
Comorbidities in Chronic Spontaneous Urticaria

Müzeyyen Gönül, Hawva Hilal Ayvaz and
Selda Pelin Kartal

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67911>

Abstract

Chronic spontaneous urticaria (CSU) is a disease that makes people's lives miserable with unknown etiology. In recent years, there have been many studies trying to explain the etiology of CSU, and many of them reported that there are some comorbidities or triggering factors related to CSU. However, it has not been clearly known yet that whether these conditions are true comorbidities associated with CSU or they are coincidentally found at the same time. In this chapter, related comorbidities and conditions have been told.

Keywords: chronic spontaneous urticaria, autoimmunity, infectious diseases, psychological comorbidities, coagulation factors, metabolic syndrome

1. Introduction

Chronic spontaneous urticaria (CSU) is a common mast cell-driven skin disorder characterized by the occurrence of recurrent and spontaneously daily or frequent wheals with or without angioedema, for more than 6 weeks with symptoms present at least three times weekly [1, 2]. CSU affects 0.1–5% of the population, especially during the third and fourth decades and predominantly women [3]. There are many studies that some disorders or conditions may be related to CSU.

2. Comorbidities and possible triggering factors

There are studies showing that CSU affects not only the skin but also the life quality and psychology of the person. At the same time, there has been a relation between CSU and other

diseases which can be based on similar pathogenesis such as autoimmune thyroiditis. After these data researches have mainly focused on the relationship between comorbidities and CSU.

The possible mechanisms and triggering factors underlying CSU have been identified as acute or chronic infections, stress, nonallergic hypersensitivity reactions to foods and drugs (pseudoallergic), and autoreactivity including autoimmunity mediated by functional autoantibodies directed against the IgE receptor [4]. Stress is a major triggering and risk factor along CSU patients [5]. Furthermore, several studies revealed that stress can trigger or aggravate some skin diseases by the alternation of the functions of T cells and local neuroimmunoendocrine circuitry [6]. Most of the patients with CSU experience a stressor event within 6 months before the onset of the symptoms [7].

CSU patients have a higher level of stressful life events, perceived stress, and psychiatric comorbidity [7]. And many studies have shown that CSU patients more frequently have psychiatric comorbidities [7–11]. The most common psychiatric situations in these patients are depression, somatoform, and anxiety disorders [11, 12]. Both these disorders and CSU symptoms could affect the quality of life (QoL) of the patients. Also, it was shown that CSU patients had lower social relationship scores compared to healthy controls [8, 11]. CSU patients reportedly suffer more sleep disturbance, fatigue, emotional upset, and physical and mental restrictions at home and work [8]. Furthermore, in a study which compared patients with CSU to patients with psoriasis, physical impairment and effects of the disorder on QoL were found higher in patients with CSU than patients with psoriasis [13]. In a study QoL impairment in CSU patients was found higher than in patients with vitiligo [14]. Interestingly, Staubach et al. reported no significant relation between impact of QoL and age-sex, concurrent angioedema, and duration of CSU condition of the patients [8]. They also reported that the severity of the concomitant depression-anxiety or somatoform disorders in patients with CSU is important, because these patients, with concomitant severe psychiatric conditions, had significant impairment of QoL than patients with CSU who did not exhibit psychiatric comorbidity. Moreover, these psychiatric problems could be the primary factors in these patients or might arise as psychosocial consequences of underlying dermatological disorders [8]. As a result, an interdisciplinary approach that combines dermatological and psychiatric treatments is necessary for the management of CSU.

In recent years, associations between CSU and autoimmunity have been increasingly recognized in many studies [15–19]. Approximately 30–50% of patients with chronic urticaria produce specific IgG antibodies against the alpha subunit of the mast cell IgE receptor, and approximately 5–10% produce IgG antibodies against IgE itself [15]. Autoimmune mechanisms have been proposed as responsible for the development of some of the cases. Especially, intradermal autologous serum injections were applied, and urticarial responses were seen in 60% of patients with CSU [16].

