

# Sexual Functioning Is Frequently and Markedly Impaired in Female Patients with Chronic Spontaneous Urticaria



Ragıp Ertaş, MD<sup>a</sup>, Kemal Erol, MD<sup>b</sup>, Tomasz Hawro, MD<sup>c</sup>, Halim Yılmaz, MD<sup>d</sup>, and Marcus Maurer, MD<sup>c</sup> Kayseri and Konya, Turkey; and Berlin, Germany

**What is already known about this topic?** The impact of chronic spontaneous urticaria (CSU) on female sexual functioning remains largely unknown.

**What does this article add to our knowledge?** Our results show that sexual functioning is markedly reduced and sexual dysfunction is very frequent in female patients with CSU, especially in patients with angioedema.

**How does this study impact current management guidelines?** Physicians who treat patients with CSU should talk about sexual health and functioning with their patients and should take sexual dysfunctioning into account in the management of CSU.

**BACKGROUND:** Chronic spontaneous urticaria (CSU) is common, chronic, and debilitating, and has serious effects on quality of life and mental health. Three of 4 patients with CSU are women. The impact of CSU on female sexual functioning remains largely unknown.

**OBJECTIVE:** To determine the prevalence of sexual dysfunction in female patients with CSU and to characterize their impairment of sexual functioning and its drivers.

**METHODS:** Fifty-six female patients with CSU and 55 female aged-matched healthy control subjects were evaluated for sexual functioning with the Female Sexual Function Index. Patients were also assessed for their duration, activity, and control of disease, as well as angioedema, anxiety, depression, fatigue, and quality-of-life impairment.

**RESULTS:** Sexual functioning, that is, total Female Sexual Function Index scores and all subscores, was markedly reduced in female patients with CSU versus control subjects, and 2 of 3

patients (67.9%) had sexual dysfunction. Impaired sexual functioning was linked to high disease activity and poor disease control. Sexual dysfunction was more common in patients with CSU with angioedema and vice versa. Angioedema was a significant predictor of sexual dysfunction in female patients with CSU (odds ratio, 7.3). Reduced sexual functioning was associated with anxiety, depression, and fatigue and significantly linked to impaired quality of life, more so in patients with angioedema as compared with those without.

**CONCLUSIONS:** CSU has strong negative effects on female sexual function, especially in patients with angioedema. Additional studies on sexual health in patients with CSU are needed and should focus on the impact of effective treatment on sexual functioning. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1074-82)

**Key words:** Angioedema; Sexual health; CSU; Female sexual dysfunction

<sup>a</sup>Department of Dermatology, Kayseri City Education and Research Hospital, Kayseri, Turkey

<sup>b</sup>Department of Rheumatology, Kayseri City Education and Research Hospital, Kayseri, Turkey

<sup>c</sup>Dermatological Allergology, Department of Dermatology and Allergy, Charité – Universitätsmedizin, Berlin, Germany

<sup>d</sup>Department of Physical Medicine and Rehabilitation, Health Science University, Konya, Turkey

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 14, 2019; revised October 11, 2019; accepted for publication October 21, 2019.

Available online November 18, 2019.

Corresponding author: Marcus Maurer, MD, Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: [marcus.maurer@charite.de](mailto:marcus.maurer@charite.de).

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology  
<https://doi.org/10.1016/j.jaip.2019.10.046>

## INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common, chronic, and debilitating disease characterized by the appearance of itchy wheals and/or angioedema without definite triggers, for longer than 6 weeks.<sup>1-3</sup> At least 50% of patients with CSU have angioedema, defined as swelling of the deep dermal, subcutaneous, or submucosal tissues. Angioedema, in patients with CSU, commonly affects the face (lips and eyes), hands and feet, and the genitalia.<sup>4</sup> Angioedema can be painful and is linked to impaired quality of life (QOL).<sup>4,5</sup> QOL in patients with CSU can be severely impaired, and it often is.<sup>6,7</sup> Many patients experience psychological problems and psychiatric comorbidities such as depression and anxiety during the course of their disease.<sup>8</sup>

Chronic diseases with a high burden for patients are linked to impaired sexual health and sexual dysfunction.<sup>9-12</sup> For example,

# Abbreviations used

CSU- Chronic spontaneous urticaria  
CU-QOL- Chronic Urticaria-Quality of life  
DLQI- Dermatology Life Quality Index  
FSFI- Female Sexual Function Index  
HADS- Hospital Anxiety and Depression Scale  
QOL- Quality of life  
UCT- Urticaria control test

the prevalence of sexual dysfunction in patients with diabetes, multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, fibromyalgia, asthma, allergic rhinoconjunctivitis, and atopic dermatitis has been reported to be higher than in the general population.<sup>9-17</sup> Sexual health in patients with chronic conditions including allergic diseases is reported to be more impaired in female than in male patients.<sup>17,18</sup> Female patients with inflammatory bowel diseases, asthma, or vitiligo have higher rates of sexual dysfunction than do men with these diseases.<sup>19-21</sup> The drivers of sexual dysfunction in patients with chronic diseases are heterogeneous and ill characterized, but are held to include disease features such as disease activity and duration as well as psychological and psychiatric comorbidities. In a study conducted in patients with multiple sclerosis, sexual dysfunction was significantly linked to pain levels, the duration of the disease, and associated depression.<sup>10</sup> Vice versa, impaired sexual functioning has negative effects on QOL and may increase disease activity by affecting sexual relationships and inducing stress.<sup>10,11,22</sup>

The impact of CSU on sexual health has not been assessed in detail and is not well understood. There are several reasons to suspect that sexual functioning is impaired, and that sexual dysfunction is common in patients with CSU. Patients with CSU often have a high disease burden.<sup>7,23</sup> The duration of CSU is long, several years in most patients, more than 10 years in 1 of 5 patients. Itch is a very common symptom in patients with CSU, and chronic itch has been linked to impaired sexual health.<sup>22</sup> Genitalia, together with the face and hands and feet, are the most common sites of angioedema in CSU.<sup>1,4</sup> Psychological problems and psychiatric comorbidities including depression and anxiety are frequent in patients with CSU.<sup>8,24</sup> All of this suggests that patients with CSU may frequently experience impaired sexual functioning because of their disease, which is why we performed the present study.

