ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/dermato.2021-85074

The Effect of Smoking on the Clinical Characteristics of Urticaria: A Cross-Sectional Evaluation of Smoking and Alcohol Consumption Habits of 171 Patients with Urticaria

Sigaranın Ürtikerin Klinik Özelliklerine Olan Etkisi: 171 Ürtiker Tanılı Hastada Sigara ve Alkol Tüketim Alışkanlıklarının Kesitsel Çalışma ile İncelenmesi

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ABSTRACT Objective: Urticaria is a heterogeneous disease with multiple causative factors. A thorough literature research has revealed a very limited amount of evidence about the effects of smoking and alcohol consumption habits on the clinical characteristics of urticaria. The aim of the present study was to investigate the smoking and alcohol consumption habits of patients with urticaria and to evaluate the associations of these habits with clinical characteristics of urticaria. **Material and Methods:** A total of 171 consecutive patients with urticaria and age and sex-matched healthy controls were prospectively enrolled in the study. A detailed history regarding the smoking and alcohol consumption habits, duration of urticaria, hospitalization and treatment modalities for urticaria and clinical response to treatments was recorded. Detailed statistical analyses were performed. **Results:** Smoking frequency was significantly higher in patients than in controls. Patients, who were smokers had a 5.03-fold increased risk of urticaria. The frequency of hospitalization was higher in the smokers compared to the non-smokers. Smoking increased hospitalization risk 2.2-fold. In 39.6% of the non-smokers and 52.5% of the smokers, urticarial symptom control could not be achieved with low-dose oral antihistamines. Smoking increased the risk of urticaria 1.94-fold in low-dose antihistamine responders, while 3.27-fold in low-dose antihistamine non-responders. There wasn't any statistical correlation between alcohol consumption habits and outcome of urticaria. **Conclusion:** Our results strongly suggest that smoking affects the clinical course of urticaria. Smoking should be questioned in every patient with urticaria, since promoting cessation of smoking might be effective in the management of urticaria.

Keywords: Urticaria; smoking; alcohol consumption

ÖZET Amaç: Ürtiker, birçok nedeni olan heterojen bir hastalıktır. Detaylı literatür araştırmaları, sigara ve alkol tüketiminin, ürtikerin klinik özelliklerine olan etkisini irdeleyen kısıtlı sayıda veriyi ortaya koymaktadır. Bu çalışmanın amacı, ürtiker tanılı olguların sigara ve alkol tüketim alışkanlıkları ve bu alışkanlıkların, ürtikerin klinik özellikleri üzerine etkilerini araştırmaktır. **Gereç ve Yöntemler:** Ürtiker tanısı olan 171 hasta ile yaş ve cinsiyet açısından eşleştirilmiş sağlıklı kontrol grubu prospektif olarak çalışma kapsamında değerlendirildi. Hastalardan sigara ve alkol tüketim alışkanlıkları, ürtiker süresi, hastaneye yatış durumu ve tedavi modalitelerini sorgulayan ayrıntılı hikâye alındı. Detaylı istatistiksel analizler yapıldı. **Bulgular:** Sigara tüketim sıklığı, kontrol grubuna göre hasta grubunda daha yüksekti. Hastalar arasında sigara içenlerde ürtiker 5,03 kat daha yüksek oranda tespit edildi. Hastaneye yatış oranları, sigara içen grupta içmeyenlere göre daha sıktı. Sigara tüketimi, hastaneye yatış sıklığını 2,2 kat artırıyordu. Sigara içmeyen grubun %39,6'sında ve sigara içen grubun %52,5'inde ürtiker semptomları, düşük doz oral antihistaminik tedavisi ile kontrol altına alınamıyordu. Sigara tüketimi, ürtiker riskini düşük doz antihistaminik tedavisine yanıt verenlerde 1,94; yanıt vermeyenlerse ise 3,27 kat artırıyordu. Alkol tüketimi ile ürtikerin klinik seyri arasında herhangi bir istatistiksel korelasyon saptanmadı. **Sonuç:** Çalışmamızın sonuçları, sigara tüketiminin ürtikerin klinik seyrini etkilediğini ortaya koymuştur. Sigaranın bırakılmasının, ürtikerin yönetiminde etkili olması nedeniyle sigara tüketim alışkanlıkları ürtiker tanılı her hastada sorgulanmalıdır.