Also, subsequent studies revealed that anti-IgG and anti-IgE autoantibodies, anti-FcεRI targeted at basophils, and mast cells were found in 45–55% of patients with CSU. These autoantibodies bind to mast cell-bound IgE molecules or surface IgE receptors to stimulate and eventually degranulate the cells and cause the urticarial symptoms [17–19]. It was suggested that some CSU patients have an autoimmune mechanism induced by these autoantibodies [20].

Thyroid diseases, especially Hashimoto's disease in which production of thyroid autoantibodies (antithyroid peroxidase antibodies and antithyroglobulin antibodies) and lymphocytic infiltration into the thyroid gland are seen, are the most common autoimmune diseases accompanying patients with CSU [19–21]. The etiology of thyroid autoimmunity is not known, but the genetic susceptibility and environmental factors are thought to initiate the process [22]. Leznoff and Sussman reported that 15% of the CSU patients had thyroid autoantibodies and there has been a relation between CSU and thyroid autoimmunity. The rate of high antithyroid antibodies in the patients with CSU ranges from 6.5% up to 57% in the other reports [23, 24]. The mechanism of these associations is not known. Confino-Cohen et al. hypothesized that the relationship between thyroid diseases and CSU might be based on shared susceptibility to autoimmune or chronic inflammatory processes [21]. Moreover, many small patient series and case reports reported that patients with CSU and thyroid autoimmunity benefit from levothyroxine sodium or antithyroid drug treatment. In these studies, clinical remission of chronic urticaria was seen, whereas no change has been demonstrated in thyroid antibody levels [25–27].

Although autoimmune thyroid disorders have been investigated in CSU, its relation with other autoimmune diseases has been investigated less [20]. But there is a fact that if there is an autoimmune disease in a patient, the second or third autoimmune disease more often appears even if the patient is under immunosuppressive treatment [21]. And rheumatoid arthritis (RA) was found as the second most common autoimmune disease in patients with CSU. Confino et al. reported that RA was found 13 times more in patients with CSU than healthy controls [21]. Rheumatoid factor was found significantly more often in patients with CSU [28].

In a small series of patients or case reports, celiac disease was reported higher in patients with CSU [29]. Several case reports revealed a 1.5–7-fold increased risk of urticaria in patients with celiac disease [30–32]. Also, systemic lupus erythematosus (SLE) and type I diabetes mellitus were each found significantly more prevalent in female patients with CSU [21, 33, 34].

Patients with CSU were found to have a significantly 15 times higher risk of developing SLE as compared to the control group. Furthermore, SLE was found to be 25 times higher in women than in men with CSU or women of the control group [21].

The high prevalence of these autoimmune diseases in patients with CSU makes it thinkable that somehow CSU can be also a member of autoimmunity. But the underlying mechanism of autoimmunity related to urticaria has not been known yet, but as mentioned before, susceptibility to autoimmune and/or chronic inflammatory processes might be the reason [21].

In the last few years, many researches published about the activation of the coagulation system in patients with CSU. A study revealed that the levels of plasma prothrombin fragment (PF)1+2, a marker of thrombin generation, were significantly increased in patients with CSU. They also reported that patients with CSU have more positive autologous plasma skin test result than a positive autologous serum skin test result. This study showed that there should be possible role of clotting factors in flaring symptoms induced by autologous plasma, because autoantibodies are equally present in serum and plasma [35]. Also, a statistically significant relationship between elevated plasma levels of PF1+2 and D-dimer and the severity of CSU was reported in some studies [36, 37].

CSU is characterized by the activation of the coagulation cascade [38, 39]. And it is probable that both intrinsic and extrinsic pathways are affected in CSU patients [40]. The coagulation system factors that most likely involved in the pathogenesis of CSU are tissue factor, thrombin, D-dimer, PF1+2, and activated factor VII [41, 42].

