

The Potential Association Between Inflammatory Bowel Diseases and Apical Periodontitis: A Systematic Review and Meta-Analysis

 **Esam HALBOUB**,¹  **Arwa AL-MASWARY**,^{2,3}  **Mohammed MASHYAKHY**,⁴
 **Gamilah AL-QADHI**,⁵  **Sadeq Ali AL-MAWERI**,⁶  **Raidan BA-HATTAB**,⁶
 **Saleem ABDULRAB**⁷

¹Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, Jazan University, Jazan, Saudi Arabia

²Department of Restorative and Aesthetic Dentistry, Faculty of Dentistry, Sana'a University, Sana'a, Yemen

³Department of Dentistry, Faculty of Dentistry, Ar-Rasheed Smart University, Sana'a, Yemen

⁴Department of Restorative Dental Sciences, College of Dentistry, Jazan University, Jazan, Saudi Arabia

⁵Department of Basic Dental Sciences, Faculty of Dentistry, University of Science and Technology, Aden, Yemen

⁶College of Dental Medicine, QU Health, Qatar University, Doha, Qatar

⁷Alkhor Health Centre, Primary Health Care Corporation, Doha, Qatar

ABSTRACT

Recent literature has suggested a potential association between inflammatory bowel diseases (IBD) and apical periodontitis (AP). The present systematic review and meta-analysis sought to analyse and appraise the available evidence regarding the reported association. Following 2020 PRISMA guidelines, a comprehensive search of multiple online databases (PubMed, Scopus, Web of Science, and Google Scholar) was conducted for all relevant studies published from the date of inception until 27 April 2023 using various relevant keywords. All observational studies that assessed the association between IBD and AP in humans were eligible for inclusion. The quality of the selected studies was carried out independently by two reviewers, and meta-analysis was performed using Comprehensive Meta-Analysis Version 2.2.064. Six studies (five case-control studies and one cohort study) were included. A total of 657 patients (277 with IBD) were included in 5 case-control studies, and 48,223 subjects (35,740 with AP) were included in the cohort study, where 188 developed IBD on follow-up. The pooled data from the five case-control studies revealed that IBD was significantly associated with a higher risk of AP (OR=1.71, 95% CI: 1.21–2.42; I²=10.337%, fixed-effect, p=0.002). The qualitative analysis also showed that most of the included studies found a higher mean number of teeth with AP in IBD groups than the healthy controls. Newcastle-Ottawa Scale (NOS)-based quality appraisal results demonstrated that five studies were of high quality, and one was of moderate quality. The results suggest a potential association between IBD and AP. Large-scale and prospective studies are required to further confirm and elucidate the nature of such an association.

Keywords: Apical periodontitis, Crohn's disease, inflammatory bowel disease, periapical periodontitis, ulcerative colitis

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Address for correspondence:

Arwa Al-Maswary
 Department of Restorative and Aesthetic Dentistry, Faculty of Dentistry, Sana'a University, Sana'a, Yemen/Department of Dentistry, Faculty of Dentistry, Ar-Rasheed Smart University, Sana'a, Yemen
 E-mail: arwa2008.dent@gmail.com

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HIGHLIGHTS

- The patients with inflammatory bowel disease (IBD) had a greater mean number of teeth with apical periodontitis.
- There is a potential relationship between oral inflammatory pathology and systemic health status, including IBD.
- Doctors and dentists should pay more attention to the oral health of these IBD patients to avoid dental infection consequences.

INTRODUCTION

Apical periodontitis (AP) is a pathological term that describes a local chronic inflammatory disease affecting the periradicular area surrounding the root apex caused by microbial infection of the root canal system (1). Worldwide, AP affects more than half of the adult population (52% at the individual level and 5% at the tooth level) (2). AP can be symptomatic, causing variable dentoalveolar manifestations, or asymptomatic, and appears incidentally in radiographs in routine dental visits (3, 4).

AP has been associated with many systemic diseases, such as cardiovascular disease (5), diabetes mellitus (6), and inflammatory bowel disease (IBD) (7, 8). Studies have reported a higher prevalence of AP (9, 10), dental caries (11), and periodontal disease (12) in IBD patients compared to healthy control individuals.

