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ORIGINAL RESEARCH ARTICLE

Is Tonsillolith a Protective Factor Against Covid-19 ?

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Abstract

Purpose: Tonsilloliths are the most common calcifications of the head and neck region and are also caused by inflammation of the pharyngeal lymphoid tissue. Changes that may occur in the lymphoid tissue due to tonsilloliths may affect the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This radiological study aims to investigate the potential effect of tonsilloliths on Coronavirus disease 2019 (COVID-19).
Materials and Methods: This study, which has a cross-sectional retrospective design, was carried out by evaluating the digital panoramic radiographs taken before the pandemic period of the patient group (n=402) who had COVID -19, who applied to the Akdeniz University Faculty of Dentistry Oral, Dental and Maxillofacial radiology clinic, and the control group (n:400) who did not have COVID -19, in terms of the presence of tonsilloliths. All statistical analyzes were performed with SPSS version 22.0 and p <0.05 was considered to indicate statistical significance. The Chi-square test and Student's t-test were performed.
Results: The incidence of tonsillolith was significantly lower in the patient group (29.1%) than in the control group (45%) (p <0.01). Both groups were similar in terms of age, gender, and systemic disease status (p = 0.1, 0.08, and 0.08, respectively). Tonsilotiths were located both uni and bilaterally (p = 0.09), but unilateral ones were more common on the right side (p = 0.04).
Conclusions: The results of this study showed that high-frequency tonsilloliths may have a protective effect against COVID-19.

Key words: COVID -19; dental panoramic radiography; SARS-CoV-2; tonsillolith.

Introduction

Tonsilloliths are calcified structures observed in the tonsils and are formed as a result of the accumulation of bacterial and organic debris. While tonsilloliths are observed in the consistency of soft gel with the accumulation of aerobic and anaerobic bacterial debris in the initial stage, they reach stone hardness by calcifying over time. Inflammation also plays an important role in its formation [1–3].

Tonsilloliths are living biofilm of an inflammatory character, similar to dental plaque rather than a calcified stone in the tonsils [2]. These heterogeneous microbial biofilms cause the formation of chemical gradients and microniches, as dormant bacteria form a fixed biofilm nidus in the center [2]. However, its pathogenesis is not fully understood [4]. Recurrent tonsillar inflammation causes fibrosis in the ducts of the tonsillar crypts, leading to accumulation of bacterial and epithelial debris and retention cyst formation [5]. In addition, other opinions regarding the formation of tonsilloliths are that peritonsillar abscess or saliva flow originating from minor salivary glands in the palatal region may also cause calcification. [6].

Tonsilloliths are often asymptomatic clinically, but they cause many signs and symptoms such as bad breath, cough, metallic taste, difficulty in swallowing, sore throat, earache, stinging, and stuckness in the throat [7–10]. Tonsilloliths can be of different shapes and sizes, but rarely reach large sizes [8]. They are often detected incidentally in imaging methods such as Computed Tomography (CT) [11,12], Cone Beam Computed Tomography (CBCT) [13–15], Magnetic Resonance Imaging (MR) [16], and digital panoramic radiography (DPR) [11,12,17] often performed for other reasons. In dental practice, they are frequently observed as a radiopaque structure in millimetric, single, or multiple varying forms superposed on the mandibular ramus in digital panoramic radiographs [9]. Although tonsilloliths can be seen at any age, it is very rare to see tonsilloliths in children. They are most commonly detected in the fourth decade of life [18].

Tonsilloliths can cause various complications such as chronic tonsillitis, bad breath, peritonsillar abscess [10], orofacial pain [19], and pulmonary [20] complications [1]. Recurrent episodes of chronic tonsillitis predispose to tonsillolith. In chronic tonsillitis, the tonsillar tissue cannot form an adequate intrinsic response to inflammation, and the developing chronic inflammatory state causes the balance between regional immune cells and foreign pathogens to deteriorate in favor of the infective agent [21,22].

Coronavirus disease 2019 (COVID-19), a global health problem,

is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a wide range of symptoms ranging from asymptomatic infection to severe multi-organ failure and critical respiratory failure [23]. Interindividual variability and susceptibility for COVID-19 is not fully understood [24]. The pharyngeal microenvironment is important in the transmission, modulation, and clinical progression of SARS-CoV-2 infection [25]. The secretion of angiotensin-converting enzyme-2 (ACE-2) and TMPRSS2, which SARS-CoV-2 uses for attachment to the target tissue and viral replication, is present in large amounts in the tonsillar tissue [26,27].

