CLINICAL RESEARCH

Prevalence of Apical Periodontitis in Patients with Autoimmune Liver Diseases on Immune Suppressants and Immune Modulators: A Cross-sectional Study

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SIGNIFICANCE

Based on recent literature, patients affected by autoimmune diseases are generally more prone to develop apical periodontitis. It is important to be aware of the fact that patients with autoimmune liver diseases seem to have less apical periodontitis and that this may be because of the prevalent use of immune suppressants.

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ABSTRACT

Introduction: Autoimmune liver diseases (ALDs) are chronic conditions generated by an immune-mediated autoaggressive inflammatory reaction in genetically susceptible individuals. The purpose of this study was to evaluate the prevalence of apical periodontitis (AP) in patients suffering from ALDs undergoing treatment with the immune suppressants glucocorticoids, azathioprine, and/or ursodeoxycholic acid. **Methods:** The ALD group included 46 patients (11 men and 35 women, average age = 57.9 ± 11.8 years) and 1186 teeth. The control group included 50 healthy patients not taking any medications (15 men and 35 women, average age = 58.6 ± 10.4 years) and 1251 teeth. Demographic data and medical, pharmacologic, and dental history were recorded. Dental and radiographic examinations were performed. The presence of AP; the periapical index score; decayed, missing, and filled teeth; quality of restoration, and root canal treatment were evaluated. The influence of the medications the patients were taking on the prevalence of AP was also tested. **Results:** The prevalence of AP was significantly lower in ALDs than in the control group at the patient ($P = .019$) and tooth level ($P = .014$). Smoking and age were associated with a significant increase in AP in cases and controls ($P = .045$ and $P = .001$, respectively). In both groups, endodontically treated teeth showed a higher prevalence of AP. **Conclusions:** Considering the limitations because of the observational nature of the study, the patients affected by ALDs liver diseases and undergoing treatment with immune suppressors (often associated with immune modulators) were found to exhibit a lower prevalence of AP. *(J Endod 2024;50:784–791.)*

KEY WORDS

Apical periodontitis; autoimmune liver diseases; immune modulators; immune suppressors

Autoimmune liver diseases (ALDs) are chronic diseases generated by the immune-mediated autoaggressive inflammatory reaction in genetically susceptible individuals[1]. They include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Along with these conditions, 2 overlap syndromes are included: AIH/PBC and AIH/PSC[1]. The clinical presentation of ALDs varies from asymptomatic forms to terminal liver disease[1].

AIH is a multifactorial polygenic pathology that affects females 3 to 4 times more often than males and is associated with chronic liver damage leading to necrosis of the hepatic tissue. It involves a loss of tolerance to autoantigens specific to the liver hepatocytes[2].

PBC and PSC are both characterized by inflammation and progressive destruction or impairment of the intrahepatic bile ducts with consequent cholestasis and significant morbidity and mortality[3]. Although PBC prevalently affects women (male-to-female ratio of 1:10), PSC mainly targets men[3]. The pathogenesis of these 2 ALDs includes the production of both innate and adaptive immune responses targeting cholangiocytes, the epithelial cells of the bile ducts[2].

The aim of therapy for ALDs and the overlap syndromes is the complete (biochemical and/or histologic) remission of the pathology and the prevention of the progression of liver injury to cirrhosis[4]. The first-line therapy for AIH is based on constant immunosuppression with glucocorticoids (GCs) alone or in combination with azathioprine (AZT)[4] or ursodeoxycholic acid (UDCA), a secondary bile acid[4]. The treatment of choice in PBC and PSC is lifelong administration of UDCA[5-7].

Apical periodontitis (AP) is a chronic disease that affects periapical tissues caused by an inflammatory reaction in response to the action of infectious agents, mostly bacteria, present in the root canal[8]. The pathogenesis, development, clinical presentation, and healing of AP are closely linked to the immune response of the host and the extent and duration of the inflammatory reactions associated with the release of proinflammatory and proresolving mediators[9,10].

It is well-known that the response of the host to AP may be influenced by systemic conditions characterized by an alteration of the immune system[11], such as inflammatory bowel disease (IBD)[12,13], rheumatoid arthritis (RA)[14], diabetes[15], and autoimmune diseases in general[16]. According to recent literature, patients suffering from these diseases tend to have more teeth affected by AP[11-15]. Recent studies also demonstrated that liver conditions are associated with increased numbers of teeth affected by AP[17,18] and larger bone resorption areas[19].

