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Evaluation of Nasal Mucociliary Clearance in COVID-19 Patients

COVID-19 Hastalarında Nazal Mukosilier Klirensin Değerlendirilmesi

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ABSTRACT Objective: There is no information about the relationship between coronavirus disease-2019 (COVID-19) and nasal mucociliary clearance (NMC). To investigate whether the severe acute respiratory syndrome-CoV-2 has an effect on NMC. **Material and Methods:** Thirty-two patients hospitalized in our hospital with the diagnosis of COVID-19 and confirmed by rt-PCR test were included in the study. Smokers and patients with chronic upper respiratory tract infection were excluded from the study. The saccharin test was performed to evaluate NMC. Patients over 50 and under 50 years of age were examined in two groups as the reference values change with age. Patients with and without pulmonary symptoms were compared in terms of NMC. In addition, patients with and without cough were compared in terms of NMC in their age groups. **Results:** The study included a total of 32 patients, 18 (56%) males and 14 (44%) females, with a mean age of 50.8 years (range, 17-81 years). The mean clearance time of the patients over 50 years of age (n=15) was 14.20±4.80 min, while under 50 years of age (n=17) was 11.94±3.61 min. When compared with the reference values in the literature, no significant difference was observed in both age groups (p>0.05). There was no significant difference in the patients over 50 years of age compared to the patients with lung involvement (n=11, mean=14.64, SD=5.26) and without lung involvement (n=4, mean=13, SD=3.56) (p>0.05). There was no significant difference in the patients under 50 years of age compared to the patients with lung involvement (n=7, mean=12.86, SD=4.78) and without lung involvement (n=10, mean=11.3, SD=2.63) (p>0.05). When the patients with and without cough complaint were compared between their age groups, no significant difference was observed (p>0.05). **Conclusion:** NMC has been preserved in COVID-19 patients. There is no significant difference in terms of lung involvement and cough complaints in NMC times.

Keywords: COVID-19; SARS-CoV-2; mucociliary clearance

ÖZET Amaç: Koronavirüs hastalığı-2019'da [coronavirus disease-2019 (COVID-19)], nazal mukosilier klirensin (NMK) etkilenip etkilenmediği bilinmemektedir. Çalışmamızda, şiddetli akut solunum sendromu-CoV-2'nin, NMK üzerinde bir etkisinin olup olmadığı araştırılmak istenmiştir. **Gereç ve Yöntemler:** Çalışmaya, hastanemize COVID-19 nedeni ile yatırılmış ve tanısı rt-PCR ile kesinleşmiş 32 hasta dâhil edildi. Sigara içen ve kronik üst solunum yolu enfeksiyonu olan hastalar hariç tutuldu. Tüm hastalara, NMK süresi ölçümü için sakkarin testi uygulandı. Referans değerlerinin farklılık gösterebilmesi nedeniyle 50 yaş altı ve 50 yaş üzeri hastalar 2 gruba ayrılarak incelendi. Her iki grupta da akciğer tutulumu olan ve olmayan hastalar, NMK süreleri açısından kıyaslandı. Ayrıca öksürük şikâyeti olan ve olmayan hastalar da kendi yaş gruplarında NMK açısından kıyaslandı. **Bulgular:** Çalışmaya, 18 (%56)'i erkek, 14 (%44)'ü kadın olmak üzere 32 hasta dâhil edildi. Ortalama yaş 50,8 idi (aralık 17-81). Elli yaş üstü hastaların (n=15) ortalama klirens süresi 14,20±4,80 dk iken, 50 yaşın altındaki hastaların (n=17) ortalama klirens süresi 11,94±3,61 dk idi. Literatürdeki referans değerler ile kıyaslandığında, her iki yaş grubunda da anlamlı farklılık izlenmedi (p>0,05). Elli yaş üzeri olup, akciğer tutulumu olan (n=11; ortalama=14,64; SS=5,26) ve akciğer tutulumu olmayan (n=4; ortalama=13; SS=3,56) hastalar kıyaslandığında, NMK süresinde anlamlı farklılık izlenmedi (p>0,05). Elli yaş altı hastalarda akciğer tutulumu olan (n=7; ortalama=12,86; SS=4,78) ve akciğer tutulumu olmayan (n=10; ortalama=11,3; SS=2,63) hastalarda NMK süresi arasında anlamlı farklılık izlenmedi (p>0,05). Öksürük şikâyeti olan ve olmayan hastalar, kendi yaş gruplarında kıyaslandığında anlamlı farklılık izlenmedi (p>0,05). **Sonuç:** NMK, COVID-19 hastalarında korunmuştur. NMK sürelerinde akciğer tutulumu ve öksürük şikâyeti açısından anlamlı farklılık yoktur.