Why does this study focus on female patients with CSU? CSU predominantly affects women, and women with CSU may be especially at risk of developing sexual dysfunction.<sup>1,2,25</sup> Female patients with CSU have higher rates of sexual dysfunction than do men.<sup>21</sup> Also, female patients with CSU are more severely affected than male patients in terms of their impairment of QOL.<sup>26</sup> Also, female patients with CSU more frequently suffer from sleep disturbance than do males.<sup>27</sup> Female patients with CSU tend to more often have autoimmune CSU than do males.<sup>28</sup> This is relevant because autoimmune CSU is associated with a more severe course of disease and poor treatment responses to omalizumab.<sup>29-32</sup> Indeed, women with CSU are more resistant than men to omalizumab treatment.<sup>31</sup> Female sex hormones are held to contribute to the high fluctuation of disease activity in female patients and the burden that comes with this.<sup>33</sup> For these reasons, this study was focused on sexual functioning of female patients with CSU.

**TABLE I.** Characteristics of patients with CSU and healthy control subjects

| Characteristic                | Patients with CSU (n = 56) | Healthy controls (n = 55) | P     |
|-------------------------------|----------------------------|---------------------------|-------|
| Age (y), mean ± SD            | 37.8 ± 7.3                 | 37.0 ± 8.7                | .575* |
| BMI, mean ± SD                | 28.6 ± 4.4                 | 28.3 ± 6.8                | .779* |
| No. of children, median (IQR) | 2 (2-3)                    | 3 (2-3)                   | .382† |
| Employment status, n (%)      |                            |                           |       |
| Employed                      | 15 (26.8)                  | 9 (16.4)                  | .182‡ |
| Unemployed                    | 41 (73.2)                  | 46 (83.6)                 |       |
| Education, n (%)              |                            |                           |       |
| Illiterate                    | 1 (1.8)                    | 2 (3.6)                   | .082‡ |
| Primary school                | 30 (53.6)                  | 41 (74.5)                 |       |
| High school                   | 14 (25)                    | 6 (10.9)                  |       |
| College                       | 11 (19.6)                  | 6 (10.9)                  |       |
| Smoking (+), n (%)            | 17 (30.4)                  | 14 (25.5)                 | .565‡ |

BMI, Body mass index (kg/m<sup>2</sup>); IQR, interquartile range (lower quartile–upper quartile).

\*t test for parametric variables.

†Mann-Whitney U test.

‡χ<sup>2</sup> test.

As of now, the impact of CSU on sexual health and functioning remains to be investigated in detail and is not well understood. The aims of this study were, therefore, (1) to assess sexual functioning and to determine the prevalence of sexual dysfunction in female patients with CSU, (2) to compare sexual functioning in female patients with CSU and healthy women, and (3) to correlate sexual functioning, in female patients with CSU, with demographic and clinical parameters such as age, disease activity, and angioedema as well as with QOL impairment, depression, and anxiety.

## METHODS

### Study subjects and conduct

This study, in January and February of 2019, included 56 consecutive female patients with CSU treated at our Urticaria Center of Reference and Excellence.<sup>34</sup> We only included married patients aged between 18 and 50 years. All patients had wheals with or without angioedema; that is, we did not include patients with CSU with angioedema only. Additional exclusion criteria were mental impairment or communication disorders, pregnancy, menopause, history of sexually transmitted diseases, previous hysterectomy or vaginal surgery, history of cardiovascular, pulmonary, hepatic, renal, hematological, gynecological, or major psychiatric diseases such as schizophrenia or bipolar disorders, endocrine disorders such as diabetes mellitus, and the intake of antidepressant, anticonvulsant, anxiolytic, and antiepileptic medication or oral/vaginal estrogen therapy. Our control group consisted of 55 healthy female and age-matched volunteers, all of them women without any health problems who came to our hospital for routine health screening.

Patients with CSU and control subjects were similar in terms of age (37.8 ± 7.3 and 37.0 ± 8.7 years, respectively), body mass index, the number of children, occupational and educational status, and history of smoking (Table I). Of the patients with CSU, 38 (67.9%) had angioedema, at some point during the course of their CSU.

This study was approved by the Institutional Review Board of the Kayseri City Education and Research Hospital and the local ethics committee. All participants provided written informed consent.