Importantly, some medications commonly prescribed for the treatment of some systemic diseases may affect the development and healing of AP. It has been suggested that biologic medications (also known as immune modulators [IMs]) may be associated with a lower prevalence and faster healing of AP[20,21], whereas immune suppressants (ISs) such as corticosteroids cause an early increase in bone resorption[22]. The purpose of this study was to evaluate the prevalence of AP in patients suffering from ALDs undergoing treatment with ISs (GCs or AZT) and/or UDCA.

METHODS

The dental and periodontal status of patients with ALDs (AIH, PBC, and overlap syndromes) referred to the university dental clinic from the Liver Unit of the Department of Internal Medicine of the University Hospital of Cagliari for a dental checkup between September 2022 and November 2022 was thoroughly assessed. All records (medical and dental) were collected and compared with those of a control group of healthy patients matched with ALDs for sex, age, smoking habits, and number of teeth with no history of autoimmune systemic diseases and not undergoing immunosuppressant therapy.

This study was approved by the institutional ethics committee (PROT. PG/2020/10888) and was conducted according to the guidelines of the Declaration of Helsinki of 1975 (as revised in 2000). Compliance with the Health Insurance Portability and Accountability Act of 1996 was verified. Informed consent from all the participants was obtained.

Clinical Data Collection

During the dental checkup, a full dental examination was performed, and medical and dental history and medical and dental radiographic records of the patients were obtained. The demographic data including age, sex, medical history, information on the time of onset of the main ALD, and the previous and current medications taken were recorded with a specifically designed questionnaire.

Selection of Cases

The study group (ALDs) consisted of men and women between 20 and 90 years of age affected by ALDs (AIH, PBC, and overlap syndromes) and undergoing a specific therapy (ISs and/or UDCA) for at least 3 months (63 ± 56 months average) to ensure the systemic effectiveness of the medications assumed. Patients suffering from marginal periodontitis, diabetes, cardiovascular diseases, cancer, or chronic inflammatory and systemic diseases; patients being treated with other medications; and patients with incomplete clinical documentation were excluded.

The ALD group included 46 patients (11 men and 35 women, average age = 57.9 ± 11.8 years) and 1186 teeth (Table 1). The study group was further divided into 3 subgroups based on the type of disease, and the different therapies and combinations of medications taken were noted (Table 2). The 46 patients with ALDs were then divided into 3 groups according to the period between the dental examination and the diagnosis of the disease: <5 years (18/46 patients), 5–10 years (14/46 patients), and >10 years (14/46 patients).

The control group included 50 patients with no systemic diseases and not taking any medications (15 men and 35 women, average age = 58.6 ± 10.4 years) and 1251 teeth (Table 1). The 96 patients in the overall sample resulted in 2 balanced groups homogeneous for sex, age, and smoking habits (Table 1).

Radiographic Assessment

Panoramic radiographs were used as an initial screening of the teeth for all patients included in the sample. In addition, intraoral periapical radiographs were taken for all teeth presenting with either direct or indirect restorations, root canal fillings, AP, or suspected AP in the panoramic radiograph[23] using the VistaScan Mini View image system (Dürr Dental, Bietigheim-Bissinge, Germany). They were performed using a paralleling technique using Rinn film holders (Rinn xcp-psp fit; Dentsply Sirona, Baillagues, Switzerland). Exposure times and kilovoltage were adjusted according to the manufacturer's instructions. An Excel (Microsoft, Redmond, WA) spreadsheet was used to record the following: the presence of lesions in the soft tissues (cutaneous or mucosal), the number of teeth, periodontal probing depth, the presence of caries, the presence of restorations (restorative/prosthetic), the presence of endodontic treatments, and the presence of AP.

Acquisition of Data

To report the general dental status of the patients and the dimension and severity of AP, the decayed, missing, and filled teeth (DMFT) index[24] and the periapical index (PAI) score[25] were calculated. The periapical radiographs

TABLE 1 - Descriptive Data of the Sample

	Total	Control group	ALDs group
Sex			
Overall, *N* (%)	96 (100.0)	50 (100.0)	46 (100.0)
Male, *n* (%)	26 (27.1)	15 (30)	11 (23.9)
Female, *n* (%)	70 (72.9)	35 (70)	35 (76.1)
Age, mean ± SD	58.3 ± 11	58.6 ± 10.4	
Teeth, *n* (mean ± SD)	2437 (25.4 ± 4.7)	1251 (25 ± 4.2)	
Smoke			
Overall, *N* (%)	96 (100.0)	50 (100.0)	46 (100.0)
No, *n* (%)	84 (87.5)	42 (84)	42 (91.3)
Yes, *n* (%)	12 (12.5)	8 (16)	4 (8.7)

SD, standard deviation.

