Aim: The aim of this retrospective cohort study was to investigate the prevalence of apical periodontitis (AP) in patients affected by autoimmune diseases (ADs) taking biologic medications (BMs). Methods: Ninety-nine patients (2440 teeth) with ADs referred to the university clinic for dental evaluation were investigated. The controls included 99 patients (2655 teeth) with no systemic diseases and taking no medications. The patients underwent a complete oral, dental, and radiographic examination for the presence of AP. The periapical index (PAI) and the status of endodontic and restorative treatments were obtained. Statistics were based on descriptive analysis and continuous variables for the total sample and by subgroups. Adjusted odds ratios and 95% confidence intervals were calculated.
Results: The prevalence of AP was 65.7% in the study group (AI) and 46.5% in the controls (P<.05). The association between smoking and AP was significant (P<.05). Among the AI subgroups, rheumatoid arthritis (RA) patients, at the tooth level, had a lower probability of developing AP than inflammatory bowel disease (IBD) patients (P<.05). Furthermore, each additional year of age implied a +1% risk of AP; women had a lower PAI than men in both groups (P<.05), and tocilizumab was associated with a reduced risk of AP compared to infliximab (P<.05). Conclusions: Patients with ADs taking BMs had a higher prevalence of AP. These results indicate that the status of the patients' immune system may have an effect on the development and prevalence of AP.

Introduction

Apical periodontitis (AP) is a chronic inflammatory disease of the periradicular tissues associated with the presence of a microbial infection in the root canal system (1). The perpetuation of this condition is related to the interaction between the infection and the host immune response (2). The development of AP is regulated by the activity of proinflammatory mediators in the first stage of the process and pro-resolving mediators during the resolution phase (3–4). The importance of the host immune status in the development of AP has been described in several studies (5–6).

Autoimmune diseases (ADs) result from a self-reactive immune response involving different inflammatory mediators (7). Rheumatoid arthritis (RA) is the most common inflammatory arthritis, with a global prevalence of 1%, and is often characterized by positive serology for inflammatory markers, some of which are disease-specific (rheumatoid factor and anticitrullinated protein antibody) (8). Psoriasis (Ps) is a chronic inflammatory skin disease linked to a genetic predisposition and to autoimmune pathogenic traits. Its prevalence is approximately 2%, with significant

geographic variations. Its hallmark is inflammation leading to uncontrolled proliferation of keratinocytes and their dysfunctional differentiation (9).
The pathogenesis of inflammatory bowel disease (IBD) is based on the immune reaction of the intestinal mucosa to improper stimulation by environmental, genetic, and dietary factors (10). The most common subtypes of IBDs are ulcerative colitis (UC) and Crohn's disease (CD) (11). In IBD, an alteration of physiological immune processes with the loss of immune tolerance to the intestinal microbiota has been described (12–13).

All ADs require a therapeutic approach based on a specific immune-modulating regimen. Biologic medications (BMs) have revolutionized the treatment of moderate to severe ADs due to their high efficacy and low toxicity (14–15). Biologic therapies include molecules that are native biologic preparations (i.e., blood products), recombinant peptides or proteins, antibody-based therapies, nucleic acid-based therapies and cell and gene therapies. The types of proteins in use include recombinant human proteins with immune regulatory effects, monoclonal antibodies (chimeric, humanized, and fully human), and fusion proteins. Biologic medications act against a specific biologic target that possesses a critically important function related to the initiation, perpetuation, or suppression of inflammation (16) and these medications are able to block the inflammatory cascade that characterizes chronic ADs. The most commonly used BMs are monoclonal antibodies active against TNF-α, IL-1, IL-6, T and B lymphocytes that block the inflammatory response at an early stage (17).
In addition to the use of biologics, methotrexate (MTX), a disease-modifying anti-rheumatic drug (DMARD), is also used in some forms of ADs (i.e., RA) to attenuate the activity and progression of the disease. When BMs, in particular some anti-TNF-α agents (infliximab, etanercept, adalimumab and golimumab), are administered in conjunction with MTX, an enhanced effect has been observed (18).

The relationship between ADs, biologic medications and development or healing of apical periodontitis remains unclear, as studies showed that patients with IBD had a higher prevalence of apical periodontitis and larger radiolucencies than controls (22, 23), suggesting a negative effect of ADs on the development of apical periodontitis. On the other hand, endodontic treatments of teeth with apical periodontitis in patients taking BMs resulted in faster healing than those of controls (19, 20), thereby suggesting that the activation of the proinflammatory cascade associated with immune-modulating therapy may improve the response of AP to endodontic treatment.

The aim of this retrospective cohort study was to investigate the prevalence of AP in patients affected by autoimmune diseases (RA, Ps, and IBD) being treated with biologic drugs.

Materials and methods

The medical, dental, and radiographic records of patients with autoimmune diseases (AR, IBD and Ps) who had been referred to the Dental Clinic of the University Hospital for a dental evaluation between January 2017 and December 2020 were investigated. Similarly, we collected the medical, dental, and radiographic records of the subjects included in the control group. The patients in the control group had no history of autoimmune systemic diseases and were not being treated with biologic medications.