Anahtar Kelimeler: Ürtiker; sigara tüketimi; alkol tüketimi

Urticaria is a skin disease, which is characterized by erythematous, edematous, pruritic urticarial plaques. Urticaria is a common disorder, of which symptoms occur up to 25% of general population at some point of their lives. There is a significant amount of knowledge on the pathogenesis of urticaria that has been gained in recent years, which indicates that urticaria is a mast-cell mediated disease, in which

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Peer review under responsibility of Turkiye Klinikleri Journal of Dermatology.

Received: 21 Jun 2021 ***Received in revised form:*** 12 Oct 2021 ***Accepted:*** 13 Oct 2021 ***Available online:*** 21 Oct 2021

histamine plays the central role.[1] The disproportionate activation and degranulation of mast cells are the triggering events in the pathogenesis of urticaria. On the other hand, which factors initiate this activation and degranulation process and what exactly happens after the inducement remain to be elucidated.[2] The effect of cigarette smoke on mast cells has been studied but still continuing to be obscure. The suppressive effect of cigarette smoke on mast cell degranulation and histamine release has been reported.[3] However, it has also been documented that cigarette smoke amplifies allergic inflammatory response.[4] A thorough literature review reveals only a limited data on the relation between smoking and clinical characteristics of urticaria.[5] The aim of the present study was to investigate the smoking and alcohol consumption habits of patients with urticaria and compare these findings with healthy controls in order to evaluate the associations of smoking and alcohol consumption with urticaria clinical characteristics of urticaria.

MATERIAL AND METHODS

A total of 171 consecutive patients with urticaria and 171 age- and sex-matched healthy controls were prospectively enrolled in this cross-sectional, analytic, case and control study over a period of 3 months. The study was approved by the Ankara City Hospital Medical Ethics Committee on 02.12.2020 with the number of E2-20-31 and conducted according to the Declaration of Helsinki principles. Each patient provided a written informed consent prior to being included in the study. The diagnosis of urticaria was made on the basis of clinical findings. Only patients with chronic idiopathic urticaria were included in the study. A lesional skin biopsy was performed before inclusion in any patient, of whom diagnosis of urticaria was questionable. A detailed history regarding the demographic characteristics, smoking and alcohol consumption habits, duration of urticaria, hospitalization and treatment modalities for urticaria (oral antihistamines, systemic corticosteroids, cyclosporin-A, omalizumab, montelukast sodium) was recorded. If the patient was receiving oral antihistamines, the dosage was documented (q.d./b.i.d./t.i.d./2 tablets q12h). The patients were grouped according to their treatment responses: patients with good therapeutic response to low-dose oral antihistamine (q.d./b.i.d.) (low-dose antihistamine responders), patients with therapeutic response to only high-dose oral antihistamines (t.i.d./2 tablets q12h) or other therapies (systemic corticosteroids, cyclosporin-A, omalizumab, montelukast sodium) (low-dose antihistamine non-responders).

STATISTICAL ANALYSIS

The statistical analysis was performed by using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). Associations between qualitative variables, including the differences between patient and control groups in terms of demographic characteristics, smoking and alcohol consumption habits were tested by the chi-square (χ^2) test. Logistic regression analysis was used to predict the risk of hospitalization. $p<0.05$ was considered as statistically significant.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

A total of 171 (53 men and 118 women; mean age, 47.5±15.1 years) consecutive patients with urticaria were prospectively enrolled in the present study. While acute urticaria was observed in 61 (35.7%) patients, chronic urticaria was observed in 110 (64.3%) of 171 patients. The median value of disease duration was 12 months (interquartile range: 4-48 months). 67.8% of the patients did not declare any history of hospitalization, however 32.2% of the patients were hospitalized for urticaria at least once. When the number of hospital admissions was investigated, it was revealed that the patients were most frequently applied to hospital for twice (38%).

Oral antihistamines were the most frequently prescribed drugs (72.2%), followed by systemic corticosteroids and montelukast sodium. The least commonly prescribed drug was omalizumab with a frequency of 0.6%. In 54.5% of the patients, oral antihistamines were prescribed at the dosage of q.d. Of the patients, 54.4% were low-dose antihistamine responders, while 45.6% of the patients were low-dose antihistamine non-responders. 46.8% of the patients were smokers and 17% of the patients consumed alcohol at least once a week. Table 1 demonstrates the characteristics of the study population.

