of data. The chi-square test and Mann-Whitney U test were used to compare categorical and continuous variables, respectively. A binary logistic regression test was used for the analysis of risk factors for having refractory CSU. A p-value of 0.05 or lower is generally considered statistically significant.

Results

Results of Demographics and Clinical Characteristics, and Laboratory Findings of the Patients

While the mean age of the patients was 38.95±13.08 years, the median (IQR) CSU duration time was 24 (8.5-48) months. One hundred and twenty-two (71.8%) patients were female and less than half of the patients had smoking habits (n=72, 42.4%). Whilst the number of patients accompanying angioedema history was 110 (64.7%), 114 (67.1%) patients had AO. Before the antihistamine treatment, the mean UAS7 was 34.91±5.81. Stress was the most common trigger for exacerbation of urticaria plaques in the patients (n=114, 67.1%) (Figure 1A). Before the antihistamine treatment, 160 (94.1%) patients had severe CSU and 10 (5.9%) patients had moderate CSU. While the mean BMI of the patients was 26.42±5.10 kg/m^2, the mean WC and WHtR of the patients were 90.08±13.83 cm and 0.83±0.09, respectively. One hundred and fourteen (67.1%) patients had a WHtR of more than 0.5. Baseline demographics, clinical characteristics, and laboratory findings of the patients are summarized in Table 1.

Comparison Analysis Between Refractory and Non-refractory CSU Patients

The mean ages were 40.41±13.03 years and 37.43±13.04 years in Group 1 and Group 2, respectively (p>0.05). More than half of the patients were female in both groups [n=61 (70.1%) vs n=61 (73.5%), p>0.05]. The number of patients with angioedema accompanying CSU was significantly higher in Group 1 than in Group 2 [65 (74.7%) vs 45 (54.2%), p=0.005]. Exacerbation of urticaria plaques with stress was more common in Group 1 than in Group 2 (p=0.030) (Figure 1B). BM, WC, and WHtR were similar in both groups (p>0.05 for each). While 56 (64.4%) patients had AO in Group 1, 58 (59.9%) patients had AO in Group 2 (p>0.05). Group 1 had significantly higher CRP and neutrophil counts (p=0.008 and p=0.024, respectively). The comparison analysis between Group 1 and Group 2 is summarized in Table 2.

Analysis of Associated Possible Risk Factors for Having Refractory CSU

The regression analysis, which was performed to determine associated risk factors for refractory CSU, showed that having stress and accompanying angioedema were associated risk factors for refractory CSU [odds ratio (OR)=2.05, (95% confidence interval (CI) 1.06-3.93), p=0.031 and OR=2.49, (95% CI 1.30-4.77), p=0.006, respectively]. Furthermore, higher CRP levels and neutrophil counts were associated with the presence of refractory CSU (Table 3).

Discussion

This study demonstrated that having stress and angioedema accompanying CSU are related to having refractory to antihistamine treatment in patients with CSU in the Turkish population. Furthermore, higher blood neutrophil counts and CRP levels have been linked to refractory CSU. Additionally, our current study showed, for the first time, that there is no significant relationship between having AO and having refractory CSU.

In recent years, it has been frequently reported that AO has increased and become a global problem with the changes in food consumption habits (10-13). Moreover, it is well-known that AO can play a role in the development of severe diseases, including cardiovascular disease, diabetes, musculoskeletal disorders, or autoimmune diseases such as autoimmune thyroiditis (8,11,14-17). Normally, in

Table 1. Baseline demographics, clinical characteristics, and laboratory findings of the patients