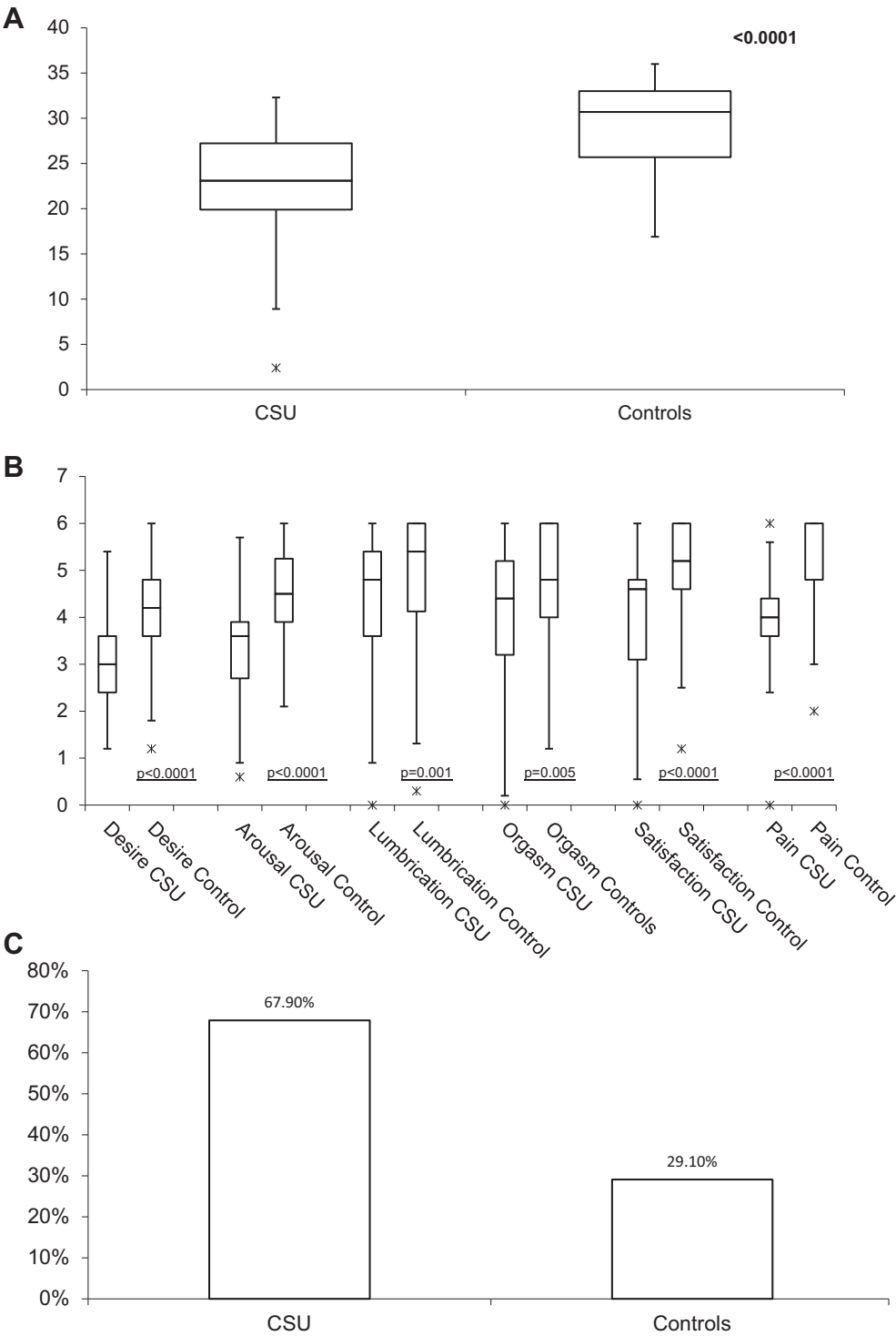


**FIGURE 1.** (A) Comparison of total FSFI scores, (B) comparison of sub-FSFI scores, and (C) female sexual dysfunction in patients with CSU and healthy controls. Mann-Whitney  $U$  test was performed; data shown as median (interquartile range [lower quartile–upper quartile]).

**Assessment of sexual functioning and sexual dysfunction**

We used the Female Sexual Function Index (FSFI) to assess levels of sexual functioning and the presence of sexual dysfunction.<sup>35</sup> The FSFI is a brief self-applied interview form that assesses female sexual

function over the past 4 weeks. It consists of 19 questions with a total score range of 0 to 36 and 6 subscales: sexual desire, arousal, lubrication, satisfaction, orgasm, and pain during sexual intercourse (dyspareunia). Each answer has point values from 0 to 5, where high and low values indicate normal and impaired sexual functioning,

**TABLE II.** Sexual functioning, in female patients with CSU, is linked to QOL impairment, anxiety and depression, and CSU activity and control

|                          | <i>r</i> | <i>P</i> |
|--------------------------|----------|----------|
| Urticaria activity score | −0.363   | .006     |
| Urticaria control test   | 0.277    | .039     |
| HADS Anxiety             | −0.358   | .007     |
| HADS Depression          | −0.370   | .005     |
| CU-QOL questionnaire     | −0.314   | .018     |
| DLQI                     | −0.231   | .087     |
| Disease duration (y)     | −0.091   | .499     |

Pearson correlation analysis was performed.

respectively. We calculated, for each study subject, the total FSFI value and all FSFI subscale values. Total FSFI values of 26 or less were taken to indicate sexual dysfunction, based on the cutoff value of 26.6 established by the FSFI validation study.<sup>35</sup>

### Assessment of autoantibodies to thyroid peroxidase and antinuclear antibodies as well as total IgE levels

Patients' serum samples were analyzed for autoantibodies to thyroid peroxidase by chemiluminescent immunoassay (Beckman-Coulter, Woerden, the Netherlands) and for antinuclear antibodies by immunofluorescence microscopy using HEp-2 slides (EUROIMMUN, AG, Luebeck, Germany). Antinuclear antibody titers of 1/100 and higher were considered as positive. Serum levels of total IgE were measured by the nephelometric method (BN II System, Siemens, Germany).

### Assessment of CSU activity, duration, and control

Disease activity in patients with CSU was assessed by using the urticaria activity score as previously described.<sup>3</sup> Briefly, patients documented wheal numbers (0-3 points, with 0 = no wheals and 3 = more than 50 wheals) and itch intensity (0-3 points, with 0 = no itch and 3 = severe itch) during the past 24 hours, and we calculated the urticaria activity score by adding the points for wheals and itch. In addition, we used a 10-cm visual analogue scale to determine patient-reported itch during the previous month (0 = no itch; 10 = maximum itch).

Disease control was determined by the use of the urticaria control test (UCT).<sup>36,37</sup> The UCT is composed of 4 questions with 5 answer options each (0-4 points). High UCT point values reflect high levels of disease control, and 12 of 16 possible points is the cutoff for well-controlled versus poorly controlled disease.

### Assessment of anxiety, depression, and fatigue

We used the Hospital Anxiety and Depression Scale (HADS), a validated self-rating questionnaire, to evaluate the presence and measure the severity of depression and anxiety in patients with CSU. The HADS includes 14 questions with 4 possible answers options each (points range from 0 to 3); 7 of them assess anxiety, with a range of 0 to 21 points, and the other 7 assess depression, with a range of 0 to 21 points. HADS point values in both the anxiety scale and the depression scale can be divided into 3 groups: 0 to 7 points = normal, 8 to 10 points = borderline case, and 11 to 21 = anxiety or depression.<sup>22</sup> However, based on the results of the Turkish validation study of the HADS, 11 or more points in the anxiety scale and 8 or more points in the depression scale were taken to indicate that patients had anxiety and depression, respectively.<sup>38</sup> A 10-cm visual analogue scale was used to assess patient-reported

fatigue during the previous month, where 0 and 10 correspond to no and maximum fatigue, respectively, and 5 cm was the cutoff value (>5 cm was considered as high and ≤5 cm as low fatigue).<sup>39</sup>

### Measurement of QOL impairment

We measured QOL impairment in patients with CSU by the use of the validated Turkish versions of the Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life (CU-QOL) questionnaire. The DLQI assesses the effect of skin diseases on QOL and consists of 10 questions that cover 6 domains: feelings, daily activities, leisure, work and school, personal relationships, and treatment. Each question relates to the last week and carries the response categories: "not at all = 0," "a little = 1," "a lot = 2," or "very much = 3." The range of the total DLQI is 0 to 30 (0 = no impairment and 30 = maximum impairment of QOL).

The CU-QOL questionnaire measures urticaria-specific QOL impairment and has 23 questions and 6 scales: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. The CU-QOL questionnaire total value ranges from 0 to 100 points, with high values indicating strong impairment.