Thrombin activation, which is derived from platelets, directed investigations toward the evaluation of mean platelet volume (MPV) and CSU correlation. MPV is a potential marker of platelet reactivity because larger platelets are metabolically and enzymatically more active. It was shown that platelets secrete a large number of mediators of thrombosis, coagulation, inflammation, and atherosclerosis [43]. And MPV values were found significantly more in patients with CSU than the control group [21, 44]. A suggested possible way in the pathogenesis of CSU is that large activated platelets might activate the coagulation cascade. The activation of the coagulation pathways elicits increase in number of protease-activated receptor-1 on mast cells, mediator degranulation from mast cells and, increase in vascular permeability [45–47]. In many studies, this activated coagulation cascade was found associated with more severe disease [40, 41, 47]. Also, some studies showed that coagulation factors decreased to normal limits after disease remission or during treatment [35, 36, 40]. In contrast to this view, some authors suggest that the activation of the coagulation cascade seems a potential intensifying mechanism in the pathogenesis of CSU but is quite likely not the main trigger of the disease [47].

Chronic persistent infections, (e.g., *Helicobacter pylori* (Hp), streptococci, staphylococci, *Yersinia*, *Giardia lamblia*, *Mycoplasma pneumoniae*, Hepatitis viruses, *Norovirus*, *Parvovirus B19*, *Anisakis simplex*, *Entamoeba* spp., and *Blastocystis* spp.) have been suspected to be triggering factors in patients with CSU [3]. Especially, Hp infection was popularly investigated in the pathogenesis of CSU [48, 49]. It is thought that Hp infections could be a triggering factor in underlying autoimmune pathology of CSU [50], and there are studies showing that Hp infection is related to production of autoreactive IgM and IgG3 antibodies [51]. Another suggestion is that Hp-associated lipoprotein 20 (lpp20) could act as an antigen that is involved in molecular mimicry to mast cells, T cells, and B cells as well [51–53]. Also in some studies, eradication of Hp infection resulted in remission of CSU symptoms [54, 55].

CSU is histopathologically characterized by infiltrating perivascular T cells, eosinophils, and neutrophils, and several studies reported that circulating levels of C-reactive protein (CRP), pro-inflammatory cytokines such as interleukin (IL)-6 and TNF- α , and matrix metalloproteinase 9 (MMP-9) have been found increasing in patients with CSU. Also, these markers are thought to appear to correlate with clinical activity score and severity of urticaria [56–58]. Metabolic syndrome (MetS) involves dyslipidemia, central obesity, glucose intolerance, and high blood pressure [59]. Furthermore it has been reported that patients suffering from MetS had higher serum levels of inflammatory markers such as IL-1, IL-6, TNF, and CRP than healthy controls [60].

In a study, the prevalence of MetS was reported higher among the patients with CSU. Thus, systemic inflammation promoted by MetS may play a role in CSU pathogenesis as well. Furthermore, some studies revealed that the levels of TNF and C3 were found significantly higher and correlated with more severe, uncontrolled urticaria symptoms in patients with CSU and MetS at the same time [59, 60].

Some studies showed that activation of eosinophils which are sources of vascular endothelial growth factor and tissue factor in lesional skin of patients with CSU may play a role in the pathogenesis of CSU [61]. Elevated serum eosinophilic cationic protein levels were found correlated with symptoms in patients with CSU and MetS. Both diseases, CSU and MetS, which may mutually trigger or exacerbate each other, have elevated systemic inflammation [60].

3. Conclusion

Studies investigating comorbidities associated with CSU have been increasing in recent years, and new disorders possibly associated with the CSU have been reported. It has not been clearly known yet that whether these conditions are true comorbidities associated with CSU or they are coincidentally found at the same time. This will be clearer as more studies on the subject are added.