TABLE 2 - Descriptive Data of the Autoimmune Liver Disease (ALD) Group and the Prevalence of Apical Periodontitis (AP)

	ALDs = 46 (100.0)	AP = 13 (28.3)
ALD, *n* (%)		
AIH	13 (28.3)	3 (23.1)
PBC	17 (37)	5 (29.4)
Overlap	16 (34.8)	5 (31.3)
Medications, *n* (%)		
Immune suppressors	9 (16.9)	4 (44.4)
GCs	5 (10.9)	2 (40)
AZT	3 (6.5)	2 (66.7)
GCs + AZT	1 (2.2)	0 (0)
Immune modulators + immune suppressors	16 (34.8)	2 (12.5)
GCs + UDCA	3 (6.5)	1 (33.3)
AZT + UDCA	9 (19.6)	0 (0)
GCs + AZT + UDCA	4 (8.7)	1 (25)
Immune modulators	21 (45.7)	7 (33.3)
UDCA	21 (45.7)	7 (33.3)

AIH, autoimmune hepatitis; AZT, azathioprine; GC, glucocorticoid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.
Medications were grouped according to the different effect on the immune system.

were saved in the JPEG format and transferred to ImageJ software (version 1.41; National Institutes of Health, Bethesda, MD) to use the plug-in application Turbo Reg (Biomedical Imaging Group, Swiss Federal Institute of Technology, Lausanne, Switzerland)[26] with the intent to reduce the dimensional changes resulting from the different angulations of the radiograph central beam at the time of the examination. The periodontal status of the patients was assessed according to the guidelines from the Consensus World Workshop on the Classification of Periodontal and Peri-Implant Diseases[27].

The PAI was attributed to each root by 2 trained and calibrated endodontists. Calibration was determined using the Cohen kappa test after the observers had evaluated 50 periapical lesions twice, 1 month apart from each other[28]. The highest PAI score given to 1 of the individual roots was chosen as representative of multirooted teeth. When the scores of the 2 examiners differed, the highest of their scores was selected. The quality of the root canal treatments and the coronal restorations were evaluated by the same examiners following the criteria described by Ng et al[29]. If the quality of 1 of the 2 treatments considered was not within the standard, the entire treatment was considered inadequate.

The results obtained for the ALD and control patients and within the subjects in the ALD subgroups were then compared considering the type of ALD, the medications taken, and the time elapsed between the onset of the disease and the dental visit. In addition, patients with ALDs were divided into the following 3 groups according to their response to the immune therapy administered: responsive patients, partially responsive patients, and nonresponsive patients. The responsiveness to treatment was based on the results of the following liver function analysis performed at the time the dental visit was undertaken: aspartate aminotransferase, alkaline phosphatase, alanine transaminase, gamma-glutamyl transferase, antinuclear antibody, immunoglobulin G, and platelet count.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 15.0; SPSS Inc, Chicago, IL). The results were assessed at the patient and the tooth level.

At the patient level, a simple binary logistic regression model was conducted to assess the relationship between the prevalence of AP and the patient groups. Odds ratios (ORs) and 95% confidence intervals were obtained. Then, the logistic models were adjusted by sex, age, smoking habit, and DMFT, and the adjusted OR was calculated. The association of the prevalence of AP with the type of ALD or medication was analyzed with a similar methodology. The chi-square, independent *t*, and Mann-Whitney tests were performed to evaluate the homogeneity of the groups. Regarding the power analysis, a sample size of 96 patients (46/50) provided a maximum error of 14.4% to estimate the true AP prevalence in each of the populations, assuming p = q = 50% and 95% confidence. Moreover, 70.9% of power to detect the rate of AP is reached at 25% and 50% as significantly different in both groups using a logistic regression model and 95% confidence.

At the tooth level, a multilevel logistic regression using generalized estimation equations was conducted to describe the risk of AP in a tooth according to the previously mentioned factors. The adjusted ORs and 95% confidence intervals were obtained from the Wald chi-square statistic.