This study was approved by the Institutional Ethics Committee (PROT. PG/2020/10888) and was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2000). Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) was verified.

All participants gave their informed consent before inclusion in this study.

Selection of cases

The inclusion criteria for the patients in the study group (AI) were as follows: men and women, 18 to 90 years of age, affected by autoimmune diseases (RA, IBD, Ps), and

treated with biologic medications for at least three months. Patients presenting with periodontitis, diabetes, cardiovascular diseases, osteoarticular pathologies different from RA, cancer, those taking other medications, or incomplete clinical documentation, were excluded. The AI group included 99 patients (42 men and 57 women, average age: 47 ± 13.2 years) and 2440 teeth (Table 1). The AI group was further divided into 3 subgroups based on the disease type, and the different types of biologic medications taken were noted (Table 2). The control group (C) included 99 patients (42 men and 57 women, average age: 48 ± 15.8 years, and 2655 teeth) with no systemic diseases and not taking medications (Table 1).

The 198 patients in the overall sample resulted in two balanced groups, homogeneous for sex, age, and smoking habits (Table 1).

Clinical data collection

At the time of their dental examination, the patients were asked to provide their detailed medical and dental history. Their medical and dental radiographic records were also obtained.

A specifically designed questionnaire was constructed to record the demographic data, including the age, sex, and medical history of the patient, followed by information about the time of onset of the main AD and the previous and current medications taken. In all patients, panoramic radiographs (OPGs) were used as initial screening of the teeth. In addition to OPG, to assess the periapical status, intraoral periapical radiographs were also routinely taken for teeth of teeth presenting with either direct or prosthetic restorations, and AP or suspected AP in the panoramic radiograph. Periapical radiographs were obtained using a film holder for the paralleling technique with the help of Rinn centerers (Rinn xcp-psp fit; Dentsply Sirona, Baillagues, Switzerland). Exposure times and kilovoltage were adjusted according to the film manufacturer’s instructions. The following data were recorded for each patient in an Excel spreadsheet: a. presence of lesions in the soft tissues (cutaneous or mucosal); b.

number of teeth; c. periodontal probing depth; d. presence of caries, e. presence of restorations (restorative/prosthetic); f. endodontic treatments; g. apical periodontitis.

Acquisition of data

The decayed, missing, filled teeth (DMFT) index (24) and periapical index score (PAI) (25) were calculated. The periapical radiographs were scanned, saved in JPEG format, and transferred to ImageJ software (version 1.41; National Institutes of Health, Bethesda, MD) to use the plug-in application TurboReg (Biomedical Imaging Group, Swiss Federal Institute of Technology, Lausanne, Switzerland) (26) to reduce the dimensional changes resulting from the different angulations of the radiograph central beam at the time of the exam. The periodontal health status was assessed following the guidelines from the Consensus World Workshop on the Classification of Periodontal and Peri-Implant Diseases (27).

The PAI was assessed by 2 trained and calibrated endodontists. Calibration was determined using Cohen's kappa test after the observers assessed the PAI on 50 periapical lesions twice, with one month interval. For multirooted teeth, the highest score given to an individual root was chosen. When the two examiners' scores differed, the highest of their scores was selected. The quality of the coronal restorations and root canal treatments was assessed by the same examiners on the basis of the criteria described by Ng et al. (29). When one of the two components was not satisfactory, the entire treatment was considered inadequate. The results obtained for AI and C patients and among the subjects in the AI subgroups were compared. Furthermore, differences in the AI group based on the medication assumed were considered.

Statistical analysis

Statistical analysis was undertaken using SPSS software (version 15.0, IBM SPSS Statistics, Chicago, IL, USA). The results were assessed both at the patient and tooth levels.

At patient level a sample size of 198 patients provided a maximum error of 6.9% to estimate the true prevalence of AP in the whole population, assuming p=q=50% and a confidence interval of 95%. Moreover, we reached a power of 81.8% in detecting AP rates of 30% and 50%, as significantly different between groups, using a logistic regression model and assuming a confidence interval of 95%.

At tooth level, a sample size of 5,095 independent teeth would provide a 99.9% power at a confidence interval of 95% to detect AP rates of 30% and 50%, as significantly different between groups. However, as teeth were not independent and each patient had an average of 25.7 teeth, a within-subject correlation CCI=0.5 (moderate) was assumed, leading to a correcting coefficient D=13.4. Therefore, 5,095 dependent teeth provided a power of 97.8% under the same conditions mentioned above, that is the same power of 380 independent teeth.

Study participant characteristics were evaluated for the total sample and differentiated by group using descriptive statistics (mean, standard deviation range and median).

A simple binary logistic regression model was applied to assess the difference between the prevalence of AP in the two groups at the patient level. Odds ratios (ORs) and 95% confidence intervals were obtained. To analyze the differences in the prevalence of AP according to the type of AD or medication, logistic models were adjusted by sex, age and smoking, and ORs were obtained. In patients with AP, multiple linear regression models were constructed to analyze factors influencing the PAI score.