Author details

Müzeyyen Gönül^{1*}, Havva Hilal Ayvaz² and Selda Pelin Kartal¹

*Address all correspondence to: muzeyyengonul@gmail.com

1 University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital in Ankara, Turkey

2 Polatlı Duatepe State Hospital, Polatlı, Ankara, Turkey

References

- [1] Van Der Valk PGM, Moret G, Kiemeneij LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol.* 2002;**146**: 110–113. DOI: 10.1046/j.1365-2133.2002.04582.x.
- [2] Vestergaard C, Deleuran M. Chronic spontaneous urticaria: latest developments in aetiology, diagnosis and therapy. *Ther Adv Chronic Dis.* 2015 Nov;**6**(6):304–313. DOI: 10.1177/2040622315603951.
- [3] Zuberbier T. Chronic urticaria. *Curr Allergy Asthma Rep.* 2012;**12**:267–272. DOI: 10.1007/s11882-012-0270-7.
- [4] Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A, Grattan CE, Kapp A, Merk HF, Rogala B, Saini S, Sanchez-Borges M, Schmid-Grendelmeier P, Schunemann H, Staubach P, Vena GA, Wedi B, Maurer M. EAACI/GA[2] LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy.* 2009;**64**:1417–1426. DOI: 10.1111/j.1398-9995.2009.02179.x.

- [5] Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. *Indian J Dermatol Venereol Leprol*. 2008 Nov-Dec;**74**(6):594–599. DOI: 10.4103/0378-6323.45100.
- [6] Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the ‘brain-skin connection’. *Trends Immunol*. 2006 Jan;**27**(1):32–39. DOI:10.1016/j.it.2005.10.002.
- [7] Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller K, Zezula P, Eckhardt-Henn A, Maurer M. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol*. 2011 Sep;**91**(5):557–561. DOI: 10.2340/00015555-1109.
- [8] Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol*. 2006;**154**:294–298. DOI: 10.1111/j.1365-2133.2005.06976.x.
- [9] Lyketsos CG, Lyketsos GC, Richardson SC, Beis A. Dysthymic states and depressive syndromes in physical conditions of presumably psychogenic origin. *Acta Psychiatr Scand*. 1987 Nov;**76**(5):529–534. DOI: 10.1111/j.1600-0447.1987.tb02914.x.
- [10] Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. *J Sex Marital Ther*. 2007 Jan–Feb;**33**(1):55–64. DOI: 10.1080/00926230600998482.
- [11] Engin B, Uguz F, Yilmaz E, Özdemir M, Mevlitoglu I. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol*. 2008 Jan;**22**(1):36–40. DOI: 10.1111/j.1468-3083.2007.02324.x.
- [12] Chung MC, Symons C, Gillioam J. The relationship between posttraumatic stress disorder, psychiatric comorbidity, and personality traits among patients with chronic idiopathic urticaria. *Compr Psychiatry*. 2010;**51**:55–63. DOI: 10.1016/j.comppsy.2009.02.005.
- [13] Weldon DR. Quality of life in patients with urticaria. *Allergy Asthma Proc*. 2006;**27**:96–99.
- [14] Poon E, Seed PT, Greaves MW, et al. The extent and nature of disability in different urticaria conditions. *Br J Dermatol*. 1999;**140**:667–671. DOI: 10.1046/j.1365-2133.1999.02767.x.
- [15] Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;**133**(5):1270–1277. DOI: 10.1016/j.jaci.2014.02.036.
- [16] Sabron RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol*. 1999;**140**:446–452. DOI: 10.1046/j.1365-2133.1999.02707.x.
- [17] Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol*. 2001 Jun;**107**(6):1056–1062. DOI: 10.1067/mai.2001.115484.
- [18] Sugiyama A, Nishie H, Takeuchi S, Yoshinari M, Furue M. Hashimoto’s disease is a frequent comorbidity and an exacerbating factor of chronic spontaneous urticaria. *Allergol Immunopathol [Madr]*. 2015 May–Jun;**43**(3):249–253. DOI: 10.1016/j.aller.2014.02.007.