For patients presenting with radiographic evidence of AP, multiple linear regression models were performed to analyze the factors influencing the PAI score using a generalized estimation equation. The level of significance used in the analysis was set at 5% ($\alpha = 0.05$).

A sample size of 2437 would provide 99.9% power with a CI of 95% to detect AP at rates of 25% and 50% as significantly different between groups. However, because teeth were not independent and each patient provided an average of 25.4 teeth, a within-subject correlation intra-class correlation coefficient = 0.5 (moderate) was assumed, leading to a correcting coefficient D = 13.2. Therefore, 2437 dependent teeth provided the same power as 185 independent teeth.

RESULTS

The patients with ALDs and the controls showed similar demographic characteristics (Table 1). The homogeneity of groups, considering the overall oral health status, was estimated as similar, with DMFT being 12.5 ± 6.2 in the ALD group and 10.7 ± 4.5 in the control group.

At the Patient Level

The prevalence of AP was significantly lower in patients with ALDs (28.3%) than in the controls (52%) ($P = .019$) (Fig. 1). Patients with ALDs showed 64% less AP compared with the controls (OR = 0.36; 95% CI, 0.16-0.85).

The final weighted kappa value of the 2 observers for scoring the PAI was .85, which was obtained as the mean of the kappa values from 2 assessments performed at time 0 ($\kappa = 0.88$) and 1 month later ($\kappa = 0.81$). The mean of the PAI score was significantly lower in patients with ALDs than in the controls (2.88 ± 0.89 vs 3.22 ± 1.11, $P = .013$).

Smoking was associated with a significant increase of AP both in the case and control groups ($P = .045$). Smokers were diagnosed with AP 4 times more often than nonsmokers (Supplemental Table S1 is available online at www.jendodon.com).

The age of the patient appeared to strongly influence the probability of developing AP both in the study group and the controls ($P = .064$). Each additional year of age implied

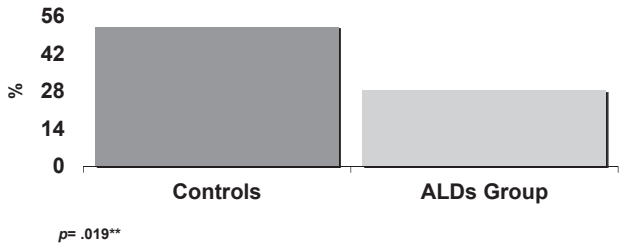

FIGURE 1 – The prevalence of AP in the controls and the patients with ALDs.

a 4% higher risk of AP; therefore, the older the subject, the higher the likelihood of AP (Supplemental Table S1 is available online at www.jendodon.com).

The prevalence of AP was comparable in patients taking different medications when considering every association of the drugs administered to the patients in the sample (GCs, AZT, UDCA, GCs + AZT, GCs + AZT + UDCA, GCs + UDCA, and AZT + UDCA) and when grouping the patients according to the different effects of the medications on the immune system (group 1: ISs [GCs, AZT, and GCs + AZT], group 2: ISs + IMs [GCs + UDCA, AZT + UDCA, and GCs + AZT + UDCA], and group 3: IMs only [UDCA]). However, group 2 showed the lowest prevalence of AP compared with group 1 and group 3 (Table 2).

The response to the immune therapy was not significantly associated with the prevalence of AP; however, patients with a positive response showed a reduced risk of AP compared with patients with a partial or no response ($P = .088$) (Supplemental Table S2 is available online at www.jendodon.com).

No significant difference in AP was detected between the groups of patients affected by the different ALDs (Table 2). No significant association between the onset of the disease and the probability of presenting an AP was found ($P = .121$) even though the 5- to 10-year group was the most represented.

At the Tooth Level

The mean of the number of teeth for each patient was similar in the 2 groups (ALDs: 25.8 teeth/patient and controls: 25 teeth/patient). The prevalence of AP was significantly different between the 2 groups (1.4% in the ALD group and 3.2% in the control group; $P = .014$) (Table 3). The probability of a tooth of a patient with ALD to show AP decreased by 56% compared with that of the control (OR = 0.44; 95% CI, 0.23-0.85) (Table 3). Older age was associated with an increased prevalence of AP in the whole sample ($P = .001$) (Supplemental Table S3 is available online at www.jendodon.com).