At the tooth level, study variables were jointly assessed in a multilevel logistic regression model using generalized estimation equations (GEE) to assess the risk of AP, that usually work with independent variables measured at both patient and tooth level. We consider this methodological approach appropriate because of the dependence of observations (many teeth per patient). The algorithms estimate a

correlation work matrix which best fits to the within-subject dependence. This consideration is key to obtain corrected standard errors and confidence intervals of coefficients (and p-values), compared to the conventional estimation on independent cases. In our calculations, convergence of models was reached in spite of the large number of teeth per patient.

Adjusted odds ratios and 95% confidence intervals were obtained from Wald´s Chi2 statistics. Similar linear models were performed for the PAI scores. The significance level was set at 5% (α=0.05).

Nine models were conducted at patient (five models) and tooth (four models) level, to calculate the prevalence of AP or PAI score in different samples, according the independent variable to be associated. On the patients, the conducted models were:

Model 1: (In all patients) Prevalence of AP by Group (AI/control) adjusted by gender, age, smoking.

Model 2: (In AI patients) Prevalence of AP by Type of AI disease adjusted by gender, age, smoking.

Model 3: (In AI patients) Prevalence of AP by Type of medication adjusted by gender, age, smoking.

Model 4: (In patients with AP) PAI score by Group (AI/control) adjusted by gender, age, smoking.

Model 5: (In AI patients with AP) PAI score by Type of AI disease adjusted by gender, age, smoking.

At tooth level, the models were carried out were:

Model 6: (All teeth) Prevalence of AP by Group (AI/control) adjusted by gender, age, smoking.

Model 7: (In teeth from AI patients) Prevalence of AP by Type of AI disease adjusted by gender, age, smoking.

Model 8: (In teeth from AI patients) Prevalence of AP by Type of medication adjusted by gender, age, smoking.

Model 9: (In teeth with AP) Treatment rate by Group (AI/control) adjusted by gender, age, smoking.

Results

The DMFT index was similar in both groups (AD=9.5 4.9, C=10.1 4.4).

At Patient level.

From the results obtained by the statistical model 1, the prevalence of AP was 65.7% in the study group (AI) and 46.5% in the control group (C), exhibiting a significant difference (p=.007) (Figure 1). AI patients had a 2.2 times increased risk of a diagnosis of AP compared to the controls. Smoking was associated with the increased prevalence of AP in both groups (p=.025) (Figure 2).

The 99 AI patients were divided into three groups according to the time period between the dental examination and the diagnosis of AD, with the following results: <10 years, (47/99, AP=59.6%), 10-30 years, (47/99, 70.2%) and >30 years, (5/99, 80%), with the average interval of 11,6 9 years. No significant difference was detected between the groups of patients affected by the different ADs (Model 2).

Most AI patients were taking infliximab (40.4%) or adalimumab (34.3%) (Table 2). The prevalence of AP was comparable in patients taking different medications (p=.943) (model 3).

The final weighted kappa value of the two observers for scoring the PAI was = 0.805, and it was obtained as the mean of the kappa values from two assessments performed at time 0 (k = 0.73) and one month later (k= 0.88).

Although AI patients showed a higher prevalence of AP than the control group, the severity of AP, as measured by PAI, was somewhat lower in AI group; however, this difference did not reach statistical significance (Supplementary table 4).

Women had a significantly lower PAI than men in both groups (p=.020) (Supplementary table 4) (model 4). Furthermore, RA patients with AP exhibited a significantly higher PAI than IBD patients with AP (p=.030) (Supplementary table 5) (model 5).

At tooth level.

Based on model 6, the number of teeth with AP was remarkably higher in AI than in C [(5.8% vs. 2.7%, (p<.001)]. Teeth in AI patients had a 2.22 times higher risk of having AP than the controls (Table 3). Considering the number of teeth, the age of the patient appeared to be a condition that significantly influenced the probability of developing AP, as each additional year resulted in a 1% increase in the risk of AP at the tooth level (Table 3).

Teeth in RA patients showed a significantly lower risk of AP than those in IBD patients (p=0.034) (Table 3) and the teeth of patients with IBD had the highest prevalence of AP (6.4% vs. 4.7% for RA and 2.6% for Ps) (Table 3) (model 7).

In contrast with the results obtained at patient level, tocilizumab seemed to reduce the risk of apical periodontitis at tooth level of compared to infliximab (p=.034) (Table 3) (model 8).

Last, the prevalence of AP was very similar in root canal-treated (RCT) teeth compared with nontreated (NT) teeth in both groups (RCT: AI =52.8% C=58.3%; NT: AI=47.2%

C= 41.67%) (model 9). The quality of RCT and coronal restoration of the endodontically treated teeth with AP was similar between groups and was judged adequate in only 15% of cases in AI and 10% in C.

Discussion

In this retrospective cohort study, patients affected by autoimmune diseases (RA, Ps and IBD) showed a higher prevalence of apical periodontitis than the controls, even if they exhibited a similar dental health condition, as shown by the DMFT values. This result is in accordance with previous reports (22, 23, 30, 31) and may be explained by the excessive production of pro-inflammatory cytokines (a common trait of all autoimmune diseases) (32,33), which is also associated with the development, progression and persistence of AP (34–35). Moreover, the longer the time elapsed between the diagnosis of AD and the dental visit, the greater was the prevalence of AP in the study group, underlining the importance of monitoring oral health in diseased patients.