- [19] Marone G, Spadaro G, Palumbo C, Condorelli G. The anti-IgE/anti-FcεpsilonRIα autoantibody network in allergic and autoimmune diseases. *Clin Exp Allergy*. 1999 Jan;**29**(1):17–27. DOI: 10.1046/j.1365-2222.1999.00441.x.
- [20] Kolkhir P, Pogorelov D, Olishova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus—a systematic review. *Clin Exp Allergy*. 2016 Feb;**46**(2):275–287. DOI: 10.1111/cea.12673.
- [21] Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg AA. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;**129**:1307–1313. DOI: 10.1016/j.jaci.2012.01.043.
- [22] Pan XF, Gu JQ, Shan ZY. The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis. *Endocrine*. 2015 Apr;**48**(3):804–810. DOI: 10.1007/s12020-014-0367-y.
- [23] Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol*. 1989 Jul;**84**(1):66–71. DOI: [http://dx.doi.org/10.1016/0091-6749\(89\)90180-2](http://dx.doi.org/10.1016/0091-6749(89)90180-2).
- [24] Turktas I, Gokcora N, Demirsoy S, Cakir N, Onal E. The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol*. 1997 Mar;**36**(3):187–190. DOI: 10.1046/j.1365-4362.1997.00187.x.
- [25] Kim DH, Sung NH, Lee AY. Effect of levothyroxine treatment on clinical symptoms in hypothyroid patients with chronic urticaria and thyroid autoimmunity. *Ann Dermatol*. 2016;**28**(2):199–204. DOI: 10.5021/ad.2016.28.2.199.
- [26] Aversano M, Caiazzo P, Iorio G, Ponticciello L, Laganá B, Leccese F. Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response? *Allergy*. 2005 Apr;**60**(4):489–493. DOI: 10.1111/j.1398-9995.2005.00723.x.
- [27] O'Donnell BF, Francis DM, Swana GT, Seed PT, Kobza Black A, Greaves MW. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol*. 2005 Aug;**153**(2):331–335. DOI: 10.1111/j.1365-2133.2005.06646.x.
- [28] Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: rheumatoid arthritis. *J Autoimmun*. 2010 Aug;**35**(1):10–14. DOI: 10.1016/j.jaut.2009.12.009.
- [29] Meneghetti R, Gerarduzzi T, Barbi E, Ventura A. Chronic urticaria and celiac disease. *Arch Dis Child*. 2004;**89**:293. DOI: 10.1136/adc.2003.037259.
- [30] Ludvigsson JF, Lindelöf B, Rashtak S, Rubio-Tapia A, Murray JA. Does urticaria risk increase in patients with celiac disease? A large population-based cohort study. *Eur J Dermatol*. 2013 Sep–Oct;**23**(5):681–687. DOI: 10.1684/ejd.2013.2158.
- [31] Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, Sferlazzas C, Pajno GB. Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol*. 2005 Aug;**16**(5):428–432. DOI: 10.1111/j.1399-3038.2005.00309.x.