TABLE 1: Characteristics of the study group.

	n (%)
Age, year*	47.5 (15.1)
Sex	
Women	118 (69)
Men	53 (31)
Urticaria type	
Acute	61 (35.7)
Chronic	110 (64.3)
Disease duration, month**	12 (4-48)
Hospitalization	
Present	55 (32.2)
Absent	116 (67.8)
Admission to hospital in the last month	
1	45 (26.3)
2	65 (38)
3	29 (17)
4	32 (18.7)
Treatment modalities	
Oral antihistamines	132 (77.2)
Systemic corticoteroids	31 (18.1)
Cyclosporin-A	3 (1.8)
Omalizumab	1 (0.6)
Montelukast sodium	4 (2.3)
Dosage of oral antihistamines	
q.d.	72 (54.5)
b.i.d.	21 (15.9)
t.i.d.	13 (9.8)
2 tablets q12h	26 (19.7)
Response to low-dose antihistamines	
Responders	93 (54.4)
Non-responders	78 (45.6)
Smoking	
Present	80 (46.8)
Absent	91 (53.2)
Alcohol consumption	
Present	29 (17)
Absent	142 (83)

*Mean (standard deviation); **Median (interquartile range).

COMPARISON OF STUDY AND CONTROL GROUPS IN TERMS OF SMOKING AND ALCOHOL CONSUMPTION HABITS

Ratio of smokers was 45% (n=90) in the patient group and 14% (n=28) in the control group. Smoking frequency was significantly higher in patients than in the control group (p<0.001). Patients, who were smokers had a 5.03-fold increased risk of urticaria (95% confidence interval: 3.09-8.18; p<0.001). Seventeen percent of the patient group, 13.5% of the control group declared consuming alcohol at least once a week. Patient and control groups were statistically similar in terms of alcohol consumption habits (p=0.37). Table 2 shows comparison of patient and control groups in terms of smoking and alcohol consumption habits.

EVALUATION OF THE RELATIONSHIP BETWEEN SMOKING HABITS AND CLINICAL CHARACTERISTICS OF URTICARIA IN THE STUDY GROUP

The frequency of smoking was significantly higher among men than women (p=0.001). The frequency of hospitalization was higher in smokers compared to non-smokers (41.3% vs. 24.2%; p=0,017). Logistic regression analysis revealed that smoking increased hospitalization risk 2.2-fold (95% confidence interval: 1.14-4.23; p=0.018). 60.4% of the non-smokers and 47.5% of the smokers had good therapeutic response to low-dose oral antihistamines. However, in 39.6% of the non-smokers and 52.5% of the smokers, symptom control could not be achieved with low-dose oral antihistamines and they needed high-dose oral antihistamines or additional therapies. On the other hand, it was disclosed that the difference between therapeutic responses among smokers and non-smokers did not reach a statistical level of significance (p=0.090).

Smoking increased the risk of urticaria 1.94-fold (95% confidence interval: 1.13-3.31; p=0.015) in low-dose antihistamine responders, while 3.27-fold (95% confidence interval: 1.87-5.72; p<0.001)

TABLE 2: Comparison of patient and control groups in terms of smoking and alcohol consumption habits.

	Patients (n=171)	Controls (n=171)	p value
Smoking			
Present	80 (46.8)	45 (26.3)	<0.001
Absent	91 (53.2)	126 (73.7)	
Alcohol consumption			
Present	29 (17)	23 (13.5)	0.37
Absent	142 (83)	148 (86.5)	

in low-dose antihistamine non-responders. There weren't any differences between smokers and non-smokers in terms of age, urticaria type, disease duration, the frequency of hospital admission in the last month, treatment modalities and antihistamine dosage. The frequency of alcohol consumption was higher among smokers compared with non-smokers (p=0.002). Table 3 demonstrates the characteristics of smokers and non-smokers.

EVALUATION OF THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND CLINICAL CHARACTERISTICS OF THE PATIENTS

The frequency of alcohol consumption was higher among men and smokers (p<0.001 and p=0.002, respectively). However, there wasn't any statistical correlation between alcohol consumption habits and outcome of urticaria (Table 4).

TABLE 3: Comparison of characteristics of smokers and non-smokers.