Anahtar Kelimeler: COVID-19; SARS-CoV-2; mukosilier klirens

Coronavirus disease-2019 (COVID-19) is a condition caused by the severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), which emerged in the Wuhan province of China in December 2019 and has rapidly spread all over the world, leading to a pandemic. The disease begins with the proliferation of the virus taken through the respiratory tract by attaching to the oropharyngeal or nasopharyngeal mucosa and causing an immune response, and in some patients, the disease may be limited to this response, while in others, it leads to lung involvement, progressing to pneumonia. The course of the disease depends on the interaction between the virus and the individual's immune system. The viral factors include factors such

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as virus type, mutation, viral load, while factors such as the individual's immune system, genetics (HLA genes), age, gender, nutritional status, neuroendocrine and immune system also play a role.[1]

Mucociliary clearance is a very important innate defense system that protects the airway from foreign bodies such as dust, allergens, pathogens, and transports these inhaled foreign bodies out of the airway. It mainly provides these functions with two components: mucus and cilia. Mucus is a thin layer of fluid that covers the respiratory tract. Cilia, on the other hand, are eyelash-like structures that are found on the surface of the cell and have extensions into the mucus. Foreign bodies and pathogens in the air that enter the nasal cavity by inhalation are entrapped in the mucus covering the respiratory tract mucosa, and this mucus is unidirectionally transported out of the respiratory tract by means of the cilia.[2] This mechanism is the primary innate defense mechanism that protects the airway in mammals.[3] Recurrent respiratory infections in diseases such as cystic fibrosis, primary ciliary dyskinesia, in which the mucociliary clearance is genetically defective, clearly demonstrates the importance of this defense system.

The saccharin test is a simple, easy-to-perform, widely used, inexpensive test. It was first described by Andersen and is used to measure nasal mucociliary clearance (NMC) time.[4] It is based on measuring the time until the taste of the saccharin placed 1 cm behind the anterior end of the lower concha is felt. In healthy adults, this time varies depending on the studies; however, it is 10-15 minutes on average.[2] Values over 20 min have been reported to be prolonged NMC.[5] It has also been reported that there is a correlation between NMC obtained by the saccharin test and tracheobronchial mucociliary clearance.[6]

In our study, NMC, a defense mechanism that protects the respiratory tract from foreign pathogens, was measured in COVID-19 patients. NMC was compared in COVID-19 patients with and without pneumonia.

MATERIAL AND METHODS

Our study was conducted in accordance with the principles of Helsinki Declaration and was approved by the local ethics committee of Hitit University Faculty of Medicine (date: 5.5.2020-number: 230) and informed consent was obtained from the patients. Our study included 32 patients who were admitted to our hospital with the diagnosis of COVID-19 between 03-18 April 2020, and whose COVID-19 diagnosis was confirmed by the rt-PCR test of the combined swab sample taken from the oropharynx and nasopharynx. Smokers and patients with chronic upper respiratory tract infection were excluded from the study because it can prolong the NMC time. The saccharine test was performed on all patients using appropriate personal protective equipment to measure NMC. Oral intake was discontinued within 1 hour before the test and the patients were rested for 30 minutes. A 0.5-mm saccharin particle was then placed approximately 1 cm behind the medial surface of the lower concha with the help of a bayonet while the patient was seated in the upright position, and the patients were asked not to sneeze, sniff or wipe their nose throughout the test. During the test, the patient was asked to swallow at 30-second intervals and report when s/he felt the taste of saccharin. The time from the placement of saccharin in the nasal cavity to the perception of taste was evaluated as NMC time. The NMC times of all patients were calculated and compared in their own age group according to the reference values reported in the literature, and the effect of SARS-CoV-2 on NMC was analyzed. The correlation between lung involvement and mucociliary clearance time was also assessed by comparing the patients with and without pneumonia on thorax computed tomography and the patients with and without cough complaint in themselves.

