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Does Celiac Disease Affect Smell Sensation, Mucociliary Clearance and Nasal Smear?

Çölyak Hastalığı Koku Duyusunu, Mukosiliyer Klirensi ve Nazal Smearı Etkiler mi?

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ABSTRACT Objective: We aimed to evaluate olfactory function and nasal smear cytology in patients with celiac disease (CD) and healthy volunteers. **Material and Methods:** In this study, a total 74 subjects including 38 CD patients and 36 healthy controls were involved. CD has been verified by serological tests and small intestine biopsy. Sniffin Stick test was used to evaluate olfactory function. Nasal mucociliary clearance (MCC) time was measured with saccharin test. Neutrophils, eosinophils, basophilic and goblet cells were evauluted in nasal cytology. Sniffin test findings, MCC, nasal cytology and response to treatment with diet findings of CD patients and control group have been compared. **Results:** In CD group, normosmia was detected in 20 patients, and hiposmia in 17 patients. Total smell score (TDI) was 35±4 in control group, while it was 31±8 in CD group. The difference between two groups was statistically significant (p=0.009). While there was no statistically significant difference between the groups in terms of discrimination (DIS) and identification (ID) scores (p=0.277; p=0.960), the mean theroshold (THR) was found to be statistically significantly lower in the CD group (p=0.018). No evident difference has been determined between the two groups in terms of nasal MCC duration (p=0.948). While there was no statistically signicant difference in the average goblet cell grade, eosinophil, neutrophil, and lymphocyte grade average differences were significant (p=0.001). There was no statistically remarkable difference between diet compliant and non-diet compliant group in terms of THR, DIS, ID, and TDI scores (p>0.05). **Conclusion:** In our study, deterioration of nasal functions and nasal cytological findings-in particularly lymphocyte infiltration-makes it possible to think that CD group is a systemic disease that affects all organs, especially mucous membranes.

Keywords: Cytology; olfactory disorders; celiac disease

ÖZET Amaç: Çölyak hastalığı (ÇH) olan ve sağlıklı gönüllülerde koku fonksiyonunu ve nazal yayma sitolojisini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Bu çalışmaya 38 ÇH tanısı alan hasta ve 36 sağlıklı kontrol olmak üzere toplam 74 kişi dâhil edildi. ÇH tanısı serolojik testler ve biyopsi ile koyuldu. Olfaktör fonksiyonu değerlendirmek için Sniffin Stick test kullanıldı. Nazal mukosiliyer klirens [mucociliary clearance (MCC)] süresi sakkarin testi ile ölçüldü. Nazal sitolojide nötrofil, eozinofil, bazofil ve goblet hücreleri değerlendirildi. ÇH hastalarının ve kontrol grubunun Sniffin Stick testi bulguları, MCC, nazal sitoloji sonuçları karşılaştırıldı. Diyet verilen ÇH hastalarında da bu testlerdeki değişiklikler değerlendirildi. **Bulgular:** ÇH grubunda 20 hastada normozmi, 17 hastada ise hipozmi belirlendi. Toplam koku puanının (TDI) kontrol grubunda 35±4, ÇH grubunda ise 31±8 olduğu görüldü. Gruplar arasında anlamlı fark bulundu (p=0,009). Gruplar arasında koku ayırt etme [discrimination (DIS)] skoru ve koku tanımlama [identification (ID)] skorları açısından istatistiksel olarak anlamlı fark bulunmazken (p=0,277; p=0,960), çölyak grubunda ortalama eşik değer [theroshold (THR)] skoru istatistiksel olarak anlamlı derecede düşüktü (p=0,018). İki grup arasında MCC süresinde fark saptanmadı (p=0,948). Ortalama goblet hücre derecesinde istatistiksel olarak anlamlı bir fark bulunmazken, eozinofil, nötrofil ve lenfosit derecesinde ortalama farklar anlamlıydı (p=0,001). THR, DIS, ID ve TDI skorlarında diyet uygulayan ve diyet yapmayan grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (p>0,05). **Sonuç:** Çalışmamızda, nazal koku fonksiyonlarda bozulma ve nazal sitolojik bulgularda, özellikle lenfosit infiltrasyonu görüldü. Çalışmamız çölyak hastalığının başta mukozalar olmak üzere tüm organları etkileyen sistemik bir hastalık olduğunu düşündürmektedir.