Demographic, clinical and laboratory features of patients	Patients (n=170)
Age (years, mean ± SD)	38.95±13.08
Gender Female (n,%) Male (n,%)	 122 (71.8%) 48 (28.2%)
Current smokers (n,%)	72 (42.4%)
Disease duration time (years, median-IQR)	24 (8.5-48)
Accompanying angioedema (n,%)	110 (64.7%)
BMI (kg/m^2, mean ± SD)	26.42±5.10
WC (cm, mean ± SD)	90.08±13.83
WHtR (mean ± SD)	0.83±0.09
Having AO (n,%)	114 (67.1%)
Baseline UAS7 (mean ± SD)	34.91±5.81
CSU severity before antihistamine treatment Moderate (n,%) Severe (n,%)	 160 (94.1%) 10 (5.9%)
CBC Neutrophil (10^3/µL, median-IQR) Lymphocyte (10^3/µL, median-IQR) Basophil (10^3/µL, median-IQR) Eosinophil (10^3/µL, median-IQR) N/Lr (mean ± SD) **Fasting Blood Glucose (mg/dL, mean ± SD)** **Lipid profile** HDL (mg/dL, mean ± SD) LDL (mg/dL, mean ± SD) Triglyceride (mg/dL, mean ± SD) **CRP (mg/dL, median-range)** **Anti-TPO (IU/mL, median-range)** **Total IgE (IU/mL, median-range)**	 3200 (2700-5100) 1860 (1750-2300) 0 (0-0) 170 (100-250) 2.0±0.88 91.0±23.99 47.19±10.94 120.84±33.39 129.05±58.95 2.10 (1.46-4.99) 28 (9-48) 126 (56-273.5)

AO: Abdominal obesity, Anti-TPO: Anti-thyroid peroxidase, BMI: Body mass index, CBC: Complete blood count, CRP: C-reactive protein, HDL: High densitiy lipoprotein, IgE: Immunoglobin E, LDL: Low density lipoprotein, N/Lr: Neutrophil/lymphocyte ratio, UAS7: Seven days urticaria activity score, SD: Standard deviation, WC: Waist circumference; WHtR: Waist-to-height ratio

Table 2. Comparison analysis of the refractory and non-refractory CSU patients			
Features	**Group 1 (n=87)**	**Group 2 (n=83)**	**p-value**
Age (years, mean ± SD)	40.41±13.03	37.43±13.04	NS
Gender Female (n,%) Male (n,%)	 61 (70.1%) 22 (29.9%)	 61 (73.5%) 22 (26.5%)	 NS
Current smokers (n,%)	42 (48.3%)	45 (51.7%)	NS
Accompanying angioedema (n,%)	65 (74.7%)	45 (54.2%)	**0.005***
Disease duration time (years, median-IQR)	24 (9-48)	18 (8-48.5)	NS
Having AO (n,%)	56 (64.4%)	58 (69.9%)	NS
BMI (kg/m^2, mean ± SD)	26.55±4.72	26.28±5.49	NS
WC (cm, mean ± SD)	89.81±13.75	90.37±13.99	NS
WHtR (mean ± SD)	0.54±0.86	0.54±0.86	NS
Baseline UAS7 (mean ± SD)	35.03±5.74	34.78±5.90	NS
CBC Neutrophil (10^3/µL, median-IQR) Lymphocyte (10^3/µL, median-IQR) Basophil (10^3/µL, median-IQR) Eosinophil (10^3/µL, median-IQR) N/Lr (mean ± SD) **Fasting Blood Glucose (mg/dL, mean ± SD)** **Lipid profile** HDL (mg/dL, mean ± SD) LDL (mg/dL, mean ± SD) Triglyceride (mg/dL, mean ± SD) **CRP (mg/dL, median-IQR)** **Anti-TPO (IU/mL, median-IQR)** **Total IgE (IU/mL, median-IQR)**	 3700 (2800-5100) 1900 (1750-2420) 0 (0-0) 170 (100-200) 2.04±0.88 97.84±28.49 48.15±11.05 123.4±34.31 125.6±56.4 3.03 (1.6-7.37) 28 (2-43) 195 (51-232)	 2800 (2700-5100) 1800 (1750-2100) 0 (0-0) 190 (100-270) 1.96±0.89 94.96±18.26 46.21±10.81 118.1±32.39 132.6±61.66 2 (1.42-3.68) 18 (1-25.2) 140 (63.2-360)	 **0.024**** NS NS NS NS NS NS NS NS **0.008**** NS NS