The major severity of AP in the control group, expressed with a (not significantly) higher PAI, also suggests that in AI patients, the immune modulation associated with the use of BMs, might have a somewhat positive influence on the bone resorptive processes caused by apical periodontitis. These findings are consistent with those of recent studies on AP (19, 21, 36), and specifically on apical abscesses in individuals treated with BMs (37).

Patients with an autoimmune disease who have a genetic predisposition to immune hyper-reactivity (38–39) may show a higher prevalence of AP, caused by the intensity of the host response to an infection of the root canal (1, 40); however, AI patients included in the present study were taking strong immune modulators, which could render the immunologic response to endodontic infection comparable or even superior to that of the controls, resulting in a lesser gravity of the disease (17).

Our results showed that the prevalence of AP was similar in the teeth of patients affected by different autoimmune diseases, with a slightly higher prevalence in patients affected by IBDs (6.4%) (Table 3). These data confirmed the figures reported

in previous investigations (22, 23) and may be interpreted with the higher number of IBD patients represented in the AD sample, and with the context of the nature of these diseases. There is some evidence that the development of IBD is influenced by dysbiosis of the gut microbiota, which seems to be involved in the pathogenesis of both intestinal and extraintestinal disorders (41). Moreover, in IBD, the immune alteration of the patients involves the production of salivary cytokines and antibodies (42–43), and it is known that AP elicits an increase in the salivary levels of IgGs, IgAs, cross-reactive antibodies and pro-inflammatory mediators (43–45). The tendency of IBD patients to produce high levels of pro-inflammatory molecules during the active phase of the disease (42), could also favor the development of AP (44–49), and, at the same time, a predisposition of a patient to oral infections (such as AP) may influence their risk of getting IBD (50, 51).

When comparing IBD and RA, teeth in RA patients had a significantly lower risk of AP than those in IBD patients (OR=0.55; p=.034), despite the higher PAI. Interestingly, a very recent article based on the integrated data of a large number of hospital cases reported that patients affected by RA developed more abscesses than controls, but abscesses had a lower incidence in the group of RA patients treated with an anti-TNFα medication (etanercept) (37).
Additionally, in this regard, the effects of medications taken by RA patients should not be underestimated. While IBD patients were taking anti-TNFα BMs as monotherapy, in patients with RA, anti-TNFα BMs were usually taken in combination with MTX. Combination therapy with MTX makes the immune system more tolerant to high levels of anti-TNFα in RA, thus prolonging their therapeutic effect (18). Nonetheless, this two-level approach to RA may affect the severity of AP, with larger radiolucencies, as the immunomodulation from the BM is potentiated by methotrexate, with a consequent increased rate of destruction of the periapical bone (52).

Rituximab, another medication of choice to treat RA, is a human/murine chimeric monoclonal antibody that targets CD20 (53), a surface marker unique to B cells diffusely present in the lymphocytic infiltrate of endodontic lesions (54). Rituximab could have also influenced the size of AP due to its suppressive effect on B cells. The different medications taken did not seem to have affected the prevalence of apical periodontitis in AI patients, although tocilizumab (an anti-IL-6) appeared to marginally reduce the risk of AP at the tooth level compared with infliximab. This may be explained because interleukin-6 (IL-6), together with TNF-α and interleukin-1 (IL-1), is highly involved in bone resorption and tissue degradation (3).

In the total sample, women showed significantly lower PAI values than men ($p=.020$). This finding is in contrast with the data from a preliminary study where women with IBD treated with BMs exhibited a significantly higher number of teeth with AP ($P < .05$) (22). This difference can be justified by the larger number of patients and the multiplicity of ADs considered in this study.

Age was also a significant prognostic factor for AP in both groups, increasing the risk of developing the disease by 1% for each additional year. This finding is highly expected, as the prevalence of AP varies among patients of different ages, ranging from 33% in young people (20–30 years) to 62% in people older than 60 (55). Another possible explanation could be the slower bone metabolism in the elderly due to the aging of the immune system, which results in a documented increase in the healing time of AP following RCT (56).

Smoking was associated with an increase of AP prevalence in both groups, therefore it did not influence the comparison between the cases and controls in terms of prevalence or severity of the disease. As discussed in previous reports, smoking affects the immune response, causing a stronger inflammatory reaction and increasing the RANKL/OPG ratio, with negative effects on periapical tissues (57).

Finally, the prevalence of AP was not significantly different in treated teeth when compared to nontreated teeth, both in AI and control patients, a finding that is not

consistent with the most recent reports (55). However, the low quality of the RCTs and coronal restorations observed in most cases easily explains the high prevalence of AP in treated teeth.