The tonsillar tissue forms the first line of defense in the upper respiratory tract against SARS-CoV-2 and other microorganisms [22]. Changes in the pharyngeal lymphoid tissues cause both chronic tonsillitis and tonsillectomy. These changes in the pharyngeal lymphoid tissue may also cause changes in the response to SARS-CoV-2 [22].

Tonsilloliths can cause changes in the pharyngeal lymphoid tissue's response to inflammation. As far as we know, there is no study evaluating the relationship of tonsilloliths with COVID-19. In this study, it was aimed to evaluate the potential effect of the presence of tonsillolith on COVID-19 by comparing a group of individuals with COVID-19 who applied to the Faculty of Dentistry Oral, Dental, and Maxillofacial radiology clinic with the control group who did not have COVID -19 in terms of the presence of tonsilloliths.

Material and Methods

Study Design- Ethics Approval

This study was designed as a single-center retrospective study. The clinical research ethics board of Akdeniz University Faculty of Medicine accepted the study which complied with the Declaration of Helsinki. (approved number, date: 70904504/272, 24.05.2021).

Study groups

A total of 802 patients aged >18 years, with pre-pandemic DPRs, who applied to Akdeniz University Faculty of Dentistry Oral, Dental and Maxillofacial Radiology and Department between April 1, 2020, and April 1, 2021, for various reasons were included in the study. Demographic data, anamnestic characteristics, and DPRs of the patients were obtained from electronic patient files. The patients were divided into 2 groups as Group 1 = patient group (have had COVID-19) (n=402) and Group 2= control group (not have had COVID-19) (n=400). Systemic diseases of all individuals, such as some endocrine system diseases (diabetes mellitus and hypothyroidism), hypertension, asthma, chronic kidney disease, presence of malignancy, hematological, rheumatological, and immunological diseases were recorded.

COVID-19 diagnoses were made if they tested positive for SARS-CoV-2 RNA by polymerase chain reaction on nasopharyngeal and throat swabs performed according to the World Health Organization recommendation. In the patient group, digital panoramic radiographs taken before the pandemic period of 402 individuals who had COVID -19 in the last 3 months were included in the study. The reason for using DPRs in the pre- COVID -19 pandemic period is to rule out the risk of developing tonsilloliths caused by COVID -19, although it is not included in the literature to the best of our knowledge. Demographic, anamnestic data, and DPRs of individuals in the control group (n: 400) who did not have COVID -19, were used. Similarly, digital panoramic radiographs taken before the pandemic period for the control group were used to evaluate the presence of tonsilloliths. The inclusion and exclusion criteria are listed below.

Inclusion Criteria

The mandibular ramus and its surroundings should be visible on the DPR. Exclusion Criteria

1. Lack of previous (pre-COVID-19 pandemic) DPR records of individuals in study group 1 2. Intrinsic-extrinsic artifacts on DPR. 3. DPRs with patient positioning errors and insufficient image quality 4. History of tonsillectomy operation 5. History of maxillofacial trauma 6. Opacities less than 2 mm in the evaluated region and suspicious images were excluded from the study. (DPRs of the patients with unilateral/bilateral tonsilloliths and control group are shown in Figure 1)

Data Collection

All DPRs were obtained by the same X-ray technician using the same Planmeca ProMax panoramic device (Planmeca Oy, 00880 Helsinki, Finland), by the manufacturer's instructions (66 kVp, 7 mA, and 16 seconds). Radiologically visible radiopacities in the mid-portion of the mandibular ramus region were evaluated as a tonsillolith by the radiologists. All DPRs were evaluated on Romexis 4.6.2. All radiographic evaluations were made on a 24-inch Philips medical monitor with an NVDIA Quadro FX 380 graphics card and 1,920 × 1,080-pixel resolution. The DPRs were evaluated by the same researcher, who is an expert in dental radiology with ten years of experience. A maximum of ten DPRs were evaluated per day, to avoid investigators' fatigue. The presence or absence of tonsillolith was defined by considering the presence of a radiopaque nodular mass or masses on the mandibular ramus and soft palate reported by Ram et al. [9].