STATISTICAL ANALYSIS

In the analysis of the data, descriptive statistics were expressed as mean and standard deviation values. The Mann-Whitney U test was used to test the significance of difference by lung involvement and cough complaint in the study. A correlation analysis was carried out to determine the correlation between age and mucociliary clearance time. A p value of <0.05 was considered statistically significant in the study. All analyses were made using SPSS 22.0 software package.

RESULTS

In 32 patients (mean age, 50.8 years) included in the study, NMC time was measured an average of 5 days after the onset of symptoms, and the NMC time was 13 minutes. The mean NMC time of the patients over 50 years of age (15 patients) was 14.2±4.8 min, while the mean NMC time of the patients under 50 years of age (17 patients) was 11.9±3.6 min. When the obtained values were compared with these values, the results were found to be consistent with the literature. Although different values have been reported in the literature, the mean reference saccharin test time was between 10-15 minutes.[2] Values over 20 minutes should be considered as prolonged NMC.[2,5] Mean NMC times measured in healthy subjects by different studies in the literature are shown in Table 1.

In line with the literature, it was seen that age significantly affected the mucociliary clearance time in our study. The mucociliary clearance time of the patients over 50 years of age (14.20±4.80) was significantly longer compared to the patients under 50 years of age (11.94±3.61) ($p=0.02$, $p<0.05$).

Considering regardless of age, the NMC time was longer in the patients with lung involvement ($p<0.05$). However, the fact that lung involvement was more common at advanced ages suggested that this difference was mostly due to age. In fact, when the patients with and without lung involvement were compared in their own age groups, there was no significant difference in NMC time ($p>0.05$) (Table 2).

When the patients with and without cough complaints were compared between their age groups, no significant difference was observed ($p>0.05$).

DISCUSSION

Mucociliary clearance is the primary innate defense mechanism of the respiratory tract and protects the respiratory tract from foreign bodies such as small particles, dust, and pathogens. It provides its functions through mucus and cilia. Mucociliary clearance has been reported to decline during viral upper respiratory infections.[2,12] When the normal NMC mechanisms are disrupted, this is followed by mucus stasis, and secondary infections occur as a result of increased exposure of the airway to antigens. Therefore, the preservation of mucociliary clearance during viral infections will positively contribute to the disease course.

Studies reporting the frequency of upper respiratory symptoms in COVID-19 disease have been published.[13-15] Guan et al. evaluated 1,099 patients and reported pharyngodynia in 153 patients and nasal congestion in 53 patients, while Lovato and de Filippis examined 1,536 patients in their systematic review and reported pharyngodynia in 191 patients and

TABLE 1: Nasal mucociliary clearance times measured by the saccharin test in healthy volunteers in different studies.

Study	Number of volunteers:	Mean saccharin test time
Deniz et al.[7]	46	12.18
Rosen et al.[8]	20	9.2
Cinar et al.[9]	38	10.97
Plaza Valía et al.[10]	85 (under 50 years of age)	15.67
	80 (over 50 years of age)	19.75
Ho et al.[11]	49 (under 50 years of age)	9.67
	41 (over 50 years of age)	11.83.

TABLE 2: Comparison of nasal mucociliary clearance in patients with and without lung involvement.

Age group	Lung involvement	n	Mean	SD	p value
Over 50 years of age	No	4	13.00	3.56	0.58
	Yes	11	14.64	5.26	
Under 50 years of age	No	10	11.30	2.63	0.40
	Yes	7	12.86	4.78	
Total	No	14	11.79	2.89	0.04*
	Yes	18	13.94	5.01	

*Significant difference according to the level of 0.05.

nasal congestion in 57 patients.[13,14] Likewise, studies reporting that olfactory functions are also affected by this virus have started to be reported. Mao et al. evaluated 214 patients with the diagnosis of COVID-19 and reported anosmia (5.1%) in 11 patients.[16] In the study by Vaira et al., this incidence was reported to be higher with 19.4%.[17] Again, in the same study, it was thought that this resulting odor disorder may be directly related to olfactory cell damage since nasal symptoms such as nasal obstruction and rhinitis are rare in COVID-19.[17] These results have shown that the SARS-CoV-2 virus also has effects on nasal airway epithelium. In our study, we observed that NMC was not adversely affected in COVID-19 patients. In all patients included in the study, the virus was detected in the combined swab samples taken from the oropharynx and nasopharynx. In other words, they were patients with upper respiratory epithelium actively infected with the virus. In line with the literature, we found findings of upper respiratory tract infection such as runny nose, nasal congestion, sore throat in some of the patients (12.5%). However, we observed that the NMC mechanism has been preserved in these patients, and the saccharin test time was within the reference values as reported in the literature.

