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EVALUATION OF PERIODONTAL BONE LOSS AND TREATMENT NEEDS OF PATIENTS ACCORDING TO THE COVID-19

HASTALARIN PERİODONTAL KEMİK KAYBI VE TEDAVİ İHTİYACININ COVID-19'A GÖRE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: This study aimed to evaluate patients' periodontal bone loss and treatment needs according to the COVID-19 and determine whether there is a relationship between COVID-19 and periodontal disease.

Method: This cross-sectional study included patients admitted to the periodontology department for treatment between April 2021 and July 2021. According to the personal health system records of the patients, a positive real-time polymerase chain reaction (PCR) test indicated a positive COVID-19 history [COVID(+)], whereas no positive PCR in the records was defined as a negative history [COVID(-)]. Periodontal treatment need was assessed by the Community Periodontal Index of Treatment Needs (CPITN). In addition, periodontal bone loss (PBL) was measured from the digital panoramic radiographs according to the Progressive Rate Index (PRI).

Results: The study was conducted with 138 patients [COVID(+) 73, COVID(-) 65]. There was no statistically significant difference between COVID(+) and COVID(-) in terms of age and sex. The number of smokers in COVID(-) was significantly higher than COVID(+) (p: 0.045). No significant difference was found between the groups regarding the PRI and the presence of PBL. While COVID(+) had a greater percentage of score 0, 1, 3, and 4 than COVID(-); COVID(-) had a higher percentage of score 2 (p<0.000). However, it was found that the mean CPITN score did not differ significantly between the groups.

Conclusion: This study revealed that there is no trend regarding the association between COVID-19 and periodontal disease. Future studies with more hospitalized patients are needed.

Key Words: COVID-19, Periodontal Disease, Periodontal Bone Loss, CPITN

ÖZ

Amaç: Bu çalışma, hastaların periodontal kemik kaybı ve tedavi ihtiyaçlarını COVID-19'a göre değerlendirmeyi ve COVID-19 ile periodontal hastalık arasında bir ilişki olup olmadığını belirlemeyi amaçladı.

Yöntem: Bu kesitsel çalışmaya Nisan 2021 ile Temmuz 2021 tarihleri arasında periodontoloji bölümüne tedavi için başvuran hastalar dahil edildi. Hastaların kişisel sağlık kaydı sistemine göre, pozitif bir polimeraz zincir reaksiyonu (PCR) testi pozitif COVID-19 hikayesi [COVID(+)] olarak tanımlanırken, kayıtlarda pozitif PCR olmaması negatif hikaye [COVID(-)] olarak tanımlandı. Periodontal tedavi ihtiyacı, Toplum Periodontal Tedavi İhtiyacı İndeksi ile değerlendirildi. Ayrıca dijital panoramik radyograflardan Progresif Hız İndeksi'ne (PRI) göre periodontal kemik kaybı (PBL) ölçüldü.

Bulgular: Çalışma 138 hasta [COVID(+) 73, COVID(-) 65] ile yürütüldü. COVID(+) ve COVID(-) arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı bir farklılık tespit edilmedi. COVID(-)'de sigara içenlerin sayısı COVID(+)'den önemli ölçüde yüksekti (p: 0.045). PRI ve PBL varlığı açısından gruplar arasında anlamlı farklılık bulunmadı. COVID(+), COVID(-)'den daha yüksek skor 0, 1, 3 ve 4 yüzdesine sahipken; COVID(-) daha yüksek skor 2 yüzdesine sahipti (p< 0.000). Ancak, ortalama CPITN skorunun gruplar arasında anlamlı farklılık göstermediği bulundu.

Sonuç: Bu çalışma, COVID-19 ile periodontal hastalık arasındaki ilişkiye dair bir eğilim olmadığını ortaya koymuştur. Hastanede yatan hasta sayısının arttırıldığı ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Periodontal Hastalık, Periodontal Kemik Kaybı, CPITN

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a pandemic that has been affecting the world since March 2020 [1]. The common symptoms of COVID-19 are cough, sore throat, fever, diarrhea, headache, myalgia, fatigue, dysgeusia, and anosmia. However, SARS-CoV-2 can cause serious illnesses such as pneumonia, acute respiratory distress syndrome, multiple organ dysfunction.

The severe consequences of COVID-19 are assumed to be associated with several risk factors [2]. These are age, sex, and comorbidities such as hypertension, cardiovascular disease, diabetes, and obesity.