The main limitation of this study is its retrospective design, that makes it difficult to distinguish whether the results are due to either the disease, the medication used, or both conditions. Additionally, the evaluation of the periapical status of teeth was conducted using periapical radiographs, while a three-dimensional system (CBCT) could surely provide more precise information on the presence and size of the radiolucencies (58). Finally, the sample size is limited, and the diseases considered show some heterogeneity under the umbrella of their common autoimmune pathogenesis, potentially affecting the prevalence and development of AP to different extents.

Conclusion

Patients affected by autoimmune diseases showed a higher prevalence of AP, confirming the role of an altered immune system in the pathogenesis of this condition. The immunomodulatory drugs taken by these patients also seemed to influence the manifestations of AP. Understanding the interaction between the host predisposition to inflammatory diseases and the effect of immune modulators on the development of AP may help in designing new treatment strategies for AP.

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

References:

1. Nair PNR. Apical periodontitis: a dynamic encounter between root canal infection and host response. Periodontol 2000 1997;13:121–48.
2. Kawashima N, Okiji T, Kosaka T, et al. Kinetics of macrophages and lymphoid cells during the development of experimentally induced periapical

lesions in rat molars: a quantitative immunohistochemical study. J Endod 1996;22:311–6.

3. Marton IJ, Kiss C.Overlapping protective and destructive regulatory pathways in apical periodontitis. J Endod 2014;40:155–63.
4. Cotti E, Ideo F, Pedrazzini A, et al. Proresolving Mediators in Endodontics: A Systematic Review. J Endod. 2021;47:711-720.
5. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. Int Endod J. 2015; 48:933-51.
6. Márton IJ, Kiss C. Protective and destructive immune reactions in apical periodontitis. Oral Microbiol Immunol. 2000;15:139-50.
7. Rose NR. Prediction and Prevention of Autoimmune Disease in the 21st Century: A Review and Preview. Am J Epidemiol. 2016;183:403-6.
8. Wasserman A, Rheumatoid Arthritis: Common Questions About Diagnosis and Management American Family Physician 2018; 97, 7.
9. Rendon A. and Schäkel K. Psoriasis Pathogenesis and Treatment Int. J. Mol. Sci. 2019; 20, 1475;
10. Ramos GP, Papadakis KA. Mechanisms of Disease: Inflammatory Bowel Diseases. Mayo Clin Proc. 2019;94:155-165.
11. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019;12:113-122.
12. Laroux FS, Pavlik KP, Wolf RE, et al. Dysregulation of intestinal mucosal immunity: implications in inflammatory bowel disease. News Physiol Sci 2001;16:272–7.
13. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009;361:2066–78.
14. Agarwal SK. Biologic agents in rheumatoid arthritis: an update for managed care professionals. J Manag Care Pharm 2011;17:14–8.
15. Wilkins T, Jarvis K, Patel J. Diagnosis and management of Crohn's disease. Am Fam Physician 2011;84:1365–75.
16. Sandborn WJ, Targan SR. Biologic therapy of inflammatory bowel disease. Gastroenterology. 2002;122:1592-608.
17. Purcell RT, Lockey RF. Immunologic Responses to Therapeutic Biologic Agents. J Investig Allergol Clin Immunol 2008; Vol. 18: 335-342.
18. Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. Ann Rheum Dis. 2013;72:1897-904.

19. Cotti E, Mezzena S, Schirru E, et al. Healing of Apical Periodontitis in Patients with Inflammatory Bowel Diseases and under Anti-tumor Necrosis Factor Alpha Therapy. J Endod. 2018;44:1777-1782.
20. Cotti E, Careddu R, Schirru E, et al. A case of SAPHO syndrome with endodontic implications and treatment with biologic drugs. J Endod 2015;41:1565–70.
21. Cotti E, Abramovitch K, Jensen J, et al. The influence of adalimumab on the healing of apical periodontitis in Ferrets. J Endod 2017;43:1841–6
22. Piras V, Usai P, Mezzena S,et al. Prevalence of Apical Periodontitis in Patients with Inflammatory Bowel Diseases: A Retrospective Clinical Study. J Endod. 2017;43:389-394.
23. Poyato-Borrego M, Segura-Sampedro JJ, Martín-González J, et al. High Prevalence of Apical Periodontitis in Patients With Inflammatory Bowel Disease: An Age- and Gender- matched Case-control Study. Inflamm Bowel Dis. 2020;26:273-279.
24. World Health Organization. Oral Health Surveys: Basic Methods, 4th ed. Geneva: World Health Organization; 1997
25. Ørstavik, D., Kerekes, K. and Eriksen, H.M. The periapical index: A scoring system for radiographic assessment of apical periodontitis. Dental Traumatology, 1986; 2: 20-34
26. Bose R, Nummikoski P, Hargreaves K. A retrospective evaluation of radiographic outcomes in immature teeth with necrotic root canal systems treated with regenerative endodontic procedures. J Endod. 2009;35:1343-9.
27. Papapanou PN, Sanz M, Buduneli N,et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018;45 Suppl 20:S162-S170
28. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
29. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of non surgical root canal treatment: part 1: periapical health. Int Endod J 2011;44:583–609.
30. Karataş E, Kul A, Tepecik E. Association between Rheumatoid Arthritis and Apical Periodontitis: A Cross-sectional Study. Eur Endod J. 2020; 5:155-158.
31. Karataş E, Kul A, Tepecik E. Association of ankylosing spondylitis with radiographically and clinically diagnosed apical periodontitis: A cross-sectional study. Dent Med Probl. 2020; 57:171-175.
32. Sozzani S, Del Prete A, Bosisio D. Dendritic cell recruitment and activation in autoimmunity. J Autoimmun. 2017; 85:126-140.
33. McInnes IB, Buckley CD, Isaacs JD. Cytokines in rheumatoid arthritis - shaping the immunological landscape. Nat Rev Rheumatol. 2016; 12:63-8.