Anahtar Kelimeler: Sitoloji; koku bozuklukları; çölyak hastalığı

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Celiac disease (CD) is an autoimmune disorder which is characterised by damage of small intestine mucosa after having gluten foods by genetically predisposed individuals. It has been suggested that both autoimmune and allergic diseases could be seen together because of genetic risk factors with environmental factors.[1-4]

In the large series of studies, it has been reported that autoimmune and atopic diseases pose a risk for each other.[1,2] The clinical symptoms of the disease vary from severe malabsorption to minimal symptomatic or asymptomatic presentations. Skin, hematologic system, liver, thyroid, and musculosceletal system effects are common.[5] However, knowledge about lung and respiratory involvement are limited.[6]

In our study, we aimed to investigate olfactory functions, mucociliary clearance (MCC), and nasal inflammatory markers (neutrophils, eosinophils, basophilic and goblet cells) of CD patients and how diet affects those functions.

MATERIAL AND METHODS

In this study, 38 patients and 36 healthy control subjects, total 74 individuals involved. The study was performed between January 2019 and June 2020 in our clinic after approval of Ethics Committee of the Okmeydanı education and research hospital 23.07.2019/48670771-000-11501. Patients with the diagnosis of CD, and aged between 19 and 66 years were included. Olfactory test findings, MCC, nasal cytology, and response findings to treatment with diet treatment of CD patients and control group were compared.

Our study was conducted in line with the principles of the Declaration of Helsinki.

Informed consent was obtained from the patients.

1.Diagnosis of CD

CD has been verified by serological tests [immunoglobulin (Ig)A and IgG endomysial antibodies (EMA), IgA and IgG gliadin antibodies and IgA and IgG human body tissue transglutaminase antibodies (tTG)], demonstrating cyrpt hyperplasia, villous atrophy, and an increase in intraepitelial lymphocytes in small intestine biopsy.

2. Adherence to Diet

Patients with CD who were followed up for at least 1 year and those were adhered to gluten-free diet and whose EMA and tTG became negative were defined as compatible to diet.

3. Olfactory Function Measurment

"Sniffin' Sticks" (Burgart GmbH, Wedel, Germany) is a nasal chemosensor performance test which consists of scenting markers. One physician applied Sniffin' Sticks test to all patients in a bright, clean, and odorless room. Test kit consists of 3 sub-tests; smell threshold, definition of odor and distinction of odor. The cap is removed to present odor, approximately 3 second duration and the tip of pen is brought proximity to both nostrils about 2 cm.[7]

3.1. Odor threshold (THR): For threshold measurements, n-butanol was used with single ladder step system based on forced choice with three alternatives. 16 different dilutions were used in geometrically decending order by starting 4% n-butanol. Triple markers of which two are odorless and 1 having odorous molecules have been smelled to the patient randomly. It is asked to the patient to determine the scented pen. Markers are sniffed as triple and there were 20 seconds interval between them. Stair step was reversed when the odor was correctly detected in two different trials. Threshold is defined as the average of the last four of reversing seven ladder. The points of subjects were changing between 1 to 16.

3.2. Odor discrimination (DIS): In the test based on forced choice system with 3 alternatives was applied again. Triple pens which consists of 2 with the same odor and one with a different odor, were randomly sniffed to the patient and asked to discriminate the correct odor. Time intervals were approximately 20-30 seconds between each marker sets and 3 seconds between each individual markers. 16 units triple pens are smelled and the score is assigned between 0 and 16. Patient's eyes were closed during determining of threshold value and discrimination scores in order not to recognize scented ones.