In severe cases of COVID-19, cytokine storm has been identified and associated with disease severity [3]. The cytokine storm is triggered by the dysregulated immune response and manifested by the overproduction of proinflammatory cytokines.

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Periodontal disease, an inflammatory condition of the periodontium, results from an immune response to periodontal pathogens [4]. Periodontal pathogens induce the production of proinflammatory cytokines by host immune cells. The secretion of these host-derived mediators into the bloodstream also triggers systemic inflammation, which is suggested to be responsible for the association between periodontal disease and systemic diseases such as diabetes, cardiovascular disease, and obesity [5]. Due to the shared risk factors and comorbidities, it has been hypothesized that periodontal disease and severe COVID-19 may be related [6].

Regardless of these risk factors and comorbidities, the proximity and continuity of the oral cavity and lower respiratory tract allow the aspiration of oral pathogens into the lung [7]. In addition, host-pathogen interactions and cytokine production in periodontal disease may also affect the lower respiratory tract and facilitate respiratory infection by changing the respiratory epithelium.

The oral cavity can also act as a reservoir for respiratory pathogens. As is known, angiotensin-converting enzyme 2 (ACE-2) is the host cellular receptor for entry of SARS-CoV-2 and thus viral infection. ACE-2 is highly expressed not only in the lung but also in the oral mucosa, especially in the tongue, buccal mucosa, and gingiva [8]. The oral cavity, therefore, poses a risk for the promotion of SARS-CoV-2 infection.

According to the literature, a relationship between COVID-19 and periodontal disease is possible. However, a limited number of studies have evaluated the association between periodontal disease and COVID-19 [9-12]. This study aimed to evaluate patients' periodontal bone loss and treatment needs according to their COVID-19 history with clinical and radiographic indices.

METHOD

This cross-sectional study included patients who applied to the Department of Periodontology, Faculty of Dentistry, Kütahya Health Sciences University for periodontal treatment between April 2021 and July 2021. The study protocol was approved by the Ethics Committee of Kutahya Health Sciences University (Decision Number: 2021/06-21) and the Scientific Research Platform of the Turkish Ministry of Health (No. 2021-03-20T16_25_47). The protocol was prepared according to the Declaration of Helsinki [13]. Written informed consent was obtained from all patients as part of the pandemic measures taken by the institution.

The clinical nurse, who did not participate in the study, recorded demographic characteristics, medical information, and smoking habit. The history of COVID-19 was determined by the aid of the personal health system records of the Turkish Ministry of Health, taking into account the last six months. A positive real-time polymerase chain reaction (PCR) test indicated a positive COVID-19 history [COVID(+)], whereas no positive PCR in the records was defined as a negative history [COVID(-)]. Hospitalization due to COVID-19 was also questioned.

Periodontal treatment need was assessed by the Community Periodontal Index of Treatment Needs (CPITN). CPITN was administered by one investigator (EC) before periodontal treatment, according to Ainamo et al. [14]. Six sextants were evaluated for each patient with a specially designed WHO periodontal probe. The index teeth were: 17, 16, 11, 26, and 27 in the maxilla and 47, 46, 31, 36, and 37 in the mandible.

Periodontal bone loss (PBL) was measured from digital panoramic radiographs taken just before periodontal treatment. Panoramic radiographs were obtained using a Veraviewepocs panoramic X-ray machine (Morita, Kyoto, Japan). The exposure parameters were 8.9 mA, 64 kVp, and 7.4 seconds. Panoramic images were stored on a desktop computer, and an assessment of PBL was performed by one investigator (EG) under standard conditions.

The measurement of PBL was made in six sextants (in the mesial of maxillary and mandibular first molars, second premolars, and central incisors) according to the Progressive Rate Index (PRI) recommended by Beckstrom et al. [15]. PBL was considered when the alveolar crest was 1 mm apical from the cementoenamel junction (CEJ). The percentage of bone loss was determined for each tooth when the distance from the CEJ to the alveolar crest minus 1 was divided by the root length (from the CEJ to the root tip) and multiplied by 100. The percentage for each patient was calculated by averaging all index teeth.

In addition to the above-mentioned evaluations, the number of missing teeth (MT) was also recorded.