Evaluation of Intraobserver Reliability

The presence/absence of tonsillolith and being unilateral or bilateral were evaluated independently by an oral radiologist. About 20% of the samples (80 controls and 80 patients) were randomly selected and these evaluations were repeated two weeks apart to evaluate intraobserver reliability. The Kappa statistics were used to evaluate intraobserver reliability values for the presence of tonsilloliths, location (right, left), and being unilateral/bilateral. We chose to use the criteria recommended by Koo and Li [28 28] for the interpretation of kappa values of categorical data. (poor: < 0.5, moderate: 0.5-0.75, good: 0.75-0.9, excellent: 0.9-1).

Statistical Analysis

All statistical analysis was made using SPSS-version 22 for Windows (IBM Corp., Armonk, NY, USA) Basic descriptive statistical analysis and normality tests of all variables were performed. The normality test of the distribution was evaluated using the Shapiro-Wilk method. Tonsillolith status (present/absent), gender, age, and control-patient group distribution were showed normal distribution. To compare the results of the subjects with patient and control groups, the Student t-test was used for qualitative data (age), and the chi-squared test was used for quantitative data; gender, systemic disease status (present/absent), tonsillolith status (present/absent), uni/bilateral sided, its direction (right/left). Statistical significance level was considered as the value of $p < 0.05$.

Results

The Kappa coefficients were 0.984, 0.926, and 0.962 for the tonsillolith status (present/absent), unilateral/bilateral sided, and its direction (right/left), respectively. The study included DPRs of 802 individuals, 402 of whom had COVID-19 (patient group) and 400 individuals who had not had COVID-19. Of the study group, 337 (42%) were male and 465 (58%) were female ((Table 1)). Of the 402 individuals in the patient group, 221 were female, and 181 were male, and of the 400 individuals in the control group, 244 were female

Figure 1. A. Bilateral tonsilloliths, B. Unilateral tonsillolith, C. Control group.

Table 1. Demographic and radiological characteristics of the study groups

Parameters	All group	Patient group	Control group	p values
*Number, [%]	802	402, 50.1%	400, 49,9 %	0.10
**Age [years]	38.37 ± 15.12	37.51 ± 14.23	39.23 ± 15.94	0.10
*Gender [M/F] [n]	337/465	181/221	156/244	0.08
*Systemic disease (A/P) [n]	557/245	300/102	257/143	0.08
* Tonsillolith incidence rate [n, %]	298, 37.2%	117, 29.3%	181, 45%	**<0.01**
*Tonsillolith unilateral/bilateral [n]	201/97	76/41	125/56	0.09
* Tonsillolith right/left [n]	127/74	61/15	66/59	**0.04**

Significant p values are indicated in bold
Abbreviations: *: Chi square test **: student t test, M: Male, F: Female, n: Number, A: Absent, P: Present

and 156 were male. There was no statistical difference between the two groups in terms of gender (p = 0.08) ((Table 1)).

The mean age of the entire study group (minimum/maximum:16/82) was 38.37 ± 15.12. The mean age was 37.51 ± 14.23 years for the patient group and 39.23 ± 15.94 years for the control group. There was no significant difference in age between the two groups concerning age (p = 0.11) ((Table 1)).

The incidence of tonsillolith was 33.9% (n = 151) in individuals under the age of 40 (n = 446) and 41% (n = 147) in the individuals over the age of 40 (n = 356) in the entire study group, and a statistically significant difference was found (p = 0.03) ((Table 1)). There was no statistically significant difference in the incidence of tonsilloliths in the entire study group (n = 245) and individuals (n = 557) with and without the systemic disease (p = 0.53). When the individuals in the study group were examined in terms of the presence of systemic disease (healthy, hypertension, endocrine diseases: hypothyroidism/diabetes mellitus, anemia, asthma, allergic conditions, chronic kidney diseases, autoimmune diseases, malignant diseases, and others); in the patient group, there were 25.4% with systemic disease (n. = 102) and non-and 74.6% (n=300). In the control group, there were 35.8% (n= 143) had the systemic disease and 64.2% (n= 257) without systemic disease, and systemic disease status was statistically insignificant between the groups (p = 0.08). The distribution of systemic diseases in the whole study group is given in (Table 2).