- [32] Gabrielli M, Candelli M, Cremonini F, Ojetti V, Santarelli L, Nista EC, Nucera E, Schiavino D, Patriarca G, Gasbarrini G, Pola P, Gasbarrini A. Idiopathic chronic urticaria and celiac disease. *Dig Dis Sci*. 2005 Sep;**50**(9):1702–1704. DOI: 10.1007/s10620-005-2919-8.
- [33] Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. *Autoimmun Rev*. 2010;**9**:277–287. DOI: 10.1016/j.autrev.2009.12.008.
- [34] Asero R, Orsatti A, Tedeschi A, Lorini M. Autoimmune chronic urticaria associated with type 1 diabetes and Graves' disease. *J Allergy Clin Immunol*. 2005 May;**115**(5):1088–1089. DOI: 10.1016/j.jaci.2004.12.009.
- [35] Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol*. 2006;**117**:1113–1117. DOI: 10.1016/j.jaci.2005.12.1343.
- [36] Takeda T, Sakurai Y, Takahagi S, Kato J, Yoshida K, Yoshioka A, Hide M, Shima M. Increase of coagulation potential in chronic spontaneous urticaria. *Allergy*. 2011;**66**:428–433. DOI: 10.1111/j.1398-9995.2010.02506.x.
- [37] Takahagi S, Mihara S, Iwamoto K, Morioka S, Okabe T, Kameyoshi Y, Hide M. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. *Allergy*. 2009;**65**:649–656. DOI: 10.1111/j.1398-9995.2009.02222.x.
- [38] Asero R, Tedeschi A, Coppola R, Griffini S, Paparella P, Riboldi P, Marzano AV, Fanoni D, Cugno M. Activation of the tissue pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol*. 2007;**119**:705–710. DOI: 10.1016/j.jaci.2006.08.043.
- [39] Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. *Allergy*. 2008;**63**:176–180. DOI: 10.1111/j.1398-9995.2007.01514.x.
- [40] Triwongwanat D, Kulthanan K, Chularojanamontri L, Pinkaew S. Correlation between plasma D-dimer levels and the severity of patients with chronic urticaria. *Asia Pac Allergy*. 2013 Apr;**3**(2):100–105. DOI: 10.5415/apallergy.2013.3.2.100.
- [41] Cirino G, Cicala C, Bucci MR, Sorrentino L, Maraganore JM, Stone SR. Thrombin functions as an inflammatory mediator through activation of its receptor. *J Exp Med*. 1996;**183**:821–827.
- [42] Cugno M, Tedeschi A, Borghi A, et al. Activation of Blood Coagulation in Two Prototypic Autoimmune Skin Diseases: A Possible Link with Thrombotic Risk. Picardo M, ed. *PLoS ONE*. 2015;**10**(6):e0129456. DOI: 10.1371/journal.pone.0129456.
- [43] Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP, et al. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood*. 2004;**103**:2096–2104. DOI: 10.1182/blood-2003-08-2804.

- [44] Magen E, Mishal J, Zeldin U, Feldman V, Kidon M, Schlesinger M, et al. Increased mean platelet volume and C-reactive protein levels in patients with chronic urticaria with a positive autologous serum skin test. *Am J Med Sci*. 2010;**339**:504–508. DOI: 10.1097/MAJ.0b013e3181db6ed5.
- [45] Nobe K, Sone T, Paul RJ, Honda K. Thrombin-induced force development in vascular endothelial cells: contribution to alteration of permeability mediated by calcium-dependent and -independent pathways. *J Pharmacol Sci*. 2005 Nov;**99**(3):252–263. <http://doi.org/10.1254/jphs.FP0050679>. (Bunun DOI numarası boyle site adresi seklinde verilmiş, başka bulamadım :S Denedim açılıyor makale direk bu şekilde).
- [46] Asero R, Tedeschi A, Cugno M. Heparin and tranexamic acid therapy may be effective in treatment-resistant chronic urticaria with elevated d-dimer: a pilot study. *Int Arch Allergy Immunol*. 2010;**152**(4):384–389. DOI: 10.1159/000292947.
- [47] Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Coagulation cascade and fibrinolysis in patients with multiple-drug allergy syndrome. *Ann Allergy Asthma Immunol*. 2008 Jan;**100**(1):44–48. DOI:10.1016/S1081-1206(10)60403-6.
- [48] Ojetti V, Armuzzi A, De Luca A, Nucera E, Franceschi F, Candelli M, et al. *Helicobacter pylori* infection affects eosinophilic cationic protein in the gastric juice of patients with idiopathic chronic urticaria. *Int Arch Allergy Immunol*. 2001;**125**(1):66–72. DOI: 10.1159/000053798.
- [49] Akelma AZ, Cizmeci MN, Mete E, Tufan N, Bozkurt B. A neglected cause for chronic spontaneous urticaria in children: *Helicobacter pylori*. *Allergol Immunopathol (Madr)*. 2015 May–Jun;**43**(3):259–263. DOI: 10.1016/j.aller.2013.12.001.
- [50] Chiu YC, Tai WC, Chuah SK, Hsu PI, Wu DC, Wu KL, Huang CC, Ho JC, Ring J, Chen WC. The clinical correlations of *Helicobacter pylori* virulence factors and chronic spontaneous urticaria. *Gastroenterol Res Pract*. 2013;**2013**:436727. DOI:10.1155/2013/436727.
- [51] Yamanishi S, Iizumi T, Watanabe E, Shimizu M, Kamiya S, Nagata K, et al. Implications for induction of autoimmunity via activation of B-1 cells by *Helicobacter pylori* urease. *Infect Immun*. 2006;**74**(1):248–256. DOI: 10.1128/IAI.74.1.248-256.2006.
- [52] Curth HM, Dinter J, Nigemeier K, Kütting F, Hunzelmann N, Steffen HM. Effects of *Helicobacter pylori* eradication in chronic spontaneous urticaria: results from a retrospective cohort study. *Am J Clin Dermatol*. 2015 Dec;**16**(6):553–558. DOI: 10.1007/s40257-015-0152-6.
- [53] Magen E, Mishal J. Possible benefit from treatment of *Helicobacter pylori* in antihistamine-resistant chronic urticaria. *Clin Exp Dermatol*. 2013 Jan;**38**(1):7–12. DOI: 10.1111/j.1365-2230.2012.04467.x.
- [54] Fukuda S, Shimoyama T, Umegaki N, Mikami T, Nakano H, Munakata A. Effect of *Helicobacter pylori* eradication in the treatment of Japanese patients with chronic idiopathic urticaria. *J Gastroenterol*. 2004;**39**(9):827–830. DOI: 10.1007/s00535-004-1397-7.