Subjects who did not receive periodontal treatment during the pandemic period were included. Subjects with personal health records for PCR research and at least four sextants for clinical and radiographic index evaluation participated in the study. Patients demonstrating the following conditions were excluded from the study: (a) under the age of 18; (b) missing index teeth; (c) low-quality panoramic radiographs; (d) COVID-19 comorbidities (diabetes, hypertension, cardiovascular disease, hypercholesterolemia, asthma, and chronic obstructive pulmonary disease); (e) pregnancy; (f) metabolic bone disorder or presence of drugs known to affect bone metabolism; and (g) antibiotic use in the last three months.

Statistical Analysis

Statistical analysis was performed with the Python 3 Jupyter Notebook program using Pandas, Scipy, Numpy, and Seaborn libraries. Proportional differences between 2x2 categorical variables were analyzed with the Fischers' exact test and the differences in nxn dimensional tables with the Chi-square test. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess normality between the variables. For non-normally-distributed continuous variables, mean differences between the groups were calculated using the Mann-Whitney U test. Statistical significance was tested at alpha=0.05 level.

RESULTS

The study population consisted of 154 patients. Sixteen subjects were excluded from the study; ten had low-quality panoramic radiographs, three were under 18 years old, one was edentulous, and two had missing panoramic radiographs. The study was conducted with 138 patients (95 female and 43 male, mean age: 40.73).

COVID(+) consisted of 73 subjects and COVID(-) consisted of 65 subjects. Since very few cases (n=3) were hospitalized due to COVID-19, the effect of hospitalization on study parameters could not be evaluated within the COVID(+) group.

Table 1 shows demographic information and the results of MT, PRI, and PBL. There was no statistically significant difference between COVID(+) and COVID(-) in terms of age, sex, and MT. The number of smokers in COVID(-) (n=27) was significantly higher than COVID(+) (n=18) (p: 0.045). No significant difference was found between the groups regarding the PRI and the presence of PBL.

The results of the CPITN are presented in Table 2. The highest percentage in the study population belonged to the score 2 (45.9%), followed by the score 0 (22.1%), 1 (17.9%), 3 (7.2%), and 4 (6.9%), respectively. CPITN scores showed a similar distribution within the groups. The significant difference was examined considering the comparison between the groups. While COVID(+) had a greater percentage of score 0, 1, 3, and 4 than COVID(-); COVID(-) had a higher percentage of score 2 ($p<0.000$). However, it was found that the mean CPITN score did not differ significantly between the groups (Table 3).

Table 1. Demographic and radiographic results

Variables		COVID(+)			COVID(-)			p
		Mean	SD	Median	Mean	SD	Median	
Age		40.32	15.33	40.00	41.20	9.95	41.00	0.389
PRI		0.09	0.09	0.06	0.10	0.10	0.07	0.344
MT		6.70	5.87	5.00	6.71	5.62	5.00	0.918
		Count	**Column %**	**Row %**	**Count**	**Column %**	**Row %**	
Gender	Male	22	30.1%	51.2%	21	32.3%	48.8%	0.855
	Female	51	69.9%	53.7%	44	67.7%	46.3%	
Smoking	Nonsmokers	55	75.3%	59.1%	38	58.5%	40.9%	0.045*
	Smokers	18	24.7%	40.0%	27	41.5%	60.0%	
PBL	(-)	16	21.9%	59.3%	11	16.9%	40.7%	0.523
	(+)	57	78.1%	51.4%	54	83.1%	48.6%	

Mann-Whitney U test, Fischers' exact test, SD:Standard deviation, PRI: Progressive Rate Index, MT: Missing Teeth, PBL: Periodontal Bone Loss

Table 2. Distribution and comparison of CPITN scores

CPITN		COVID (+)	COVID (-)	Total	p
0	%	55.8%	44.2%	100.0%	<0.0001*
	% within group	24.1%	19.9%	22.1%	
1	%	63.6%	36.4%	100.0%	
	% within group	22.3%	13.3%	17.9%	
2	%	41.3%	58.7%	100.0%	
	% within group	37.1%	55.1%	45.9%	
3	%	60.4%	39.6%	100.0%	
	% within group	8.5%	5.8%	7.2%	
4	%	58.8%	41.2%	100.0%	
	% within group	8.0%	5.8%	6.9%	

Chi-square test

Table 3. Comparison of the mean and standard deviation of CPITN scores between the groups

Group	CPITN			p
	Mean	SD	Median	
COVID(+)	1.56	0.99	1.50	0.491
COVID(-)	1.67	0.90	2.00	

Mann-Whitney U test, SD: Standard Deviation

DISCUSSION

Despite many efforts and studies regarding COVID-19, the mystery remains about the underlying mechanisms that make patients susceptible to SARS-CoV-2 infection. Besides well-known risk factors (age, sex, hypertension, cardiovascular disease, diabetes, and obesity), periodontal disease has been associated with severe COVID-19 [6, 16-18].