34. Graunaite I, Lodiene G, Maciulskiene V. Pathogenesis of apical periodontitis: a literature review. J Oral Maxillofac Res. 2012;2:e1.
35. Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. Crit Rev Oral Biol Med. 2004;15:348-81
36. Peddis N, Musu D, Ideo F,et al. Interaction of biologic therapy with apical periodontitis and periodontitis: a systematic review. Aust Dent J. 2019; 64:122-134.
37. Rotstein I, Katz J. Prevalence of periapical abscesses in patients with rheumatoid arthritis. A cross sectional study. Am J Dent. 2021;34:211-214)
38. Niewold TB, Goulielmos GN, Assassi S. Autoimmune disease genetics 2013. J Immunol Res. 2014;2014:487643.
39. Blach-Olszewska Z, Leszek J. Mechanisms of over-activated innate immune system regulation in autoimmune and neurodegenerative disorders. Neuropsychiatr Dis Treat. 2007;3:365-72.
40. Braz-Silva PH, Bergamini ML, Mardegan AP, et al. Inflammatory profile of chronic apical periodontitis: a literature review. Acta Odontol Scand. 2019;77:173-180.
41. Carding S, Verbeke K, Vipond DT, et al. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191.
42. Szczeklik K, Owczarek D, Pytko-Polończyk J, et al. Proinflammatory cytokines in the saliva of patients with active and non-active Crohn's disease. Pol Arch Med Wewn. 2012;122:200-8.
43. Savage NW, Barnard K, Shirlaw PJ, et al. Serum and salivary IgA antibody responses to Saccharomyces cerevisiae, Candida albicans and Streptococcus mutans in orofacial granulomatosis and Crohn's disease. Clin Exp Immunol. 2004;135:483-9.
44. Haug SR, Marthinussen MC. Acute Dental Pain and Salivary Biomarkers for Stress and Inflammation in Patients with Pulpal or Periapical Inflammation. J Oral Facial Pain Headache. 2019;33:227–233.
45. Pietiäinen M, Liljestrand JM, Akhi R,et al. Saliva and Serum Immune Responses in Apical Periodontitis. J Clin Med. 2019;8:889.
46. Figueredo CM, Brito F, Barros FC, et al. Expression of cytokines in the gingival crevicular fluid and serum from patients with inflammatory bowel disease and untreatedchronic periodontitis. J Periodontal Res 2011;46:141–6.
47. Noack B, G€orgens H, Hoffmann T, Schackert HK. CARD15 gene variants in aggressive periodontitis. J Clin Periodontol 2006;33:779–83.
48. Oz HS, Chen T, Ebersole JL. A model for chronic mucosal inflammation in IBD and periodontitis. Dig Dis Sci 2010;55:2194–202.
49. Tatakis DN, Guglielmoni P. HLA-B27 transgenic rats are susceptible to accelerated alveolar bone loss. J Periodontol 2000;71:1395–400.
50. Van Dyke TE, Dowell VR, Offenbacher S, et al. Potential role of microorganisms isolated from periodontal lesions in the pathogenesis of inflammatory bowel disease. Infect Immun 1986;53:671–7.

51. Kojima A, Nakano K, Wada K, et al. Infection of specific strains of Streptococcu mutans, oral bacteria, confers a risk of ulcerative colitis. Sci Rep 2012;2:1–11.
52. Oh WM, Hwang IN, Son HH, et al. Rapid periapical bone destruction during endodontic treatment of a patient with rheumatoid arthritis. J Endod. 2008;34:1261-3.
53. Smith, M. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003; 22, 7359–7368.
54. Philippi CK, Rados PV, Sant'ana Filho M, et al. Distribution of CD8 and CD20 lymphocytes in chronic periapical inflammatory lesions. Braz Dent J. 2003;14:182-6.
55. Jakovljevic A, Nikolic N, Jacimovic J, et al. Prevalence of Apical Periodontitis and Conventional Nonsurgical Root Canal Treatment in General Adult Population: An Updated Systematic Review and Meta-analysis of Cross-sectional Studies Published between 2012 and 2020. J Endod. 2020; 46:1371-1386.e8
56. Azim AA, Griggs JA, Huang GT. The Tennessee study: factors affecting treatment outcome and healing time following nonsurgical root canal treatment. Int Endod J. 2016;49:6-16.
57. Segura-Egea JJ, Martín-González J , Castellanos-Cosano L - Endodontic medicine: connections between apical periodontitis and systemic diseases - Int Endod J 2015; 48:933-51.
58. Kanagasingam S, Lim CX, Yong CP, et al. Diagnostic accuracy of periapical radiography and cone beam computed tomography in detecting apical periodontitis using histopathological findings as a reference standard. Int Endod J. 2017 May;50:417-426.