### Statistical analyses

Parametric variables were presented as means and SDs, and nonparametric variables were presented as medians and interquartile ranges. The Kolmogorov-Smirnov test and histogram analyses were used to determine whether continuous variables were normally distributed. Levene test was used for the evaluation of homogeneity of variances. Number of cases and percentages were used for categorical variables. Two independent groups of parametric variables were compared using Student *t* test. For nonparametric variables, Mann-Whitney *U* test was administered. Categorical data were analyzed by  $\chi^2$  test. For the multivariate analyses, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hosmer-Lemeshow goodness-of-fit statistics were used to determine model fit. A 5% type I error was used to infer statistical significance.

## RESULTS

### Sexual functioning, in female patients with CSU, is impaired, and 2 of 3 patients have sexual dysfunction

Sexual functioning was considerably reduced, across all domains of sexual functioning, in patients with CSU as compared with control subjects; that is, total FSFI values and all FSFI subscale values were significantly and markedly lower (Figure 1, A and B). Two of 3 female patients with CSU (67.9%) had sexual dysfunction as compared with 29.1% of healthy control subjects (*P* < .001) (Figure 1, C).

### Impaired sexual functioning is linked to high disease activity and poor disease control in female patients with CSU

In female patients with CSU, sexual functioning, based on total FSFI values, was linked to disease activity (urticaria activity scores): The higher the disease activity, the more impaired the sexual functioning (*r* = −0.363; *P* = .006). Disease control as assessed by the UCT was also linked to impaired sexual functioning: the lower patients' control of their disease, the more impaired their sexual functioning (*r* = 0.277; *P* = .039; Table II).

**TABLE III.** Female patients with CSU with sexual dysfunction more often have angioedema and exhibit higher levels of fatigue

|                                        | FSD (+), n = 38   | FSD (−), n = 18    | P     |
|----------------------------------------|-------------------|--------------------|-------|
| Age (y), mean ± SD                     | 37.95 ± 7.117     | 37.56 ± 7.117      | .853* |
| Disease duration (y), median (IQR)     | 4.0 (1.0-10.0)    | 3.0 (0.9-8.3)      | .488† |
| Urticaria activity score, median (IQR) | 4 (2-6)           | 2.5 (0.75-4.0)     | .083‡ |
| Urticaria control test, mean ± SD      | 8.55 ± 4.228      | 10.33 ± 3.941      | .139* |
| Angioedema (+), n (%)                  | 30 (78.9)         | 8 (44.4)           | .010‡ |
| HADS Depression, mean ± SD             | 8.26 ± 3.607      | 6.11 ± 5.016       | .072* |
| HADS Anxiety, mean ± SD                | 10.24 ± 3.605     | 7.94 ± 4.856       | .053* |
| CU-QOL questionnaire, mean ± SD        | 31.92 ± 18.853    | 24.89 ± 13.957     | .165* |
| DLQI, median (IQR)                     | 7.5 (2.8-16)      | 4 (1-11)           | .193† |
| VAS fatigue, median (IQR)              | 5.0 (2.0-8.0)     | 2.0 (0.50-4.5)     | .030† |
| VAS pruritus, median (IQR)             | 5.5 (2.8-8.0)     | 3.0 (2-6.25)       | .163† |
| Anti-TPO (+), n (%)                    | 6 (15.8)          | 3 (16.7)           | .933‡ |
| ANA (+), n (%)                         | 9 (23.7)          | 5 (27.8)           | .492‡ |
| IgE in (IU/mL), median (IQR)           | 65.8 (33.0-236.0) | 102.4 (21.0-226.8) | .970† |

ANA, Antinuclear antibody; FSD, female sexual dysfunction; IQR, interquartile range (lower quartile—upper quartile); TPO, thyroid peroxidase; VAS, visual analogue scale. Bold indicates statistical significance ( $P < .05$ ).

\* $t$  test for parametric variables.

†Mann-Whitney  $U$  test.

‡ $\chi^2$  test.

**TABLE IV.** Predictors of sexual dysfunction in female patients with CSU

|                        | OR (95% CI)*      | P†   |
|------------------------|-------------------|------|
| Angioedema             | 7.31 (1.56-34.26) | .012 |
| VAS pruritus           | 0.77 (0.52-1.17)  | .227 |
| VAS fatigue            | 1.23 (0.91-1.67)  | .168 |
| HADS Depression        | 0.93 (0.74-1.17)  | .519 |
| HADS Anxiety           | 1.27 (0.97-1.66)  | .080 |
| CU-QOL questionnaire   | 0.98 (0.93-1.03)  | .471 |
| Urticaria control test | 0.79 (0.58-1.07)  | .130 |

OR, Odds ratio; VAS, visual analogue scale.

Depression and anxiety were included independently as covariates to the multinomial regression model, and their influence on the dependent variable tested. There was no significant influence of the covariate (anxiety or depression).

\*OR: Estimated relative risk indicated by the OR and the 95% CI.

†Logistic regression analysis was performed; Hosmer-Lemeshow test,  $P = .39$ .

### Sexual dysfunction is more common in patients with CSU with angioedema, and angioedema is more common in patients with CSU with sexual dysfunction

Of 38 patients with CSU with angioedema, 30 (79%) had sexual dysfunction as compared with 8 of 18 patients with CSU without angioedema (44%;  $P = .010$ ; Table III). Vice versa, patients with CSU with sexual dysfunction had angioedema almost twice as often as patients without sexual dysfunction (Table III).

Angioedema was a significant predictor of sexual dysfunction in female patients with CSU (odds ratio, 7.3;  $P = .012$ ; 95% CI, 1.56-34.26; Table IV). Autoantibodies to thyroid peroxidase, antinuclear antibodies, and total IgE levels were not linked to sexual functioning and did not predict sexual dysfunction.

### Reduced sexual functioning is associated with anxiety, depression, and fatigue in female patients with CSU

One in 3 patients (18 of 56; 32.1%) had anxiety, and almost half had depression (26 of 56; 46.4%) as assessed by the HADS.

Both of these comorbid conditions were associated with impaired sexual functioning (anxiety:  $r = -0.358$ ;  $P = .007$ ; depression:  $r = -0.370$ ;  $P = .005$ ) (Table II). Among the subscales of the FSFI, lubrication values were significantly lower in patients with CSU who had depression ( $P = .042$ ) or anxiety ( $P = 0.026$ ; Table V). Depression was seen in 22 of 38 patients with CSU who had angioedema (58%) versus 4 of 18 patients with CSU without angioedema (22%;  $P = .012$ ). Female patients with CSU with sexual dysfunction showed higher levels of fatigue as assessed by visual analogue scale (median, 5; interquartile range, 2-8) than did patients without sexual dysfunction (median, 2; interquartile range, 0.5-4.5;  $P = .030$ ). Of 38 patients with CSU with sexual dysfunction, 14 (36.8%) had high fatigue as compared with 2 of 18 patients with CSU without (11.1%;  $P = .047$ ).