AO: Abdominal obesity, Anti-TPO: Anti-thyroid peroxidase, BMI: Body mass index, CBC: Complete blood count, CRP: C-reactive protein, HDL: High densitiy lipoprotein, IgE: Immunoglobin E, LDL: Low density lipoprotein, N/Lr: Neutrophil/lymphocyte ratio, NS: Not significant, UAS7: Seven days urticaria activity score, SD: Standard deviation, WC: Waist circumference, WHtR: Waist-to-height ratio
*T-test was used and p<0.05
**Mann-Whitney U test was used and p<0.05

healthy fit people, visceral adipose tissue is important for the immune system due to the metabolism of adipocytes, which regulate immune cell function and produce antibacterial peptides or proinflammatory cytokines (8). However, the uncontrolled increase in visceral adipose tissue (such as AO) may trigger autoimmune diseases by causing an excessive increase in proinflammatory cytokines (18). In our study, in which we investigated the possible impact of AO on refractory CSU, contrary to expectations, we did not observe a difference in terms of AO in patients with and without refractory CSU. However, when we evaluated the all-study population, we observed that more than half of the patients (114) had AO before the antihistamine therapy. Therefore, we may not have been able to show the effect of AO on refractory CSU since most of the patients already had AO. Further studies with a control group without AO and larger numbers of CSU patients are needed to demonstrate the real AO impact on the refractory CSU.

Previously, in the literature, Alen Coutinho et al. (19) characterized the phenotypes of CU refractory to antihistamine treatment and they observed that

Table 3. Factors in association with presence of refractory CSU according to the binary regression analysis			
	OR	**95% CI for OR (Lower-upper)**	**p-value**
Factors			
Angioedema accompanying CSU	2.49	1.30-4.77	**0.006**
Having stress	2.05	1.06-3.93	**0.031**
Baseline CRP level	1.09	1.01-1.18	**0.016**
Baseline blood neutrophil count	1	1.0-1.19	**0.045**

Binary logistic regression analysis is used for all p-values and p<0.05. Parameters that are not found to be statistically significant are not included in the table
CRP: C-reactive protein, NS: Not significant, CSU: Chronic spontaneous urticaria

angioedema accompanying CSU and higher baseline UAS7 are possible predictors of poor control of CSU and treatment should be chosen crucially in the Portugal study. In another study, Sussman et al. (20) reported that angioedema accompanying CSU has a negative effect on QoL. Similar to the literature, in our study, we determined that angioedema accompanying CSU is an

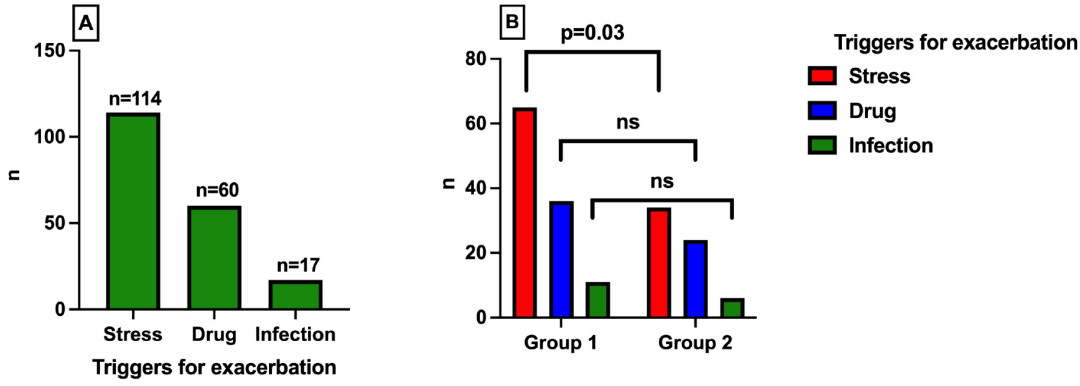

Figure 1. A) Triggers for exacerbation of urticaria plaques in all patients with CSU B) Comparison of triggers for exacerbation of urticaria plaques in Group 1 and Group 2
CSU: Chronic spontaneous urticaria

associated risk factor for having refractory antihistamine therapy in CSU patients. CSU is a mast-cell related disease, furthermore, mast cells can play a role in the development of angioedema (1,21). In line with this knowledge, we may speculate that in the presence of angioedema accompanying CSU, standard and four-fold antihistamine therapy may not be sufficient for symptom control, since the mast cell load will be higher compared to the presence of both diseases alone. In contrast to Alen Coutinho et al.'s (19) study, we did not observe any relationship between baseline UAS7 and poor control of CSU. The reason for this difference between our and Alen Coutinho et al.'s (19) study may be that most patients who applied to us had severe CSU (n=160, 94.1%) than in their study.