3.3. Odor* identification *(ID): ID was evaluated for 16 common smells. For each odor, the patient is asked to choose one in four alternatives with multiple choice system. Again, scores of subjects were be-

tween 0 and 16. Outcomes of three sub-tests have been represented as a compound "TDI (THR+DIS+ID) score" which is an aggregation of collected results of threshold, discriminitation, and identication. TDI score of 16.5 means anosmia, 16-30.5 indicates hyposmia, and 30.5 shows normosmia.[4]

4. Measurement of nasal MCC:

Nasal MCC time was measured with saccharin test which is carried out by the same physician. Patients were asked to blow their noses and not to consume any food and drink 1 hour before the test. Approximately one 1.5 mm. diameter saccharin pill was placed to inferior concha by using bayonet forceps while the patient is sitting in the upright position. After installation of saccharin pill until tasting time of saccharin, patients were instructed to swallow with 30 seconds periods and to inform the time of when they tasted saccharin. Time from particle placement to sweet taste perception was measured by a chronometer and recorded as MCC time.

5. Nasal smear:

Nasal cytology samples were obtained from CD and control group. Rhino-Probe™ (Arlington Scientific,USA) curettes were used to obtain smears in both nasal cavities. All cytograms were evaluated using light microscopy after haematoxylin and eosin staining. Prepared smears were fixed in alcohol and histochemically painted with Papanicolaou (PAP). Five randomized areas were selected for each smear: neutrophils, eosinophils, basophilic and goblet cells were evauluted in 400 magnification. Cell counting was performed in 10 high power area and averaged. Grades higher than 1+ were accepted as positive. Grading was accomplished with four scales.[8]

RESULTS

Gender and age distributions of the groups were observed to be similar. The mean age was 40±10 years in the CD group and 40±8 in the control group. The difference between groups is not statistically significant (p=0.481) (Table 1). While there were 15 males and 22 females in the control group, the CD group consisted of 26 female, and 11 male patients. The difference is not statistically significant (p=0.465). The mean time for the patients to be diagnosed with CD was 5-6 years.

In the CD group, following findings have been detected; normosmia in 20 patients, hiposmia in 17 patients, and anosmia in none. In the control group, findings were as follows; normosmia in 33 subjects, hiposmia in 4 subjects, and anosmia in none. The difference between the CD and control group is statistically significant (p=0.001) (Table 2).

While the mean THR was 9±6 in the CD group, it was 12±3 in the control group. The difference is statistically significant (p=0.018). Total odor score has been detected as 31±8 in CD and as 35±5 in the control group. The difference is statistically distinctive (p=0.009). No statistically evident difference has been detected in DIS and ID scores (p=0.277; p=0.960) (Table 3).

While the mean duration of nasal MCC was 11±6 minutes in the CD group, it was determined to be 10±2 minutes in the control group. The difference is not statically significant (p=0.948) (Table 3).

In the CD group, the mean eosinophil grade was 1±0.8, the mean neutrophil grade was 2±1.1, the mean goblet cell grade was 1±0, and the mean lymphocyte grade was 0.8±0.4. In the control group, fig-

TABLE 1: Characteristics of CD group vs. control group.

		CD group		Control group		
		n	(%)	n	(%)	p value
Gender	Male	11	29.7	15	40.5	0.465
	Female	26	70.3	22	59.5	
Age (X̄±SD)		41±10		40±8		0.481

CD: Celiac disease; SD: Standard deviation.

TABLE 2: Evalution of odor in CD group and control group.

	CD group n (%)	Control group n (%)	p value
Normosmia	20 (54.1)	33 (89.82)	**0.001**
Hyposmia	17 (45.9)	4 (10.8)	

CD: Celiac disease.

ures were as follows, respectively; 0.3±0.6, 0.3±0.6, 1±0, and none. While there was no statistically significant difference in the mean goblet cell grade between groups, in terms of eosinophil, neutrophil lymphocyte grade averages, the difference between the CD and control group was significant (p=<0.01) (Table 4).