Figure and tables LEGENDS:

Table 1. Descriptive data of the sample
Table 2. Descriptive data of AI group
Table 3. Prevalence of AP in the sample (teeth), according to the diseases and medications
Figure 1. Prevalence of AP in controls and AI Patients
Figure 2. Prevalence of AP in smoker and non-smoker patients

SUPPLEMENTARY TABLE 4. PAI score by group (AI/Control), adjusted by gender, age, smoking habit.

SUPPLEMENTARY TABLE 5. PAI score by type of AI disease adjusted by gender, age, smoking habit.

TABLE 1. Descriptive Data of the Sample

	Total	Control group	AI group
Gender Number (%)			
Overall	198 (100.0)	99 (100.0)	99 (100.0)
Male	84 (42.4)	42 (42.4)	42 (42.4)
Female	114 (57.6)	57 (57.6)	57 (57.6)
Age Mean ± SD			
	47.5±14.5	48.0±15.8	47.0±13.2
Teeth Number (Mean ± SD)			
	5095 (25.7±5.4)	2655 (26.8±4.2)	2440 (24.6±6.2)
Smoke Number (%)			
Overall	198 (100.0)	99 (100.0)	99 (100.0)
No	158 (79.8)	79 (79.8)	79 (79.8)
Yes	40 (20.2)	20 (20.2)	20 (20.2)

Results are presented as percentage frequency (%), Mean ± Standard Deviation.

TABLE 2. Descriptive Data of AI group

	AI = 99 (100.0)
ADs Number (%)	
IBD	69 (69.7)
RA	24 (24.2)
PS	6 (6.1)
BMs (action) Number (%)	
Tocilizumab (IL-6 inhibitor)	5 (5.1)
Rituximab (CD20 inhibitor)	4 (4.0)
Golimumab (TNF-alpha inhibitor)	7 (7.1)
Etanecerpt (TNF-alpha inhibitor)	5 (5.1)
Abatecept (T cells- inhibitor)	2 (2.0)
Infliximab (TNF-alpha inhibitor)	40 (40.4)
Adalimumab (TNF-alpha inhibitor)	34 (34.3)
Denosumab (RANKL inhibitor)	1 (1.0)
Secukinumab (IL-17A inhibitor)	1 (1.0)

Results are presented as percentage frequency (%)

TABLE 3. Prevalence of AP in the sample, according to disease and medications (Teeth)

	Overall	No	Yes	OR	95% CI	p-value
Overall	5095 (100.0)	4881 (95.8)	214 (4.2)			
Control group	2655 (100.0)	2583 (97.3)	72 (2.7)	1		
AI group	2440 (100.0)	2298 (94.2)	142 (5.8)	2.22	1.50 – 3.29	**.001*** **
Age				1.01	1.00 - 1.03	**.039***
ADs Number (%)						**.041***
Overall	2440 (100.0)	2298 (94.2)	142 (5.8)			
IBD	1758(100.0)	1645 (93.6)	113 (6.4)	1		
RA	531 (100.0)	506 (95.3)	25 (4.7)	0.55	0.32 – 0.96	**.034***
PS	151 (100.0)	147 (97.4)	4 (2.6)	0.37	0.11 - 1.23	.105
BMs Number (%)						.149
Overall	2440 (100.0)	2298 (94.2)	142 (5.8)			
Infliximab (TNF-alpha inhibitor)	1032 (100.0)	978 (94.8)	54 (5.2)	1		
Tocilizumab (IL-6 inhibitor)	126 (100.0)	123 (97.6)	3 (2.4)	0.35	0.13 – 0.93	**.034***
Rituximab (CD20 inhibitor)	66 (100.0)	63 (95.5)	3 (4.5)	0.62	0.22 – 1.75	.367
Golimumab (TNF-alpha inhibitor)	161 (100.0)	152 (94.4)	9 (5.6)	0.93	0.44 – 1.98	.846
Etanecerpt (TNF-alpha inhibitor)	133 (100.0)	128 (96.2)	5 (3.8)	0.57	0.20 – 1.59	.281
Abatecept (T cells- inhibitor)	36 (100.0)	32 (88.9)	4 (11.1)	1.53	0.49 – 4.78	.465
Adalimumab (TNF-alpha inhibitor)	837 (100.0)	774 (92.5)	63 (7.5)	1.23	0.62 – 2.45	.549
Denosumab (RANKL inhibitor)	17 (100.0)	16 (94.1)	1 (5.9)	0.73	0.37 – 1.45	.362
Secukinumab (IL-17A inhibitor)	32 (100.0)	32 (100.0)	0 (.0)	-	-	-

Results are presented as total number of teeth with AP and as percentage frequency (%)