### Reduced sexual functioning, in female patients with CSU, is linked to impaired QOL

Reduced sexual functioning, in female patients with CSU, was linked to impaired QOL as assessed by the CU-QOL questionnaire ( $r = -0.314$ ;  $P = .018$ ) and the DLQI ( $r = -0.231$ ;  $P = .087$ ; Table II), albeit not statistically significantly for the latter. Specifically, reduced sexual functioning correlated with problems with social relationships ( $r = -0.409$ ;  $P = .002$ ), sleep ( $r = -0.324$ ;  $P = .015$ ), keeping concentrated ( $r = -0.320$ ;  $P = .016$ ), feeling in a bad mood ( $r = -0.317$ ;  $P = .017$ ), using cosmetics ( $r = -0.313$ ;  $P = .019$ ), and going to public places ( $r = -0.264$ ;  $P = .049$ ). The 2 aspects of sexual functioning that were most markedly linked to QOL impairment were arousal and orgasm (Table VI). The link between impaired sexual functioning and impaired QOL was stronger in patients with angioedema as compared with those without (Table VII).

### DISCUSSION

Our study has 3 major findings: 7 of 10 female patients with CSU suffer from sexual dysfunction. Sexual dysfunction is linked to high disease activity and angioedema, and it

TABLE V. HADS in patients with CSU

|              | Anxiety          |                  | <i>P</i>    | Depression       |                  | <i>P</i> |
|--------------|------------------|------------------|-------------|------------------|------------------|----------|
|              | ≥11 (n = 18)     | <11 (n = 38)     |             | ≥8 (n = 26)      | <8 (n = 30)      |          |
| Total FSFI   | 22.1 (14.4-26.2) | 24.0 (21.1-27.4) | .086        | 22.7 (18.5-25.8) | 25.0 (20.1-27.9) | .094     |
| Arousal      | 3.2 (2.2-3.8)    | 3.6 (3.0-3.9)    | .142        | 3.3 (2.4-3.6)    | 3.6 (2.7-4.5)    | .186     |
| Desire       | 3.0 (1.8-3.8)    | 3.0 (2.4-3.6)    | .342        | 3.0 (2.4-3.6)    | 3.0 (2.9-3.6)    | .246     |
| Lubrication  | 4.1 (3.2-5.1)    | 5.0 (4.1-5.4)    | <b>.026</b> | 4.5 (3.3-5.1)    | 5.1 (3.8-5.7)    | .042     |
| Satisfaction | 3.8 (1.8-4.8)    | 4.8 (3.5-5.2)    | .125        | 4.0 (2.3-4.8)    | 4.8 (3.5-5.3)    | .082     |
| Orgasm       | 3.8 (1.9-4.8)    | 4.4 (3.6-5.2)    | .052        | 4.0 (2.3-4.8)    | 4.4 (3.6-5.2)    | .069     |
| Pain         | 4.0 (3.0-4.5)    | 4.4 (3.6-4.4)    | .448        | 4.0 (3.5-4.4)    | 4.4 (4.0-4.4)    | .286     |

IQR, Interquartile range.

Bold indicates statistical significance ( $P < .05$ ).Mann-Whitney *U* test was performed, data shown as median (IQR [lower quartile–upper quartile]).

TABLE VI. Correlations of CU-QOL questionnaire questions and FSFI

|                           |                            | Desire | Arousal | Lubrication | Orgasm | Satisfaction | Pain  | Total FSFI |
|---------------------------|----------------------------|--------|---------|-------------|--------|--------------|-------|------------|
| Pruritus                  | 1. Pruritus                | –.348* | –.405*  | –.176       | –.316† | –.181        | .006  | –.304†     |
|                           | 2. Wheals                  | –.285† | –.285†  | .037        | –.139  | –.116        | .057  | –.158      |
| Swelling                  | 3. Eye swelling            | –.075  | –.259   | –.144       | –.212  | –.119        | .035  | –.157      |
|                           | 4. Lip swelling            | .118   | –.029   | –.158       | –.142  | –.089        | .139  | –.029      |
| Impact on life activities | 5. Work                    | –.062  | –.203   | –.075       | –.057  | –.035        | .067  | –.079      |
|                           | 6. Physical activities     | –.145  | –.373*  | –.181       | –.232  | –.138        | –.002 | –.228      |
|                           | 7. Sleep                   | –.430* | –.301†  | –.299†      | –.323† | –.109        | –.084 | –.324†     |
|                           | 8. Spare time              | –.197  | –.221   | –.129       | –.215  | –.188        | –.046 | –.193      |
|                           | 9. Social relationships    | –.304† | –.445*  | –.325†      | –.405* | –.312†       | –.169 | –.409*     |
|                           | 10. Eating behavior        | –.035  | –.253   | –.239       | –.318† | –.231        | .034  | –.237      |
| Sleep problems            | 11. Falling asleep         | –.160  | –.336†  | –.210       | –.267† | –.233        | .045  | –.237      |
|                           | 12. Wake-up during night   | –.187  | –.187   | –.097       | –.156  | –.110        | .057  | –.114      |
|                           | 13. Bad night sleep        | –.063  | –.121   | –.038       | –.171  | –.016        | .120  | –.064      |
|                           | 14. Bad concentration      | –.243  | –.370*  | –.328†      | –.389* | –.250        | .022  | –.320†     |
|                           | 15. Feel nervous           | –.110  | –.192   | –.107       | –.130  | –.059        | .072  | –.086      |
|                           | 16. Feel in a bad mood     | –.293† | –.269†  | –.257       | –.317† | –.283†       | –.029 | –.317†     |
| Limits                    | 17. In choosing food       | .116   | –.162   | –.181       | –.182  | –.095        | .059  | –.070      |
|                           | 18. Sport activities       | .062   | –.176   | –.138       | –.138  | –.087        | .244  | –.081      |
| Looks                     | 19. Drugs' side effects    | .054   | –.195   | –.065       | –.075  | .012         | .147  | –.050      |
|                           | 20. Embarrassed            | .002   | –.252   | –.085       | –.169  | –.195        | .061  | –.141      |
|                           | 21. Going to public places | –.166  | –.326†  | –.243       | –.300† | –.286†       | –.067 | –.264†     |
|                           | 22. Using cosmetics        | –.093  | –.267†  | –.211       | –.399* | –.296†       | .036  | –.313†     |
|                           | 23. Choosing clothes       | –.077  | –.214   | –.121       | –.285† | –.195        | .148  | –.194      |
|                           | Total score Cu-QOL         | –.251  | –.418*  | –.262       | –.380* | –.241        | –.005 | –.314†     |

\**r* (moderate correlation): Spearman-rho correlation analysis was performed.†*r* (low correlation).

correlates with significant and broad impairment in QOL. The results of our study are alarming and must prompt a call to action.