The incidence of tonsillolith in the entire study group was 37.2% (n = 298). While the incidence of tonsilloliths was 29.1% (n=117) in the patient group, it was 45% (n=181) in the control group. There was a statistically significant difference between the two groups in terms of tonsilloliths (p <0.01) ((Table 1)).

When the unilateral or bilateral appearance of tonsilloliths in the jaws was evaluated, 67.4% (n = 201) were unilateral and 32.6% (n = 97) were bilateral (p = 0.04). In the patient group, 64.96% were unilateral (n = 76, right: 61, left: 15) 35.04% (n =41) were bilateral; In the control group, 69% (n = 125, right: 66, left: 59) were unilateral and 31% (n = 56) were bilateral, and there was no statistically significant difference between the groups in terms of unilateral and bilateral tonsilloliths (p = 0.09). However, the presence of tonsillolith on the right side among the groups was statistically significantly higher in the patient group (p = 0.03) (Table 1).

Table 2. Medical characteristics of the study groups

Parameters	All group	Patient group	Control group
Healthy [n], [%]	557	300, 53.85%	257, 46.15 %
Hypertension [n]	78	35	43
Asthma [n]	22	7	15
Endocrine system diseases [n]	44	19	25
Anemia [n]	24	9	15
Chronic kidney diseases [n]	11	7	4
Autoimmune diseases [n]	5	1	4
Malignant [n]	7	2	5
Allergic conditions [n]	13	5	8
Other [n]	41	17	24
Total [n]	802	402	400
p value		0.08	

Chi square test was performed
Abbreviations: n: Number

Discussion

This study is the first study in the literature to evaluate the relationship between tonsillolith and SARS-CoV-2, and COVID-19 was detected statistically significantly less in individuals with tonsilloliths. This result suggests that tonsillolith may be a protective barrier/mechanism against COVID-19 infection.

As far as we know, there is no study evaluating the relationship between tonsillolith-SARS-CoV-2 in the literature. In the study of Huang et al., a significant level of ACE-2 expression was observed in tonsillar crypts [29]. The possible mechanisms may be the following: Tonsillolith forming a protective biofilm layer on tonsils just like dental plaques on teeth [2] and/or it is the inability of SARS-CoV-2 to sufficiently adhere to the tonsillar tissue due to the decrease in the expression of ACE-2 receptor, which SARS-CoV-2 uses to enter the cell, in the tonsillar tissue of the tonsillolith [29]. Another speculative mechanism is; SARS-CoV-2 may have less adhesion due to the decrease in the surface area of the tonsillar crypts, which are the tonsillar tissue to which the tonsillolith is attached (where the expression of ACE-2, which allows the virus to enter the cell, is observed more). The most common calcifications in the head and neck region are tonsilloliths [15,18,30]. Due to the high prevalence of tonsilloliths, this association may be of potential importance for the COVID-19 pandemic.

Capriotti et al reported that pharyngeal-associated lymphoid

organs play a potentially independent role in the host response to SARS-CoV-2 infection in a study comparing the COVID-19 transmission status of a group of patients who had and did not undergo tonsillectomy [22]. They argued that an uncontrolled inflammatory reaction to the virus, mediated by a dysfunctional Waldeyer ring, could lead to high fever and associated symptoms, and that previous tonsillectomy could be seen as an indicator of the altered host response to SARS-CoV-2 infection. Conversely, individuals with a functional Waldeyer ring may develop milder and less intense symptoms, possibly leading to an identification of viral carriers [22]. However, in this study, we determined that the frequency of tonsillitis was lower in individuals with COVID-19. This situation aroused the thought that tonsillolith may create a protective mechanism for COVID-19, contrary to the knowledge that it causes chronic inflammations in the tonsillar tissue and causes unwanted complications such as a peritonsillar abscess.