Figure 1. Prevalence of AP in Controls and AI Patients

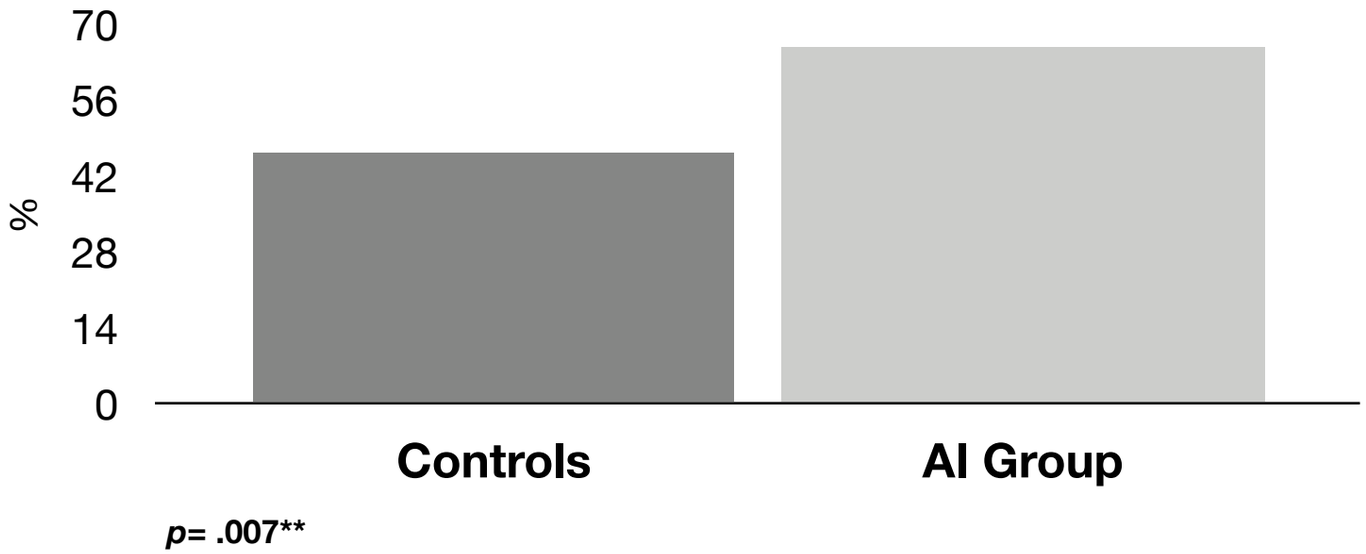
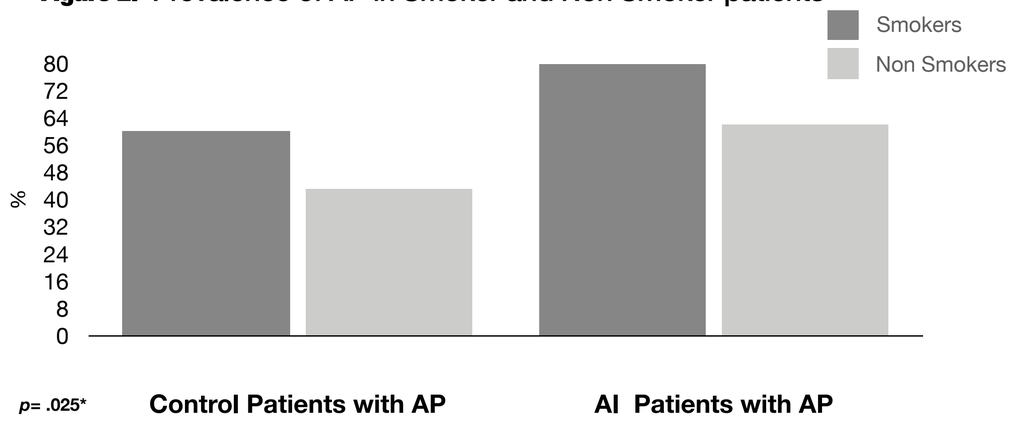


Figure 2. Prevalence of AP in Smoker and Non Smoker patients



Supplementary TABLE 4. PAI score by Group (AI/control) adjusted by gender, age, smoking

	Beta	95% CI	p-value
Group			
Control	0		
AI	-0.34	-0.68 – 0.01	0.055
Gender			
Male	0		
Female	-0.42	-0.78 – -0.07	**0.020***
Age	0.01	-0.01 – 0.02	0.333
Smoking			
No	0		
Yes	-0.02	-0.41 – 0.37	0.925

*p<0.05; **p<0.01; ***p<0.001

Supplementary TABLE 5. PAI score by Type of AI disease adjusted by gender, age, smoking

	Beta	95% CI	p-value
AI Disease			
IBD	0		
RA	0.52	0.05 – 0.99	**0.030***
Gender			
Male	0		
Female	-0.50	-0.90 – -0.09	**0.018***
Age	0.01	-0.02 – 0.02	0.818
Smoking			
No	0		
Yes	0.21	-0.25 – 0.68	0.364

*p<0.05; **p<0.01; ***p<0.001