Our finding that 2 of 3 female patients with CSU exhibit sexual dysfunction as assessed by the FSFI is very similar to the result of an earlier and smaller study from 2007 in which 70.5% of female patients with CSU had sexual dysfunction as assessed by the use of the Arizona Sexual Experience Scale.<sup>21</sup> Also, our study confirms the results of a recent study that showed that sexual functioning is markedly reduced in female patients with CSU and significantly lower as compared with healthy control subjects, although FSFI values of female patients with CSU in this study were somewhat higher than in ours, 27.1 versus 23.1.<sup>40</sup> One of the reasons for this difference in absolute FSFI

values may be the fact that the mean age of our patient group was 38 years versus 35 years in the previous study. Older age is known to be correlated with lower FSFI scores.<sup>41</sup> Another possible reason for this difference may be sociocultural differences between the patient groups.

That impaired sexual functioning is linked to high disease activity and poor disease control in female patients with CSU does not come as a surprise. High disease activity and patient burden are known drivers of poor sexual health in a number of chronic diseases including diabetes, multiple sclerosis, and rheumatoid arthritis.<sup>10,13,14</sup> A multicenter study on sexual health in several dermatological diseases showed that impairment of sexual life was strongly associated with severity of the disease and itch.<sup>22</sup> Skrzypulec-Frankel et al<sup>40</sup> also found a significant

TABLE VII. Correlations of CU-QOL questionnaire questions and FSFI according to history of angioedema

|       | Angioedema – (n = 18) |         |             |        |              |       |            | Angioedema + (n = 38) |         |             |        |              |       |            |
|-------|-----------------------|---------|-------------|--------|--------------|-------|------------|-----------------------|---------|-------------|--------|--------------|-------|------------|
|       | Desire                | Arousal | Lubrication | Orgasm | Satisfaction | Pain  | Total FSFI | Desire                | Arousal | Lubrication | Orgasm | Satisfaction | Pain  | Total FSFI |
| Q1    | –.484*                | –.486*  | –.233       | –.409  | –.302        | –.353 | –.420      | –.302                 | –.372*  | –.131       | –.249  | –.114        | .141  | –.193      |
| Q2    | –.261                 | –.099   | .195        | .046   | .043         | –.347 | –.037      | –.335*                | –.385*  | –.005       | –.190  | –.167        | .188  | –.180      |
| Q3    | .038                  | –.127   | –.090       | .026   | –.074        | –.281 | –.071      | –.105                 | –.314   | –.123       | –.226  | –.045        | .163  | –.118      |
| Q4    | .287                  | –.047   | –.261       | –.056  | –.273        | .067  | –.077      | .117                  | –.011   | –.075       | –.138  | .019         | .181  | .022       |
| Q5    | .104                  | .028    | –.104       | –.104  | .027         | –.237 | –.024      | –.139                 | –.316   | –.052       | –.025  | –.065        | .179  | –.081      |
| Q6    | –.087                 | –.157   | –.271       | –.282  | –.090        | –.401 | –.218      | –.166                 | –.452†  | –.130       | –.184  | –.144        | .127  | –.194      |
| Q7    | –.451                 | –.334   | –.257       | –.251  | –.169        | –.262 | –.345      | –.398*                | –.262   | –.301       | –.335* | –.069        | –.012 | –.280      |
| Q8    | –.107                 | –.020   | .124        | .033   | –.185        | –.067 | –.059      | –.218                 | –.333*  | –.239       | –.307  | –.178        | –.032 | –.240      |
| Q9    | 0.000                 | –.076   | .131        | –.109  | –.121        | –.261 | –.065      | –.416†                | –.570†  | –.461†      | –.450† | –.318        | –.124 | –.492†     |
| Q10   | –.020                 | –.122   | –.151       | –.181  | –.198        | –.193 | –.138      | .044                  | –.193   | –.211       | –.284  | –.199        | .164  | –.155      |
| Q11   | .055                  | –.124   | .100        | –.124  | –.252        | –.061 | –.124      | –.293                 | –.532†  | –.435†      | –.415† | –.313        | .059  | –.376*     |
| Q12   | .121                  | .023    | .046        | –.127  | –.165        | .136  | –.050      | –.349*                | –.340*  | –.200       | –.198  | –.126        | .023  | –.204      |
| Q13   | .040                  | –.019   | .051        | .051   | .016         | .044  | .036       | –.148                 | –.223   | –.126       | –.283  | –.075        | .133  | –.150      |
| Q14   | –.010                 | –.059   | –.108       | –.105  | –.251        | .070  | –.106      | –.350*                | –.490†  | –.408*      | –.473† | –.241        | .008  | –.377*     |
| Q15   | .317                  | .290    | .116        | .171   | .103         | .127  | .235       | –.319                 | –.445†  | –.229       | –.295  | –.177        | .035  | –.247      |
| Q16   | –.032                 | .199    | .166        | .120   | –.015        | .134  | .105       | –.434†                | –.428†  | –.421†      | –.468† | –.401*       | –.084 | –.481†     |
| Q17   | .343                  | .311    | .192        | –.021  | .007         | .424  | .250       | .039                  | –.362*  | –.333*      | –.238  | –.119        | –.071 | –.182      |
| Q18   | .075                  | .147    | .032        | .111   | –.021        | –.002 | .074       | .111                  | –.238   | –.166       | –.148  | –.051        | .341* | –.083      |
| Q19   | .149                  | .146    | –.010       | .153   | .279         | –.212 | .138       | .080                  | –.248   | –.005       | –.036  | .024         | .301  | .005       |
| Q20   | .286                  | .238    | .398        | .385   | .157         | –.078 | .257       | –.104                 | –.418†  | –.219       | –.257  | –.229        | .101  | –.238      |
| Q21   | –.153                 | –.153   | –.225       | –.250  | –.267        | –.261 | –.236      | –.121                 | –.317   | –.187       | –.206  | –.224        | .039  | –.161      |
| Q22   | .072                  | .169    | .190        | –.047  | –.137        | –.180 | .041       | –.126                 | –.318   | –.295       | –.443† | –.261        | .149  | –.370*     |
| Q23   | .034                  | .047    | –.003       | –.110  | –.250        | .086  | –.017      | –.122                 | –.253   | –.079       | –.297  | –.136        | .227  | –.196      |
| Total | –.024                 | –.065   | –.025       | –.113  | –.132        | –.135 | –.099      | –.309                 | –.526†  | –.329*      | –.414† | –.247        | .053  | –.340*     |