The oropharyngeal region is considered a possible source of hospital-acquired pneumonia [7]. Therefore, poor oral hygiene can increase the risk of lower respiratory tract infections. Bacterial superinfections in severe COVID-19 cases highlight the risk of respiratory infections caused by inadequate oral hygiene [16]. Indeed, metagenomic analysis of severe COVID-19 patients revealed high amounts of periodontal pathogens (e.g., Prevotella, Fusobacterium) [19].

The aforementioned pathogens have been hypothesized to play a role in the exacerbation of COVID-19 by various mechanisms. Speculated mechanisms are the aspiration of oral pathogens into the respiratory tract, promoting ACE-2 expression, and inducing viral infection by degrading the viral spike (S) protein of SARS-CoV-2 [17].

The present cross-sectional study compared patients' demographics, periodontal bone loss, and treatment needs according to their COVID-19 history. The results revealed that there was no significant difference between the groups in terms of age and sex. However, it was found that smoking habit was affected by the COVID-19 history. COVID(-) included significantly more smokers than COVID(+). There are conflicting results in the literature regarding the effect of smoking on COVID-19. It was reported that increased expression of ACE-2 in smokers might predispose individuals to SARS-CoV-2 infection [20]. However, Paleiron et al. [21] concluded that smoking is associated with low susceptibility to SARS-CoV-2 infection and recommended that smoking cessation should not be a public health measure for COVID-19. In addition, the results of a meta-analysis indicated that smoking is not associated with COVID-19 severity [22]. Lippi et al. [23] mentioned a double-edged relationship between COVID-19 and smoking when considering the effect of angiotensin II and angiotensin 1-7 on tissue injury. Also, they stated that prospective studies are needed since smoking has many known unhealthy effects. Currently, the outcome of our study can be attributed to its relatively small sample, low incidence of serious COVID-19, and lack of smoking details.

The results regarding periodontal bone loss and treatment needs should be interpreted with caution. While bone loss and mean CPITN did not differ significantly between the groups, the distribution of CPITN scores differed significantly. COVID(+) had more healthy sextants (score 0) than COVID(-) but also had more bleeding (score 1), more shallow pockets (score 3), and more deep pockets (score 4). Interestingly, COVID(-) displayed more calculus sextants (score 2). Although COVID(+) had more significant needs for intensive treatment (scores 3 and 4) than COVID(-), given the significantly higher percentage of score 0 in COVID(+), it can be concluded that COVID(-) has more treatment needs than COVID(+). Therefore, there is no trend regarding the association between COVID-19 and periodontal disease.

A case-control study aimed to investigate the association of periodontitis with complications of COVID-19, and it was concluded that periodontitis is significantly associated with higher admission to intensive care units (ICU), the need for assisted ventilation, and death

[9]. The study had a larger sample selected from the national electronic health records and included more patients with COVID-19 complications (n=40) than our study (n=3). Similarly, a radiographic study suggesting that hospitalization for COVID-19 was positively associated with higher dental damage (including dental caries, periapical and periodontal infection) also had more hospitalizations (n=40) than our study [10]. This may be attributed to the difference in study design as the current sample was selected from patients admitted to the local periodontology department. In addition, patients who have seriously recovered from COVID-19 may not prioritize dental examination and request periodontal consultation during the pandemic period. A recent study with a similar design to the present study reported that there is a relationship between periodontitis and COVID-19 [12]. The severity of COVID-19 was not questioned in the study. Therefore, the effect of hospitalization was not evaluated similarly to this study. However, the clinical indices used to assess periodontal disease were different. There is no doubt that the indices such as probing depth and clinical attachment level used in the study are more sensitive than CPITN. However, in this study, considering the clinical conditions and the pandemic period when the patient's chair-time was limited, the CPITN, an index recommended for epidemiological screening, was used in order to evaluate the periodontal treatment needs of patients.