Numerous studies have reported that NMC declines with aging.[10,11,18] In accordance with the literature, we found in our study that the NMC time was longer in the patients over 50 years of age ($p<0.05$). It has also been reported in large series that age adversely affects prognosis in COVID-19.[19] One of the reasons for this adverse effect may be this declined protective mechanism with aging.

The NMC was prolonged in the patients with lung symptoms, regardless of age ($p<0.05$). However, the fact that lung symptoms were mostly seen in the patients over 50 years of age suggested that this prolongation was actually related to declined mucociliary functions with aging. As a matter of fact, lung involvement did not lead to a significant difference in NMC when the patients over and under 50 years of age were compared within themselves ($p>0.05$).

The lungs also have an additional mechanism to clear mucus from the lungs, called cough clearance. Cough clearance is a defense mechanism to expel mucus secretion independent of motion of cilia. This mechanism plays an important role in protecting the lungs from pathogens, especially in primary ciliary dyskinesia with impaired ciliary motion.[20] Cough is one of the common symptoms in COVID-19 disease. Zhou et al. evaluated 191 patients in their study and reported that 151 patients (79%) had cough, and that cough was the most common symptom following fever (180 patients 94%).[21] Of the 32 patients, 18 (56%) had cough complaint in our study. When the patients with and without cough were compared, there was no significant difference in NMC ($p>0.05$).

Preservation of these protective mechanisms in COVID-19 can positively affect the course of the disease. In pulmonary diseases, many ways such as mucolytics that reduce the viscosity of the mucus to increase mucociliary clearance, hypertonic saline administration that increases the water content of the mucus, and chest physiotherapy that increases the clearance have been tried.[22] N-acetylcysteine breaks the disulfide bonds in the mucoprotein complex, reducing the viscosity of the mucus and increasing mucociliary clearance. It has also been reported to reduce oxidative stress with its direct antioxidant effect.[23] With these properties, it provides positive effects in community-acquired pneumonia.[24] It has also been reported that pulmonary oxidative stress can be reduced and airway and parenchymal destruction can be reduced with the use of N-acetylcysteine in diseases where mucociliary clearance is impaired, such as cystic fibrosis.[23] Likewise, aerosolized recombinant human DNase (Dornase Alpha) positively contributes to the treatment of cystic fibrosis by reducing the viscosity of respiratory tract secretions and increasing mucus clearance.[25] In COVID-19, it would be appropriate to improve these mucociliary clearance mechanisms and to keep these approaches in mind in patient follow-up.

CONCLUSION

NMC was not adversely affected in COVID-19 patients. There was no correlation between lung involvement or cough symptom and NMC. In this context, there is a need for further studies to reveal the physiopathology.

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

Idea/Concept: *Burak Numan Uğurlu, Hüseyin Serdar Yerlikaya;* ***Design:*** *Sevim Aslan Felek, Gülay Aktar Uğurlu;* ***Control/Supervision:*** *Sevim Aslan Felek;* ***Data Collection and/or Processing:*** *Burak Numan Uğurlu, Hüseyin Serdar Yerlikaya, Gülay Aktar Uğurlu;* ***Analysis and/or Interpretation:*** *Burak Numan Uğurlu, Hüseyin Serdar Yerlikaya, Gülay Aktar Uğurlu;* ***Literature Review:*** *Burak Numan Uğurlu;* ***Writing the Article:*** *Burak Numan Uğurlu;* ***Critical Review:*** *Sevim Aslan Felek;* ***References and Fundings:*** *Burak Numan Uğurlu, Hüseyin Serdar Yerlikaya, Gülay Aktar Uğurlu;* ***Materials:*** *Burak Numan Uğurlu, Hüseyin Serdar Yerlikaya, Gülay Aktar Uğurlu.*