Psychological stress stimulates corticotropin releasing hormone (CRH). Furthermore, mast cells can synthesize CRH and express CRH receptors. Thus, psychological stress can cause mast cell degranulation (22,23). Previously, the relationship between psychological stress and increased symptoms in urticaria and mastocytosis was shown in Turkish patients (24,25). Although we collected the stress history from the anamnesis, we observed that stress is a possible associated risk factor for developing refractory CSU similar to the study. In line with this finding, we may think that stress-reducing psychological support may be needed to control refractory CSU and that multidisciplinary approaches to the CSU patients can improve the patients' QoL and control the disease activity.

Although autoimmunity, which is a result of exacerbated systemic inflammatory response, can be a reason for CU (19,26), there is limited data about the impact of autoimmunity on the control of refractory CSU in the Turkish population. In the past, it was reported that high CRP is related to poor disease control in CU (19,27). Similar to the literature, in our study, refractory CSU was associated with a higher CRP level. Although CRP has proinflammatory and anti-inflammatory features, it can be pathogenic when it is activated by autoantibodies in autoimmunity (28). CRP can also rise during an infection or an autoimmune disease (28). Blood neutrophil count can rise in infections, urticaria, and autoimmune diseases, just like CRP (29-31). Furthermore, a high blood neutrophil count may indicate the presence of urticarial syndromes such as urticarial vasculitis (UV) or cryopyrin-associated periodic syndromes (CAPS). If patients with CU undergo antihistamine treatment and have special symptoms for UV or CAPS, urticaria plaque biopsy should be performed (1,31). In our study, we observed a higher baseline neutrophil count in refractory CSU. In line with this information and our findings, we may think that in CSU patients in whom other autoimmune diseases have been excluded, those with a high baseline CRP level and a high blood neutrophil count may be predictors of the antihistamine refractory CSU, and these patients should be followed up more closely.

Study Limitations

Although this study demonstrated the possible risk factors for antihistamine refractor CSU in the Turkish population, we had some limitations. As a first limitation, we could not use a validated stress scale for evaluating the stress level. We could collect the stress history from patients' anamnesis and VAS. We believe that it will be important to conduct further larger studies, including more patients with validated scales, to support our findings. Secondly, we did not have a control group to compare the anthropometric parameters with healthy and CSU patients in the Turkish population. Therefore, we could not comment on the course of anthropometric measurement on the development of CSU; we could just comment on the AO impact on refractory CSU. Another limitation of

our study was the lack of an autologous serum skin test, which is a clue for autoimmunity in CSU patients. But we think that CRP and blood neutrophil counts are good predictors of biomarkers for autoimmunity and the autologous serum skin test.

Conclusion

AO may not have an impact on the presence of antihistamine refractory CSU. However, high baseline CRP and blood neutrophil count, stress and angioedema accompanying CSU are the associated risks of refractory CSU in the Turkish population. Multidisciplinary approaches, including psychiatric evaluation, should be required in refractory CSU. While investigating CSU, accompanying angioedema should be questioned in all patients. Further studies with a larger number of patients are needed to support our findings.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital's Ethics Committee (date: 12.05.2022, approval number: 2022-40).

Informed Consent: Written informed consent was obtained from all included patients.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., N.O., Design: S.B., N.O., Data Collection, or Processing: C.O., Analysis, or Interpretation: N.O., Literature Research: N.O., Writing: N.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