No significant difference was detected between the groups of patients affected by the different ALDs and under different therapies. The time range between the onset of the disease and the dental evaluation did not influence the probability of AP ($P = .314$). At the tooth level, the PAI score was not significantly different between the 2 groups ($P = .814$); however, female patients showed lower PAI scores ($P = .005$).

n the whole sample, endodontically root canal treated and non root canal treated teeth (RCT vs NRCT) showed proportions of AP of 19.0% and 0.9%, respectively, with similar proportions in the study (16.1% vs 0.3%) and control (21% vs 1.6%) groups. Endodontically treated teeth showed odds of AP 25 times higher than those of nontreated teeth ($P < .001$).

The quality of RCT and coronal restoration of endodontically treated teeth with AP was similar in the different groups and was judged adequate in 28.6% of cases in the ALD group and 31.8% in the control group (OR = 1.17; 95% CI, 0.25-5.43; $P = .844$) (Supplemental Table S4 is available online at www.jendodon.com). Therefore, these data were not considered as having a potential confounding effect.

DISCUSSION

In this study, patients affected by ALDs (AIH, PBC, and overlap syndromes) and undergoing treatment with AZT and/or GCs and/or UDCA exhibited a statistically lower prevalence of AP and smaller lesions than healthy controls but a similar DMFT. On the other hand, according to several recent studies, a higher prevalence of AP, teeth affected by AP, or the trend to develop AP are significantly associated with several systemic conditions such as type 1 diabetes mellitus[30] and autoimmune diseases, including ankylosing spondylitis[31] and RA[14]. Furthermore, individuals with IBD seem to consistently express a higher prevalence of AP[13,16,32], with the probability of presenting periapical lesions 5.7 times higher than healthy subjects[13].

All these findings, tentatively attributed to the subjective trend of increased production of proinflammatory cytokines (interleukin [IL]-1, IL-6, IL-17, and tumor necrosis factor alpha [TNF-α]) involved in the pathogenesis of all these conditions[12-14,16,31,32], are not consistent with the results of this study.

The only discovery similar to the previous reports[16,20,21,33,34] is that the patients in this study had smaller radiolucencies than the controls. To explain our results, it could be argued that ISs, especially in combination with UDCA, may determine a generalized suppression of the inflammation cascade, which in turn limits the size of AP[35-40], an effect that may not be present in the majority of patients suffering from other autoimmune diseases treated with IMs rather than ISs.

AZT and synthetic GCs are ISs respectively indicated to manage multiple autoimmune diseases and hematologic malignancies or to prevent tissue destruction limiting exaggerated and persistent responses to injury or infection[38,41,42]. Among other actions, AZT mediates the inhibition of DNA synthesis and reduces the levels of T, B, and natural killer cells, blocking both cellular and humoral immunity, as well as suppressing the formation of autoantibodies and prostaglandins[35-37,43,44]. The immunosuppressant effect of synthetic GCs starts with the interaction with the transcription of DNA, down-regulating the expression of target genes, including IL-1β, TNF-α, and IL-2 cytokines[45], whereas they boost the control of inflammation[41,46,47]. UDCA, besides

TABLE 3 - The Prevalence of Apical Periodontitis (AP) in the Sample (Teeth)

	Overall	Controls	ALD group	OR	95% CI	*P* value
Number of teeth, *N* (%)	2437 (100.0)	1251 (100.0)	1186 (100.0)			
AP: no, *n* (%)		1211 (96.8)	1169 (98.6	1		
AP: yes, *n* (%)		40 (3.2)	17 (1.4)	0.44	0.23–0.85	.014*

ALD, autoimmune liver disease; CI, confidence interval; OR, odds ratio.
*<.05.

controlling the synthesis and homeostasis of bile components[48], exerts its immune action mostly via the blockade of cytokine expression[49]. Importantly, UDCA reduces the production of mucosal cytokines and nitric oxide[39,50] and inhibits TNF-α induction of IL-8 secretion from monocytes, acting on IL-8 messenger RNA[40].

T lymphocytes, the main targets of the ISs cited, are strictly involved in the development and resolution of AP, producing important amounts of cytokines via antigen-specific receptors on their cell surface[51-53]. ISs and IMs both act on the immune system; however, although ISs repress or reduce the immune response by disabling multiple immune elements simultaneously or only a single lymphocytic line[54], IMs interrupt only specific immune functions often using cytokine blockade[55].