REFERENCES

1. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8. [Crossref] [PubMed] [PMC]
2. Cingi C, Bayar Muluk N. All Around the Nose: Basic Science, Diseases and Surgical Management. 1st ed. Cham, Switzerland: Springer; 2020. [Crossref]
3. Xu L, Jiang Y. Mathematical modeling of mucociliary clearance: a mini-review. Cells. 2019;8(7):736. [Crossref] [PubMed] [PMC]
4. Andersen I, Lundqvist GR, Proctor DF. Human nasal mucosal function in a controlled climate. Arch Environ Health. 1971;23(6):408-20. [Crossref] [PubMed]
5. Antunes MB, Cohen NA. Mucociliary clearance--a critical upper airway host defense mechanism and methods of assessment. Curr Opin Allergy Clin Immunol. 2007;7(1):5-10. [Crossref] [PubMed]
6. Uchida Y, Nohara K, Tanaka N, Fujii N, Fukatsu H, Kaneko N, et al. Comparison of saccharin time in nursing home residents with and without pneumonia: a preliminary study. In Vivo. 2020;34(2):845-8. [Crossref] [PubMed] [PMC]
7. Deniz M, Gultekin E, Ciftci Z, Alp R, Ozdemir DN, Isik A, et al. Nasal mucociliary clearance in obstructive sleep apnea syndrome patients. Am J Rhinol Allergy. 2014;28(5):178-80. [Crossref] [PubMed]
8. Rosen EJ, Calhoun KH. Alterations of nasal mucociliary clearance in association with HIV infection and the effect of guaifenesin therapy. Laryngoscope. 2005;115(1):27-30. [Crossref] [PubMed]
9. Cinar F, Beder L. Nasal mucociliary clearance in coal mine workers. Otolaryngol Head Neck Surg. 2004;130(6):767-9. [Crossref] [PubMed]
10. Plaza Valía P, Carrión Valero F, Marín Pardo J, Bautista Rentero D, González Monte C. [Sacharin test for the study of mucociliary clearance: reference values for a Spanish population]. Arch Bronconeumol. 2008;44(10):540-5. [Crossref] [PubMed]
11. Ho JC, Chan KN, Hu WH, Lam WK, Zheng L, Tipoe GL, et al. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. Am J Respir Crit Care Med. 2001;163(4):983-8. [Crossref] [PubMed]
12. Alho OP. Nasal airflow, mucociliary clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. Am J Rhinol. 2004;18(6):349-55. [Crossref] [PubMed]
13. Lovato A, de Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. Ear Nose Throat J. 2020;99(9):569-76. [Crossref] [PubMed]
14. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. [PubMed] [PMC]
15. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061-9. [Crossref] [PubMed] [PMC]
16. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. Infectious Diseases (except HIV/AIDS); 2020 Feb. Available from: [Crossref]
17. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. Laryngoscope. 2020; 130(7):1787. [Crossref] [PubMed] [PMC]
18. Sakakura Y, Ukai K, Majima Y, Murai S, Harada T, Miyoshi Y. Nasal mucociliary clearance under various conditions. Acta Otolaryngol. 1983;96(1-2):167-73. [Crossref] [PubMed]
19. Xie J, Hungerford D, Chen H, Abrams ST, Li S, Wang G, et al. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19. SSRN Electron J. 2020. [Crossref]
20. Knowles MR, Boucher RC. Mucus clearance as a primary innate defense mechanism for mammalian airways. J Clin Invest. 2002;109 (5):571-7. [Crossref] [PubMed] [PMC]
21. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. Erratum in: Lancet. 2020;395(10229):1038. Erratum in: Lancet. 2020;395(10229):1038. [Crossref] [PubMed] [PMC]
22. Bhowmik A, Chahal K, Austin G, Chakravorty I. Improving mucociliary clearance in chronic obstructive pulmonary disease. Respir Med. 2009;103(4):496-502. [Crossref] [PubMed]
23. Conrad C. Application of N-Acetylcysteine in pulmonary disorders. In: Frye RE, Berk M, eds. The Therapeutic Use of N-Acetylcysteine (NAC) in Medicine. Singapore: Springer Singapore; 2019. p.255-76. [Crossref]
24. Zhang Q, Ju Y, Ma Y, Wang T. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia: a randomized controlled trial. Medicine (Baltimore). 2018;97(45): e13087. [Crossref] [PubMed] [PMC]
25. McPhail GL, Acton JD, Fenchel MC, Amin RS, Seid M. Improvements in lung function outcomes in children with cystic fibrosis are associated with better nutrition, fewer chronic pseudomonas aeruginosa infections, and dornase alfa use. J Pediatr. 2008;153(6):752-7. [Crossref] [PubMed]