\**r* (low correlation);†*r* (moderate correlation): Spearman-rho correlation analysis was performed.

correlation between the severity of sexual impairment and the severity of CSU.<sup>40</sup> Interestingly, FSFI values were not linked to disease duration, suggesting that sexual functioning is impaired early after the onset of CSU. The effects of CSU on sexual health, therefore, appear to be different than those on mental health, as recent studies have shown that depression and anxiety in patients with CSU develop gradually over time.<sup>24</sup> Allergists should consider to refer patients with CSU who exhibit symptoms of depression or anxiety to mental health care professionals, and questionnaires such as the ones used in the current study can help to identify patients who can benefit from this. Importantly, our findings strongly support that CSU is associated with sexual dysfunction, and they encourage studies on the effects of effective CSU treatment on sexual functioning in female patients with CSU.

Why is angioedema, in female patients with CSU, so closely linked to sexual dysfunction? This novel finding may be explained by the fact that angioedema, in patients with CSU, often affects the genitalia and can be painful, although it is unclear how common this is. In other dermatological diseases such as psoriasis, vitiligo, and hydradenitis suppurativa, the involvement of the genital region is known to cause sexual dysfunction.<sup>22,42,43</sup> In some patients, genital angioedema may impair sexual activities and sexual activities may induce genital angioedema, causing sexual reluctance. Also, angioedema is often highly frightening and debilitating,<sup>4,5</sup> causes high levels of mental distress,<sup>44</sup> and reduces the QOL. This, in turn, can impair sexual functioning.

Our study shows that sexual dysfunction in female patients with CSU is closely linked to anxiety, depression, and fatigue. In a large number of diseases such as ankylosing spondylitis, fibromyalgia, multiple sclerosis, psoriasis, and, very recently CSU,<sup>9-11,22,40,41</sup> reduced sexual functioning has been shown to be associated with depression and anxiety. Fatigue is also known to be linked to impaired sexual desire and sexual activity.<sup>10</sup> Kool et al<sup>45</sup> reported that fatigue can predict sexual functioning in patients with fibromyalgia. This link between depression, anxiety as well as fatigue and impaired sexual functioning is bidirectional. All 3 can negatively affect sexual functioning, and sexual dysfunction can contribute to depression, anxiety, and fatigue. In a recent meta-analysis,<sup>46</sup> for example, depression has been shown to cause female sexual dysfunction and vice versa.<sup>46</sup> As for CSU, a better understanding of the connection between sexual functioning and depression and anxiety needs to come from studies that look at the effects of treating patients with CSU for their depression and anxiety on their sexual functioning.

Female sexual dysfunction is well known to negatively impact on QOL by causing stress and affecting daily life and relationships.<sup>10,11,22</sup> However, impaired QOL can decrease sexual functioning.<sup>47</sup> In our study, the link between impaired sexual functioning and reduced QOL was stronger in patients with angioedema than in those without. Together with the fact that we found angioedema to be the only significant predictor of sexual dysfunction in female patients with CSU, this strongly argues that female patients with CSU with angioedema should be routinely assessed and monitored for the impact of their disease on sexual functioning.

Our study has strengths and limitations. The former include that we comprehensively assessed patients for clinical and laboratory markers, comorbidities, and QOL and that we compared

them with healthy controls. The main limitations of our study are that it was monocentric and that our patient population was, therefore, composed mostly of women from one geographic area and with a similar cultural background. In addition, our center is a urticaria center of reference and excellence at a reference hospital, and CSU, in most of our patients, is moderate or severe. Also, we did not systematically assess the previous intake of medications such as steroids, antihistamines, and proton pump inhibitors, all of which may affect sexual functioning.<sup>48</sup> Our findings call for global and multicenter follow-up studies that include both sexes, for example, within the network of GA<sup>2</sup>LEN urticaria centers of reference and excellence.<sup>34</sup>

## CONCLUSIONS

Our study shows that CSU is linked to sexual functioning in female patients with CSU. Our results that sexual functioning is markedly reduced, and that sexual dysfunction is very frequent in female patients with CSU, should prompt physicians who treat patients with CSU to talk about sexual health and functioning with their patients and to take sexual dysfunctioning into account when making treatment decisions. Effective treatment of CSU may improve sexual functioning together with anxiety, depression, and fatigue, which, in turn, may improve QOL.

## REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73:1393-414.
2. Ertas R, Özyurt K, Karakükçü Ç, Akkuş MR, Özlü E, Avcı A, et al. Evaluation of platelet parameters and neutrophil/lymphocyte ratio during omalizumab treatment in patients with severe chronic spontaneous urticaria. *Turkish J Med Sci* 2018;48:1255-62.
3. Ertas R, Özyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy* 2018;73:705-12.
4. Powell RJ, Leech SC, Till S, Huber PAJ, Nasser SM, Clark AT. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2015;45:547-65.
5. Ertas R, Özyurt K, Yildiz S, Ulaş Y, Turasan A, Avcı A. Adverse reaction to omalizumab in patients with chronic urticaria: flare up or ineffectiveness? *Iran J Allergy Asthma Immunol* 2016;15:82-6.
6. Maurer M, Staubach P, Raap U, Richter-Huhn G, Baier-Ebert M, Chapman-Rothe N. ATTENTUS, a German online survey of patients with chronic urticaria highlighting the burden of disease, unmet needs and real-life clinical practice. *Br J Dermatol* 2016;174:892-4.
7. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
8. Barbosa F, Freitas J, Barbosa A. Alexithymia in chronic urticaria patients. *Psychol Heal Med* 2011;16:215-24.
9. Akkurt HE, Yilmaz H, Yilmaz S, Parlak L, Ordahan B, Salli A. Evaluation of sexual dysfunction in females with ankylosing spondylitis. *Arch Rheumatol* 2016;31:41.
10. Gumus H, Akpinar Z, Yilmaz H. Effects of multiple sclerosis on female sexuality: a controlled study. *J Sex Med* 2014;11:481-6.
11. Yilmaz H, Yilmaz SD, Polat HAD, Salli A, Erkin G, Ugurlu H. The effects of fibromyalgia syndrome on female sexuality: a controlled study. *J Sex Med* 2012;9:779-85.
12. Yilmaz H, Gumus H, Yilmaz S, Akkurt H, Odabas F. The evaluation of sexual function in women with stroke. *Neurol India* 2017;65:271-6.
13. Yilmaz H, Polat HAD, Yilmaz SD, Erkin G, Kucuksen S, Salli A, et al. Evaluation of sexual dysfunction in women with rheumatoid arthritis: a controlled study. *J Sex Med* 2012;9:2664-70.
14. Kolodny RC. Sexual dysfunction in diabetic females. *Diabetes* 1971;20:557-9.