In terms of bacteria and fungus presence in nasal smear, no statistically significant difference has been found between the groups (Table 4). In the CD group, been determined that 18 patients were diet-compatible and 19 were diet-noncompatible. Between diet coherent and none diet coherent groups, no statistically significant diversity has been found in THR, DIS, ID, and TDI (p>0.05) (Table 5).

DISCUSSION

In our study, nasal cellular involvement and nasal functions of celiac patients have been evaluated. Celiac patients who have respiratory system findings were reported seldom in the literature and a few respiratory diseases have been associated to CD.[9,10] Actually, diseases such as farmer's lung,

TABLE 3: TDI (THR, DIS, ID) figures in CD group and control group.

	CD group		Control group		
	X̄±SD	Median (Minimum-Maximum)	X̄±SD	Median (Minimum-Maximum)	p value
THR	9±6	8 (1-16)	12±3	12 (7-16)	**0.018**
DIS	11±2	11 (6-16)	12±2	12 (8-16)	0.277
ID	11±3	11 (3-14)	11±2	12 (7-13)	0.960
TDI	31±8	31 (16-44)	35±5	32 (30-44)	**0.009**
MCC (minutes)	11±6	10 (3-27)	10±2	10 (7±14)	0.948

TDI: Total odor score; THR: Threshold; DIS: Discrimination; ID: Identification; CD: Celiac disease; SD: Standard deviation; MCC: Mucociliary clearance.

TABLE 4: Nasal cytology in CD group and control group.

	CD group		Control group		
Grade	X̄±SD	Median (Minimum-Maximum)	X̄±SD	Median (Minimum-Maximum)	p value
Eosinophils	1±0.8	2 (0.5-4)	0.3±0.6	0 (0-2)	**<0.001**
Neutrophils	2±1.1	1 (0-4)	0.3±0.6	0 (0-2)	**<0.001**
Goblet cells	1±0	1 (0-1)	1±0	1 (0-1)	0.282
Lymphocytes	0.8±04	1 (0-2)	0	0	**<0.001**

CD: Celiac disease; SD: Standard deviation.

TABLE 5: The effect of diet compliance on TDI (THR, DIS, ID).

	Diet compliant CD group (n=18)		Diet noncompliant CD group(n=19)		
	X̄±SD	Median (Minimum-Maximum)	X̄±SD	Median (Minimum-Maximum)	p value
THR	9±5	8 (1-16)	9±6	11 (1-16)	0.890
DIS	11±2	11 (7-16)	12±2	11 (6-15)	0.665
ID	10±2	11 (6-14)	11±3	11 (3-14)	0.486
TDI	30±8	31 (16-41)	32±8	32 (18-44)	0.668

TDI: Total odor score; THR: Threshold; DIS: Discrimination; ID: Identification; CD: Celiac disease; SD: Standard deviation.

chronic obstructive airways disease, and lymphocytic broncoalveolit and some repetetive (recurrent) alveolary-intersistel lung diseases related to rhinosinusitis have been reported, their associated pathogenesis could not be explained for a long time.[9-11] But studies evaluating nasal functions in CD are infrequent in the literature.

It is believed that increased permeability in both conditions may play a role in pathogenesis where there is an increased absorption of antigenic substances. In order to investigate this hypothesis, in our study, MCC and cells in nasal cytology have been compared with the control group. Comba and Atan reported that nasal MCC was increased in celiac patients.[11] MCC has ability to keep the mucosal surface moist and clean and via respirotary mucosa which has regular activity to eject pathogens.[12] It is a vital defense mechanism of the respiratory system and protects the body from the harmful effects of inhaled particles.[13-15] Evaluating MCC time is a valid index for showing in airways clearance.[16] Normal mucociliary transit time in humans has been reported to be 12-15 min. Extended transit times are accepted as a sign of deteriorated mucociliary clearance.[17,18] Extended MCC time increases the risk of infection, inflammation, and congestion in the small airways. Therefore, deterioration of MCC increases infection risk in this area.[19,20] Infection can cause smell defect and creates a vicious circle. In this study, nasal MCC was evaluted in CD patients altough there is no evident difference with the control group, MCC increasings have been observed in 27% of CD patients. In some studies, it has been reported that MCC is also impaired in autoimmune diseases.[16] Antibodies may disrupt ciliary or mucus structure mucus-cilia interaction through immune mechanisms in CD patients and this also may worsen MCC.