References

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022;77:734-66.
2. Saini SS, Kaplan AP. Chronic Spontaneous Urticaria: The Devil's Itch. J Allergy Clin Immunol Pract 2018;6:1097-106.
3. Marzano AV, Genovese G, Casazza G, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. J Eur Acad Dermatol Venereo 2019;33:918-24.
4. Harmancı K AM, Uysal P, Asilsoy S, et al. Turkiye Ulusal Allerji ve Klinik Immunoloji Derneği Güncel Durum Raporu: Urtiker Tanı ve Tedavisi. Asthma, Allergy&Immunol 2018;16:97-122.
5. Cameron AJ, Magliano DJ, Söderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. Obes Rev 2013;14:86-94.
6. Seo DC, Choe S, Torabi MR. Is waist circumference ≥102/88cm better than body mass index ≥30 to predict hypertension and diabetes development regardless of gender, age group, and race/ethnicity? Meta-analysis. Prev Med 2017;97:100-8.
7. Tettey P, Simpson S, Taylor B, et al. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event. J Neurol Neurosurg Psychiatry 2017;88:395-401.
8. Zynat J, Li S, Ma Y, et al. Impact of Abdominal Obesity on Thyroid Auto-Antibody Positivity: Abdominal Obesity Can Enhance the Risk of Thyroid Autoimmunity in Men. Int J Endocrinol 2020;2020:6816198.
9. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0·5 could be a suitable global boundary value. Nutr Res Rev 2010;23:247-69.
10. Barzin M, Valizadeh M, Serahati S, Mahdavi M, Azizi F, Hosseinpanah F. Overweight and obesity: findings from 20 years of the Tehran lipid and glucose study. Int J Endocrinol Metabol 2018;16(4 Suppl):e84778.
11. Bosomworth NJ. Normal-weight central obesity: Unique hazard of the toxic waist. Can Fam Physician 2019;65:399-408.
12. Kim BY, Kang SM, Kang JH, et al. 2020 Korean Society for the Study of Obesity Guidelines for the Management of Obesity in Korea. J Obes Metab Syndr 2021;30:81-92.
13. Sun M, Feng W, Wang F, et al. Meta-analysis on shift work and risks of specific obesity types. Obes Rev 2018;19:28-40.
14. Real de Asua D, Parra P, Costa R, Moldenhauer F, Suarez C. Evaluation of the impact of abdominal obesity on glucose and lipid metabolism disorders in adults with Down syndrome. Res Dev Disabil 2014;35:2942-9.
15. De Pergola G, Nardecchia A, Ammirati A, Caccavo D, Bavaro S, Silvestris F. Abdominal obesity is characterized by higher pulse pressure: possible role of free triiodothyronine. J Obes 2012;2012:656303.
16. Jayawardena R, Sooriyaarachchi P, Misra A. Abdominal obesity and metabolic syndrome in South Asians: prevention and management. Expert Rev Endocrinol Metab 2021;16:339-49.
17. Kim MH, Song SW, Kim KS. Abdominal Obesity is Associated With Lower Bone Mineral Density in Non-Weight-Bearing Site in Korean Men. Am J Mens Health 2019;13:1557988318813499.
18. Dhawan D, Sharma S. Abdominal Obesity, Adipokines and Non-communicable Diseases. J Steroid Biochem Mol Biol 2020;203:105737.
19. Alen Coutinho I, Regateiro FS, Fernandes RA, et al. Refractory chronic urticaria in adults: clinical characterization and predictors of severity. Allergy Asthma Clin Immunol 2020;16:97.
20. Sussman G, Abuzakouk M, Bérard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: Analyses from ASSURE-CSU. Allergy 2018;73:1724-34.
21. Hahn J, Hoffmann TK, Bock B, Nordmann-Kleiner M, Trainotti S, Greve J. Angioedema. Dtsch Arztebl Int 2017;114:489-96.
22. Theoharides TC. The impact of psychological stress on mast cells. Ann Allergy Asthma Immunol 2020;125:388-92.
23. Theoharides TC. Stress, Inflammation, and Autoimmunity: The 3 Modern Erinyes. Clin Ther 2020;42:742-44.

24. Beyaz S, Demir S, Oztop N, et al. Psychological burden of COVID-19 on mild and moderate chronic spontaneous urticaria. Allergy Asthma Proc 2021;42:e107-15.
25. Öztop N, Demir S, Beyaz Ş, et al. Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic. Allergol Int 2022;71:109-16.
26. Dobrican CT, Muntean IA, Pintea I, Petricău C, Deleanu DM, Filip GA. Immunological signature of chronic spontaneous urticaria (Review). Exp Ther Med 2022;23:381.
27. Takahagi S, Mihara S, Iwamoto K, et al. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. Allergy 2010;65:649-56.
28. Szalai AJ. C-reactive protein (CRP) and autoimmune disease: facts and conjectures. Clin Dev Immunol 2004;11:221-6.
29. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy 2021;76:2965-81.
30. Giménez-Arnau AM, DeMontojoye L, Asero R, et al. The Pathogenesis of Chronic Spontaneous Urticaria: The Role of Infiltrating Cells. J Allergy Clin Immunol Pract 2021;9:2195-208.
31. Marzano AV, Tavecchio S, Venturini M, Sala R, Calzavara-Pinton P, Gattorno M. Urticarial vasculitis and urticarial autoinflammatory syndromes. G Ital Dermatol Venereol 2015;150:41-50.