15. Kirmaz C, Aydemir O, Bayrak P, Yuksel H, Ozenturk O, Degirmenci S. Sexual dysfunction in patients with allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2005;95:525-9.
16. Misery L, Finlay AY, Martin N, Boussetta S, Nguyen C, Myon E, et al. Atopic dermatitis: impact on the quality of life of patients and their partners. *Dermatology* 2007;215:123-9.
17. Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, et al. Epidemiology/risk factors of sexual dysfunction. *J Sex Med* 2004;1:35-9.
18. Caminati M, Giorgis V, Palterer B, Racca F, Salvottini C, Rossi O. Allergy and sexual behaviours: an update. *Clin Rev Allergy Immunol* 2019;56:269-77.
19. Ates Bulut E, Törüner M. The influence of disease type and activity to sexual life and health quality in inflammatory bowel disease. *Turkish J Gastroenterol* 2019;30:33-9.
20. Meyer IH, Sternfels P, Fagan JK, Ford JG. Asthma-related limitations in sexual functioning: an important but neglected area of quality of life. *Am J Public Health* 2002;92:770-2.
21. Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. *J Sex Marital Ther* 2007;33:55-64.
22. Sampogna F, Abeni D, Gieler U, Tomas-Aragones L, Lien L, Titeca G, et al. Impairment of sexual life in 3,485 dermatological outpatients from a multicentre study in 13 European countries. *Acta Derm Venereol* 2017;97:478-82.
23. Ertas R, Erol K. The frequency of chronic widespread pain and its impact on quality of life in patients with chronic spontaneous urticaria. *Konuralp Tıp Derg* 2019;11:101-5.
24. Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller K, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011;91:557-61.
25. Silveiras MRC, Coelho KIR, Dalben I, Lastória JC, Abbade LP. Socio-demographic and clinical characteristics, causal factors and evolution of a group of patients with chronic urticaria-angioedema. *Sao Paulo Med J* 2007;125:281-5.
26. Mlynec A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica GW, et al. The German version of the chronic urticaria quality-of-life questionnaire: factor analysis, validation, and initial clinical findings. *Allergy* 2009;64:927-36.
27. Yun J, Katelaris CH, Weerasinghe A, Adikari DB, Ratnayake C. Impact of chronic urticaria on the quality of life in Australian and Sri Lankan populations. *Asia Pac Allergy* 2011;1:25-9.
28. Asero R. Sex differences in the pathogenesis of chronic urticaria. *J Allergy Clin Immunol* 2003;111:425-6.
29. Metz M, Staubach P, Bauer A, Brehler R, Gericke J, Kangas M, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. *Theranostics* 2017;7:1266-76.
30. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, González-Aveledo L, Maurer M. Factors linked to disease severity and time to remission in patients with chronic spontaneous urticaria. *J Eur Acad Dermatology Venereol* 2017;31:964-71.
31. Ertas R, Ozyurt K, Ozlu E, Ulas Y, Avci A, Atasoy M, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;140:1749-51.
32. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;139:1059-10561.e1.
33. Avci A, Avci D, Ertas R, Atasoy M, Karakukcu C, Yontar E, et al. Does omalizumab treatment affect serum dehydroepiandrosterone sulphate levels in chronic idiopathic urticaria? *Postepy Dermatol Alergol* 2019;36:92-7.
34. Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA2LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210-8.
35. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005;31:1-20.
36. Kocatiürk O, Kızıldağ U, Can P, Öztas Kara R, Erdem T, Kızıldağ K, et al. Validation of the Turkish version of the Urticaria Control Test: correlation with other tools and comparison between spontaneous and inducible chronic urticaria. *World Allergy Organ J* 2019;12:100009.
37. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014;133:1365-1372.e6.
38. Aydemir O, Kızıldağ U, Can P, Öztas Kara R, Erdem T, Kızıldağ K, et al. Validity and reliability of Turkish version of Hospital Anxiety and Depression Scale. *Turkish J Psychiatry* 1997;8:280-7.
39. Chaufier K, Paternotte S, Burki V, Durnez A, Elhaï A, Koumakis E, et al. Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients. *Clin Exp Rheumatol* 2013;31:864-70.
40. Skrzypulec-Frankel A, Bieniek K, Kasperska-Zajac A. The association between sexual dysfunctions and severity of symptoms in patients with chronic spontaneous urticaria. *Allergy Asthma Clin Immunol* 2018;14:20.
41. Konstantinidis C, Tzitzika M, Bantis A, Nikolia A, Samarinas M, Kratiras Z, et al. Female sexual dysfunction among Greek women with multiple sclerosis: correlations with organic and psychological factors. *Sex Med* 2019;7:19-25.
42. Ryan C, Sadlier M, De Vol E, Patel M, Lloyd AA, Day A, et al. Genital psoriasis is associated with significant impairment in quality of life and sexual functioning. *J Am Acad Dermatol* 2015;72:978-83.
43. Kim DY, Lee J, Oh SH, Hann S-K, Shin YJ. Impact of genital involvement on the sexual lives of vitiligo patients. *J Dermatol* 2013;40:1065-7.
44. Fouche AS, Saunders EFH, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 2014;112:371-5.
45. Kool MB, Woertman L, Prins MA, Van Middendorp H, Geenen R. Low relationship satisfaction and high partner involvement predict sexual problems of women with fibromyalgia. *J Sex Marital Ther* 2006;32:409-23.
46. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *J Sex Med* 2012;9:1497-507.
47. Moore RH, Sarwer DB, Lavenberg JA, Lane IB, Evans JL, Volger S, et al. Relationship between sexual function and quality of life in obese persons seeking weight reduction. *Obesity* 2013;21:1966-74.
48. Lightner DJ. Female sexual dysfunction. *Mayo Clin Proc* 2002;77:698-702.