- [55] Magen E, Mishal J, Schlesinger M, Scharf S. Eradication of *Helicobacter pylori* infection equally improves chronic urticaria with positive and negative autologous serum skin test. *Helicobacter*. 2007 Oct;**12**(5):567–571. DOI: 10.1111/j.1523-5378.2007.00522.x.
- [56] Kasperska-Zajac A, Sztylec J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. *Clin Exp Allergy*. 2011;**41**:1386–1391. DOI: 10.1111/j.1365-2222.2011.03789.x.
- [57] Tedeschi A, Asero R, Lorini M, Marzano AV, Cugno M. Plasma levels of matrix metalloproteinase-9 in chronic urticaria patients correlate with disease severity and C-reactive protein but not with circulating histamine-releasing factors. *Clin Exp Allergy*. 2010;**40**:875–881. DOI: 10.1111/j.1365-2222.2010.03473.x.
- [58] Ye YM, Jin HJ, Hwang EK, Nam YH, Kim JH, Shin YS, Park HS. Co-existence of chronic urticaria and metabolic syndrome: clinical implications. *Acta Derm Venereol*. 2013 Mar;**93**(2):156–160. DOI: 10.2340/00015555-1443.
- [59] da Silva VN, Fiorelli LN, da Silva CC, Kurokawa CS, Goldberg TB. Do metabolic syndrome and its components have an impact on bone mineral density in adolescents? *Nutr Metab [Lond]*. 2017 Jan;**14**:1. DOI: 10.1186/s12986-016-0156-0.
- [60] Devaraj S, Rosenson RS, Jialal I. Metabolic syndrome: an appraisal of the pro-inflammatory and procoagulant status. *Endocrinol Metab Clin North Am*. 2004;**33**:431–453. DOI: 10.1016/j.ecl.2004.03.008.
- [61] Cugno M, Marzano AV, Tedeschi A, Fanoni D, Venegoni L, Asero R. Expression of tissue factor by eosinophils in patients with chronic urticaria. *Int Arch Allergy Immunol*. 2009;**148**:170–174. DOI: 10.1159/000155748.