In the studies of Kadriyan et al, they found the SARS-CoV-2 gene in the tonsil and debris tissues of patients with chronic tonsillitis who underwent tonsillectomy after COVID-19 [29,31]. This indicates that tonsillar tissue is important in the transmission of COVID-19 and its attachment to the upper respiratory tract. Although we have not yet been able to reach such information in the literature research; It will be important to examine tonsilloliths in terms of ACE-2 receptor expression in tonsillar tissue and adhesion or colonization of SARS-CoV-2 in tonsillar tissue in the presence of tonsilloliths. Tonsilloliths are one of the most common pathological and physiological calcifications in the head and neck region [18,30]. They can be detected clinically and radiologically. The prevalence of tonsillar calcification was reported as 16-46.1

Differences in the prevalence of tonsilloliths may be due to the difference in the mean age of the individuals included in the study [32], but studies are reporting the opposite [33,34]. In the study of Oda et al., the frequency of tonsilloliths was found to be higher in individuals over the age of 40 [11]. Some other researchers stated that the frequency of tonsilloliths did not show a significant difference in individuals younger than 40 years of age [33,34]. In this study, the frequency of tonsilloliths was significantly higher in individuals over 40 years of age.

Different imaging modalities affect the detection rate of tonsilloliths. Many studies are using various imaging methods, such as DPRs [14,17,18], CT [11,12], CBCT [12,14,15,35], and MR [16] in the evaluation of tonsilloliths. While tonsilloliths can be examined in more detail in terms of size, number, and location with advanced imaging techniques such as CT and CBCT, they can also be detected with DPRs. Takahashi et al. [18] found the frequency of tonsilloliths to be 13% in DPRs, 40.7% in CT images in their study conducted with two different imaging techniques, and similarly, Oda et al. [11] found 45% in CT, and 7.3% in DPR. Özdede et al in their study which they compared CBCT and DPRs to detect tonsilloliths, showed that tonsilloliths of 2 mm and above can be detected with DPRs, but DPRs may be insufficient in finding smaller tonsilloliths [14]. Small-sized tonsilloliths can be better visualized with advanced imaging techniques compared to DPRs. However, Yeşilova et al. found DPR and CBCT images compatible in terms of dimensional measurements and some structural features of the calcifications [15].

Takahashi et al showed that tonsilloliths can be detected widely on panoramic radiographs, but at a higher rate with CT or CBCT [12,18]. However, they also emphasized that early diagnosis of tonsilloliths through DPRs can reduce the need for unnecessary further imaging [12]. In addition, DPR is a practical method in terms of easy application and lower radiation for the evaluation of calcification.

In this study performed with DPRs, it was found 29.3% in the tonsillolith patient group, 45% in the control group, and 37.2% in the whole study group. According to studies with DPRs in the literature, Oda et al. [11], Takahashi et al. [18], and Özdede et al [14] found tonsilloliths in varying ranges of 7.7%, 13.4%, and 32.8%, respectively. In this study, the frequency of tonsilloliths was found to be high, similar to the study of Özdede et al. [14]. The reasons for this difference; may be due to the variety of panoramic devices and the effect of detectability of calcified bodies medial to the mandible, differences due to patient positioning, variations in different sensor sizes and imaging systems, and the experience of the evaluating physician [18,35].

In this study, the incidence of tonsilloliths was similar between the genders, similar to the studies in the literature [36,37]. However, there are studies in the literature stating that the frequency of tonsilloliths is higher in the male population [11,18]. Although the exact cause is unknown, chronic oropharyngeal inflammation may persist in men due to higher smoking rates and/or poor oral hygiene [18].

It has been reported in previous studies that unilateral tonsilloliths are more common than bilateral ones, and there is no significant difference between the prevalence of calcifications on the right and left sides [11,18]. On the contrary, in our study, unilateral were more numerous, but being uni or bilateral was not statistically significant. More tonsilloliths were observed on the right side.

This study has several limitations. Firstly, it had a single-center, retrospective, and cross-sectional design. Cross-sectional investigations lack the power to show true negative results and biases can appear if the case and control groups are not properly matched. Secondly, the study included a small number of patients, therefore decreasing the chance of finding significant differences and increasing the risk of missing real differences.

Conclusion

Tonsilloliths, which are found in high frequency in the general population, maybe protective against COVID-19. It is important to investigate the mechanisms of action of tonsilloliths in tonsillar tissue and their effects on ACE-2 receptor expression by histological and genetic clinical studies.

Author Contributions

S.G.Y.: Design, Definition of content, Literature search, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review.G.C.A.: Design, Literature search, Radiological studies, Data acquisition, Manuscript editing, Manuscript review

Conflict of Interest

Authors declare that they have no conflict of interest.

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