	Smoker (n=80)	Non-smoker (n=91)	p value
Age, year*	46.3 (±12.7)	48.6 (±16.8)	0.45
Sex			
Female	45 (56.3)	73 (80.2)	**0.001**
Male	35 (43.8)	18 (19.8)	
Urticaria type			
Acute	30 (37.5)	31 (34.1)	0.64
Chronic	50 (62.5)	60 (65.9)	
Disease duration, month**	19 (3-60)	12 (5-36)	0.55
Hospitalization			
Present	33 (41.3)	22 (24.2)	**0.017**
Absent	47 (58.8)	69 (75.8)	
Admission to hospital in the last month			
1	19 (23.8)	26 (28.6)	0.88
2	33 (38.8)	34 (37.4)	
3	15 (18.8)	14 (15.4)	
4	15 (18.8)	17 (18.7)	
Treatment modalities			
Oral antihistamines	52 (72.2)	80 (80.8)	0.39
Systemic corticoteroids	16 (22.2)	15 (15.2)	
Cyclosporin-A	1 (1.4)	2 (2)	
Omalizumab	0	1 (1)	
Montelukast sodium	3 (4.2)	1 (1)	
Dosage of oral antihistamines			
q.d.	27 (51.9)	45 (56.3)	0.66
b.i.d.	9 (17.3)	12 (15)	
t.i.d.	7 (13.5)	6 (7.5)	
2 tablets q12h	9 (17.3)	17 (21.3)	
Response to low-dose antihistamines			
Responders	38 (47.5)	55 (60.4)	0.090
Non-responders	42 (52.5)	36 (39.6)	
Alcohol consumption			
Present	21 (26.3)	8 (8.8)	**0.002**
Absent	59 (73.8)	83 (91.2)	

*: Mean (standard deviation), **: Median (interquartile range).

TABLE 4: Comparison of characteristics of patients with or without alcohol consumption.

	With alcohol consumption (n=80)	Without alcohol consumption (n=91)	p value
Age, year*	46.3 (±12.7)	48.6 (±16.8)	0.32
Sex			
Female	8 (27.6)	110 (77.5)	**<0.001**
Male	21 (72.4)	32 (22.5)	
Urticaria type			
Acute	11 (37.9)	50 (35.2)	0.78
Chronic	18 (62.1)	92 (64.8)	
Disease duration, month**	12 (3.5-60)	12 (4-48)	0.91
Hospitalization			
Present	11 (37.9)	44 (31)	0.47
Absent	18 (62.1)	98 (69)	
Admission to hospital in the last month			
1	7 (24.1)	38 (26.8)	0.98
2	12 (41.4)	53 (37.3)	
3	5 (17.2)	24 (16.9)	
4	5 (17.2)	27 (19)	
Treatment modalities			
Oral antihistamines	22 (75.9)	110 (77.5)	0.91
Systemic corticoteroids	5 (17.2)	26 (18.3)	
Cyclosporin-A	1 (3.4)	2 (1.4)	
Omalizumab	0	1 (0.7)	
Montelukast sodium	1 (3.4)	3 (2.1)	
Dosage of oral antihistamines			
q.d.	13 (59.1)	59 (53.6)	0.79
b.i.d.	3 (13.6)	18 (16.4)	
t.i.d.	1 (4.5)	12 (10.9)	
2 tablets q12h	5 (22.7)	21 (19.1)	
Response to low-dose antihistamines			
Responders	16 (55.2)	77 (54.2)	0.93
Non-responders	13 (44.8)	65 (45.8)	
Smoking			
Present	21 (72.4)	59 (41.5)	**0.002**
Absent	8 (27.6)	83 (58.5)	

*: Mean (standard deviation), **: Median (interquartile range).

DISCUSSION

Urticaria is a common skin disease, characterized by erythematous, pruritic urticarial plaques. The exact pathogenesis of urticaria has not been fully understood yet. Several theories have been postulated to explain the underlying mechanisms of the pathogenesis of urticaria. Although the evidence remains strong about the eventual events, that is the release of histamine by mast cells and basophils, which factors trigger these cells to degranulate and release such a variety of inflammatory mediators, still remain to be solved. In recent years, it has been demonstrated that different biologic systems, including autoimmunity, auto-allergy, inflammation and coagulation may associate to provoke a common underlying mechanism leading to urticarial symptoms. Other than histamine, which is the main mediator, tryptase, chymase, proteases, prostaglandin-D2, thromboxanes, leukotrienes, and platelet-activating factor all play a role in the pathogenesis of urticaria.[1,2,6-9]

According to the results of our study, smoking frequency was significantly higher in patients than in controls. Patients who were smokers had a 5.03-fold increased risk of urticaria. Smoking increased hospitalization risk 2.2-fold, the frequency of hospitalization was higher in smokers compared to non-smokers. It was also revealed that smoking especially increased the risk of urticaria in low-dose antihistamine non-responders. Moreover, among both low-dose antihistamine responders and non-responders, it was the smokers who had the lower therapeutic responses. All these findings suggest that smoking affects the clinical course of urticaria, since it is directly related with increased disease frequency, hospitalization and therapeutic failure.