Only 2 clinical reports were in broad agreement with the results of the present study. In the first, among patients with different autoimmune diseases (IBD, RA, and Psoriasis), those with RA exhibited a significantly lower risk of AP. This result was attributed to the management of RA with the combination of an IM with ISs, whereas the other autoimmune patients were treated with an IM only[16]. In the second study, with a similar design (patients with IBD, RA, and Ps) in which treatments included disease-modifying antirheumatic drugs (ISs) and biologic medications (IMs), patients taking disease-modifying antirheumatic drugs showed a statistically significant reduction of the prevalence of AP compared with those taking IMs[32]. These observations confirm that immune suppression and the combination of ISs and IMs might reduce the probability of developing radiographically detectable AP[16,32].

As shown in Table 2, patients affected by ALDs are treated with a combination of ISs (GCs and AZT) and/or UDCA. In light of the action of such drugs on patients' immune systems, they are likely to inhibit, to different degrees, the onset of AP. Recently, it has been hypothesized that AP may have a partial autoimmune etiology, a hypothesis supported by the observation of elevated levels of citrullinated proteins in human granulomas[56].

Citrullination is a posttranslational protein modification occurring in the presence of gram-negative anaerobic infections (ie, *Porphyromonas gingivalis*). This process often results in the production of anticitrullinated autoantibodies that may initiate an autoimmune reaction within AP and represent a potential contribution to the perpetuation of the inflammatory reaction, which in turn may be interrupted by the IMs and ISs[56].

The effects of the ISs on AP in this research were supported by the finding of a weak correlation between the good responsivity of the patients to the pharmacologic regimen administered (based on hepatic parameters) and the reduced risk of AP (Supplemental Table S2 is available online at www.jendodon.com). Drawing further conclusions on the association between ALDs, the medications (ISs + IMs), and the lower occurrence of AP will require a larger sample.

Similarly to previous reports[16,57-60], patients' age, smoking habit, and the presence of a root canal treatment were all associated with an increased prevalence of AP, findings in line with most scientific reports[16,57-59]. Smoking seems to influence the inflammatory response by increasing the immune expression of the following biomarkers: receptor activator of nuclear factor kappa B ligand, osteoprotegerin, osteopontin, and TNF-α[60]. Finally, the higher prevalence of AP in endodontically treated teeth is likely to be associated with the low quality of RCT and coronal restorations.

Study Limitations

The most relevant limitation of this study is its observational nature and, consequently, its own inability to establish causation. Being a cross-sectional study, the temporal relationship between the alteration of the immune system of the patients and the difference in the prevalence of AP cannot be directly identified. A second limitation may be attributed to the fact that our regression model did not consider the confounder concerning the quality of restorative and endodontic treatment. However, because there was not a statistically significant difference in this parameter between the 2 groups, we can assume that they were homogeneous and that these data should not be considered a confounding factor. Moreover, the small sample size affects the representativeness of the results. Furthermore, the use of OPG complemented with periapical radiographs for the diagnosis of AP implies a lack of standardization in the detection and measurement of periapical lesions, which could have been more predictably obtained using cone-beam computed tomographic (CBCT) examination. On the other hand, this is a study with an observational design in which it was considered excessive to perform CBCT imaging for prevalence assessment. Lastly, considering that different combinations of medications were taken from patients affected by different diseases, it is difficult to associate the prevalence and size of AP with specific diseases and IM/IS treatments.

CONCLUSION

Patients affected by ALDs and taking ISs, often associated with IMs, showed a lower prevalence of AP compared with the controls. Considering the observational nature of the study, a causality between the 2 conditions cannot be established yet. This information helps to understand the susceptibility of patients with ALDs to AP and provides an initial insight into the possible effects of ISs on the inception of AP. Further studies with larger sample sizes, including the use of more sensitive radiographic techniques such as cone-beam computed tomographic imaging, are warranted.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Francesca Ideo: Conceptualization, Methodology, Writing – original draft. **Sadia Niazi:** Visualization, Investigation. **Luchino Chessa:** Resources. **Michela Miglianti:** Formal analysis, Data curation. **Giulia Bardini:** Investigation, Data curation. **Francesco Mannocci:** Validation, Supervision. **Elisabetta Cotti:** Conceptualization, Writing – review & editing, Supervision.

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The authors deny any conflicts of interest related to this study.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at www.jendodon.com (https://doi.org/10.1016/j.joen.2024.02.026).

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