Some of CD patients had improved sense of smell. However, no evaluating the changes in the sense of smell in CD patients were encountered in the literature. In our study, TDI score and THR of patients were found to be low.

Studies show that local oscillattion of neutrophil, lymphocyte, and eosinophils granuler components in jejunal tissue of CD patients are increased.[21] Also, eosinophilic infiltrate was identified in duodenal mucosa of active CD patients.[22] Althogh CD and eosinophilic esophajitis are seperate gastrointestinal disorders, various studies suggest the association of esophageal eosinophilia in patients with CD.[23,24] In our study, cytological cells have been investigated in nasal mucosa. Normal nasal mucosa consists of epithelial cells, goblet cells, and basal cells. Usually, there is no eosinophils or basophilic cells in the surface layer. A moderate number of neutrophils and a few bacterias.[25-27] Basophilic cells and/or eosinophils increase the sensivity of the test to about 80% to confirm allergic diagnosis.[8]

There are studies showing that the frequency of asthma and atopic diseases is increased in CD.[1,5] The relationship between atopy and nasal eosinophilia has been searched by Kajosaari and Saarinen.[28] In that study, 178 children with atopic diseases from the age of 3 were observed, it has been reported that eosinophils and mast cells in cytograms which are obtained from the nasal mucosa are an important indicator of atopy characterised by a high specifity but a low sensivity.[29] In our study, a noticable increase was determined in eosinophil, neutrophil, and lymphocytic infitration compared to the control group. Neutrophils and bacteriae usually increase with acute, subacute, and chronic bacterial infection. It was thought that antigen sensitive lymphocytes and eosinophils in one region tend to accumulate in other mucosal regions and possibly bowel, lung, esophagus, and nasal patholigies in CD may be the evidence of the ‘ diffuse ‘ mucosal immune system.

Altough a gluten-free diet is an effective treatment for most people, a significant minority develops persistent or recurring symptoms. Ellul et al. suggested that asthma symptoms can be improved with a gluten-poor diet.[19] Similarly, Kallel-Sellami et al. and Brightling et al.reported that an adult CD patient with bronchiectasis symptoms recovered with gluten-free diet.[10,29] Özdoğan et al. reported that there was no correlation between asthma and allergic rhinitis symptoms and dietary compliance in pediatric CD patients. In our study, no relationship was discovered between diet coherence and olfactory functions and nasal cells.[30]

CONCLUSION

Deterioration of nasal functions and nasal cytological findings (especially eosinophils and lymphocyte infiltration) make it possible to consider that CD, as a systemic disease, affecting all organs especially mucous membranes. Therefore, it should be kept in mind that nasal functions may also be disrupted in CD. Nasal eosinophilia may be a representation of immunological irregularities beneath CD or occurs indepently. Future studies that form the destiny of eosinophilic immlammation following CD treatment will begin to reveal the mechanisms of those findings.

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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

Idea/Concept: *Güler Berkiten;* ***Design:*** *Belgin Tutar;* ***Control/Supervision:*** *Yavuz Uyar;* ***Data Collection and/or Processing:*** *Yasemin Gökden, Selma Şengiz Erkan;* ***Analysis and/or Interpretation:*** *Ziya Saltürk, Şeyma Gorçin Karaketir;* ***Literature Review:*** *Sabire Sitare Sarıçam;* ***Writing the Article:*** *Güler Berkiten;* ***Critical Review:*** *Semih Karaketir;* ***References and Fundings:*** *Ömer Kumaş.*

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