A national longitudinal cohort study database was used to compare the self-reported periodontal history of COVID-19 positive and negative patients, and it was concluded that periodontal disease does not affect the risk of COVID-19 infection and hospital admission [11]. The following study by this team reported that periodontal disease might exacerbate the impact of obesity on COVID-19 [24]. The non-significant results (PRI, mean CPITN) observed between our groups and the low hospitalization rate may be related to the exclusion of morbidities, and it can be concluded that periodontal disease may be a risk factor for COVID-19 along with shared risk factors such as diabetes and obesity. Considering the effect of smoking on periodontal tissues [25], the non-significant result between COVID(+) and COVID(-) may be due to the significantly higher prevalence of smokers in COVID(-). However, after stratifying the study population into nonsmokers, the mean CPITN score did not differ between COVID(+) (1.49) and COVID(-) (1.45).

This study has some limitations. We found no significant difference between COVID(+) and COVID(-) in terms of bone loss and treatment needs. First, this may be because a selection bias existed. After all, patients were selected from periodontology clinics. Second, the hospitalization rate was very low. Third, microorganisms responsible for dental caries may also participate in respiratory infections [26], and dental caries should be evaluated together with periodontal disease in future studies.

CONCLUSION

Many issues related to COVID-19 need to be clarified today. One of them is the relationship between periodontal disease and COVID-19. The hypotheses based on the existence of this relationship are plausible. However, this study conducted during the pandemic period revealed that periodontal disease is not associated with COVID-19. Future studies examining the relationship with more hospitalized patients are needed.

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REFERENCES

1. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database Syst Rev. 2021;2:Cd013665.
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
3. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130(5):2202-2205.
4. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. Int J Oral Sci. 2019;11(3):30.
5. Genco RJ, Sanz M. Clinical and public health implications of periodontal and systemic diseases: An overview. Periodontol 2000. 2020;83(1):7-13.
6. Pitones-Rubio V, Chávez-Cortez E, Hurtado-Camarena A, González-Rascón A, Serafín-Higuera N. Is periodontal disease a risk factor for severe COVID-19 illness? Med Hypotheses. 2020;144:109969.
7. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999;70(7):793-802.
8. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8.
9. Marouf N, Cai W, Said KN, et al. Association between periodontitis and severity of COVID-19 infection: A case-control study. J Clin Periodontol. 2021;48(4):483-491.
10. Sirin DA, Ozcelik F. The relationship between COVID-19 and the dental damage stage determined by radiological examination. Oral Radiol. 2021;37(4):600-609.
11. Larvin H, Wilmott S, Wu J, Kang J. The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic. Front Med (Lausanne). 2020;7:604980.
12. Anand PS, Jadhav P, Kamath KP, Kumar SR, Vijayalaxmi S, Anil S. A case-control study on the association between periodontitis and coronavirus disease (COVID-19). J Periodontol. 2022;93(4):584-590.
13. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-2194.
14. Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J, Sardo-Infirri J. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). Int Dent J. 1982;32(3):281-291.
15. Beckstrom BW, Horsley SH, Scheetz JP, et al. Correlation between carotid area calcifications and periodontitis: a retrospective study of digital panoramic radiographic findings in pretreatment cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(3):359-366.
16. Sampson V, Kamona N, Sampson A. Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? Br Dent J. 2020;228(12):971-975.
17. Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. J Oral Sci. 2020;63(1):1-3.
18. Kara C, Çelen K, Dede F, Gökmenoğlu C, Kara NB. Is periodontal disease a risk factor for developing severe Covid-19 infection? The potential role of Galectin-3. Exp Biol Med (Maywood). 2020;245(16):1425-1427.
19. Sampson V. Oral hygiene risk factor. Br Dent J. 2020;228(8):569.
20. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55(5):2000688.
21. Paleiron N, Mayet A, Marbac V, et al. Impact of Tobacco Smoking on the Risk of COVID-19: A Large Scale Retrospective Cohort Study. Nicotine Tob Res. 2021;23(8):1398-1404.
22. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med. 2020;75:107-108.
23. Lippi G, Sanchis-Gomar F, Henry BM. Active smoking and COVID-19: a double-edged sword. Eur J Intern Med. 2020;77:123-124.
24. Larvin H, Wilmott S, Kang J, Aggarwal VR, Pavitt S, Wu J. Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes. J Dent Res. 2021;100(11):1228-1235.
25. Jiang Y, Zhou X, Cheng L, Li M. The Impact of Smoking on Subgingival Microflora: From Periodontal Health to Disease. Front Microbiol. 2020;11:66.
26. Shinzato T, Saito A. A mechanism of pathogenicity of "Streptococcus milleri group" in pulmonary infection: synergy with an anaerobe. J Med Microbiol. 1994;40(2):118-123.