The effect of cigarette smoke on degranulation of mast cells still remain obscure. There have been few studies investigating the effect of cigarette smoke on mast cell mediators.[3,4,10,11] Barua et al. have demonstrated that cigarette smoke extract enhances histamine- and lipopolysaccharide-induced expression of cyclooxygenase-2 (COX-2) in endothelial cells, which suggests cigarette smoke and mast cell mediators may simultaneously boost inflammatory response in the vessel wall.[4] They further hypothesize that cigarette smoke intensifies histamine-mediated upregulation of Toll-like receptor 2 (TLR2)/TLR4 signaling in the endothelium and promotes progression of atherosclerosis, since cigarette smoke is associated with upregulation of COX-2 and TLR4 expression and activation of mast cells to release histamine.[4] Smoking also has been attributed to be linked with activation of mast cells, as the absolute number of mast cell increases in the lungs and skin of smokers.[10]

On the other hand, there are studies showing suppressive effect of cigarette smoke on mast cells.[3] In 2013, Givi et al. demonstrated that cigarette smoke medium suppresses the granularity and the surface expression of c-kit and high affinity receptor for IgE (FcεRI) receptors of mast cells.[3] The aim of this study was to investigate the effect of cigarette smoke on mast cells maturation and function, since they had previously shown the inhibitory effect of cigarette smoke medium on the degranulation of bone-marrow-derived mast cells. Although cigarette smoke medium is known to stimulate several inflammatory cells via TLR4, the suppressive effect of cigarette smoke on mast cells is thought to be independent from TLR4 signaling. This study demonstrates the deterring mast cell development and consequent reaction to allergic activation by cigarette smoke.[3]

In another study, which shows reduced allergic response by exposure to cigarette smoke, Mishra et al. demonstrated the inhibitory effect of nicotine on FcεRI-induced cysteinyl leukotrienes and cytokine production.[11] Cysteinyl leukotrienes, which play a central role in allergic inflammation, are known to be primarily produced by mast cells. The results of this study showed the suppressive effect of nicotine on leukotriene/cytokine production, but not on the degranulation of mast cells, which means histamine release. Hence, nicotine was only effective on the late phase of allergic inflammation, not on the early phase.[11] The effect of cigarette smoke on mast cells is complicated and by which mechanisms cigarette smoke affect mast cells is not clearly understood yet.

The literature about the relationship of smoking with urticaria is very limited.[5,12] In 1990, Bakke et al. investigated the associations of allergic rhinitis, eczema and urticaria with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. However, the study was mostly focused on the prevalences of the diseases and the results did not establish any indicative data about the relationship of smoking with urticartia.[12] The only study to address the relationship of smoking with urticaria was conducted by Lapi et al.[5] This study specifically aimed to investigate the epidemiological characteristic of chronic urticaria. Smoking and alcohol consumption habits were questioned in the patients. Although the results did not diclose any clue about the effect of alcohol consumption with urticaria, smoking was documented to be associated with a significantly reduced risk of chronic urticaria.[5] As far as we know, our study is the third to investigate smoking habits and the second to investigate alcohol consumption habits of patients with urticaria. However, among the available evidence, only the inhibitory effect of smoking, which was documented by Lapi et al. was meaningful.[5]

Our findings were different from those of Lapi et al.'s.[5] The diversity of the findings could relate either to the genetic heterogeneity in different populations or to the differences in the lifestyle patterns, which include smoking and alcohol consumption habits, in individual countries. We have demonstrated that smoking especially increases the risk of urticaria in low-dose antihistamine non-responders. This finding may be attibuted to the causative role of smoking in non-histamine mediated urtiaria rather than histamine mediated urticaria. Urticaria is a very complex disease with intricate web of interactions between host and environmental factors in the pathogenesis. The main mediator, histamin, is mostly responsible for the prototypic lesions of urticaria. But, the wide range of different clinical patterns of the disease and the presence of antihistamines suggest that other molecules, such as prostaglandins, leukotrienes, cytokines and chemokines are also responsible for the progression of the disease.[1,2,6-9,13]

CONCLUSION

Our study is one of the few studies in the literature investigating the effects of smoking and alcohol consumption habits on the clinical characteristics of urticaria. But, the study is subject to certain limitations, one of which is lack of a validated urticaria severity scoring system for the patients. The other is the lack of comparison between severity of the disease with the amount of cigarettes smoked, which is generally expressed as the unit of pack-years. We believe that our findings are valuable for guiding the clinicians in the management of resistant cases of urticaria. Our recommendation is to inquire smoking habits and encourage smoking cessation in patients with urticaria. Over the years, the challenge has been to discover the triggers of urticaria. We assume that these preliminary findings establishes the necessity of further studies to elucidate the effects of smoking and alcohol consumption habits not only on the severity of urticaria, but also on the clinical outcome of the disease.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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