IBD includes two main phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). Both are multifactorial, idiopathic, chronic, recurrent inflammatory processes of the gastrointestinal tract. IBD is characterised by diffuse inflammation, causing clinical episodes reflective of intestinal inflammation (13). The imbalance of pro-inflammatory and anti-inflammatory factors describes the mainstay of IBD pathogenicity (14, 15). However, many factors are also involved in IBD pathogenicity, such as environmental factors, gut microbiota, host genetic factors, and abnormal inflammatory and immune responses (16). During the active phase of the disease, patients tend to produce high levels of pro-inflammatory molecules (17), which could favour the development of AP (18). Perhaps quite the opposite, a predisposition of a patient to oral infections such as AP may influence the risk of getting IBD (19).

Immunosuppressive therapeutics such as corticosteroids or disease-modifying anti-inflammatory drugs are the first line of treatment in patients with IBD (20). Currently, biologic medications (BMs) are used, and they are recombinant human proteins with immune regulatory effects (21). The mode of action of BMs is mainly by modulation of pro-inflammatory cytokines. Indeed, anti-TNF agents have been reported to achieve disease remission (22). It has been suggested that the activation of the pro-inflammatory cascade associated with immune-modulating therapy may improve the response of AP to endodontic treatment, where two studies showed faster healing of AP after root canal therapy (RCT) in patients taking BMs (23, 24).

The available information about the interrelation between oral inflammatory pathology and systemic health status should promote greater attention to the oral health of these patients among physicians and dentists. Therefore, this systematic review and meta-analysis aimed to answer the question: Is there any potential association between IBD and AP?

MATERIALS AND METHODS

Eligibility Criteria

The present systematic review was carried out in full compliance with the PRISMA 2020 statement and PECOS principles. The protocol was registered in PROSPERO (CRD42022347756).

The PECOS-based criteria were: P (Patients): individuals aged 18 years or older; E (Exposure): the presence of IBD; C (Control): healthy individuals; O (Outcomes): occurrence of pulpal-periapical pathology (AP); S (Study design): cohort or case-control studies. Exclusion criteria included experimental studies, uncontrolled studies, case series, reviews, editorials, and lack of data on the outcome of interest.

Search Strategy and Information Sources

A bibliographic search was conducted in four electronic databases (PubMed, Scopus, Web of Science, and Google Scholar) for all relevant studies published from inception until August 2022 and updated on 27 April 2023. The following MeSH terms and free keywords were used: ("irritable bowel disease" OR "inflammatory bowel disease" OR "Crohn's disease*" OR "ulcerative colitis" AND ("periapical periodontitis" OR "apical periodontitis" OR "apical abscess" OR "endodontic infection"). The detailed search strategy is presented in (Appendix 1). Additionally, the references of the included studies were explored manually to search for additional relevant articles. The retrieved studies were exported to EndNote Reference Management Software (Clarivate Analytics, London, UK), and duplicate studies were removed. Two reviewers (SA and RB) independently screened the record titles and abstracts against the eligibility criteria and excluded irrelevant studies. After that, full texts of potentially eligible studies were sought and carefully scrutinised by the two reviewers.

Data Extraction

Two investigators (AA and GA) extracted all the data of interest using specific tables. The following data were abstracted: author(s), year of publication, country, study design, study groups, sample size, age, gender, the incidence or prevalence of AP, and diagnostic criteria for the main outcomes (AP). Some details regarding the prevalence of AP were obtained from authors via email contact.

Quality Assessment

Two investigators (AA and GA) assessed the quality of selected studies using the Newcastle-Ottawa Scale (NOS) (25). The quality of the included studies was evaluated based on three domains: selection, comparability, and exposure for the case-control studies or outcome for the cohort study. There are items for each domain. The selection domain, for example, has items relevant to the independent validation of the cases, selection of non-exposed "healthy" controls from the same community, and the controls are defined with no history of disease (See the NOS items for assessment of the case-control and cohort studies in Appendix 2). Each item is awarded a star, and the number of stars obtained for each study reflects the degree of the quality. Accordingly, the studies were assessed as either high quality (7–9 stars), moderate (4–6 stars), or low quality (0–3 stars).

Meta-analysis

Comprehensive Meta-Analysis Version 2.2.064 (Borenstein, M., Hedges, L., Higgins, J., and Rothstein, H. Biostat, Englewood, NJ 2011) was used for the meta-analysis. The pooled odds ratios (ORs) along with 95% confidence intervals (CIs)

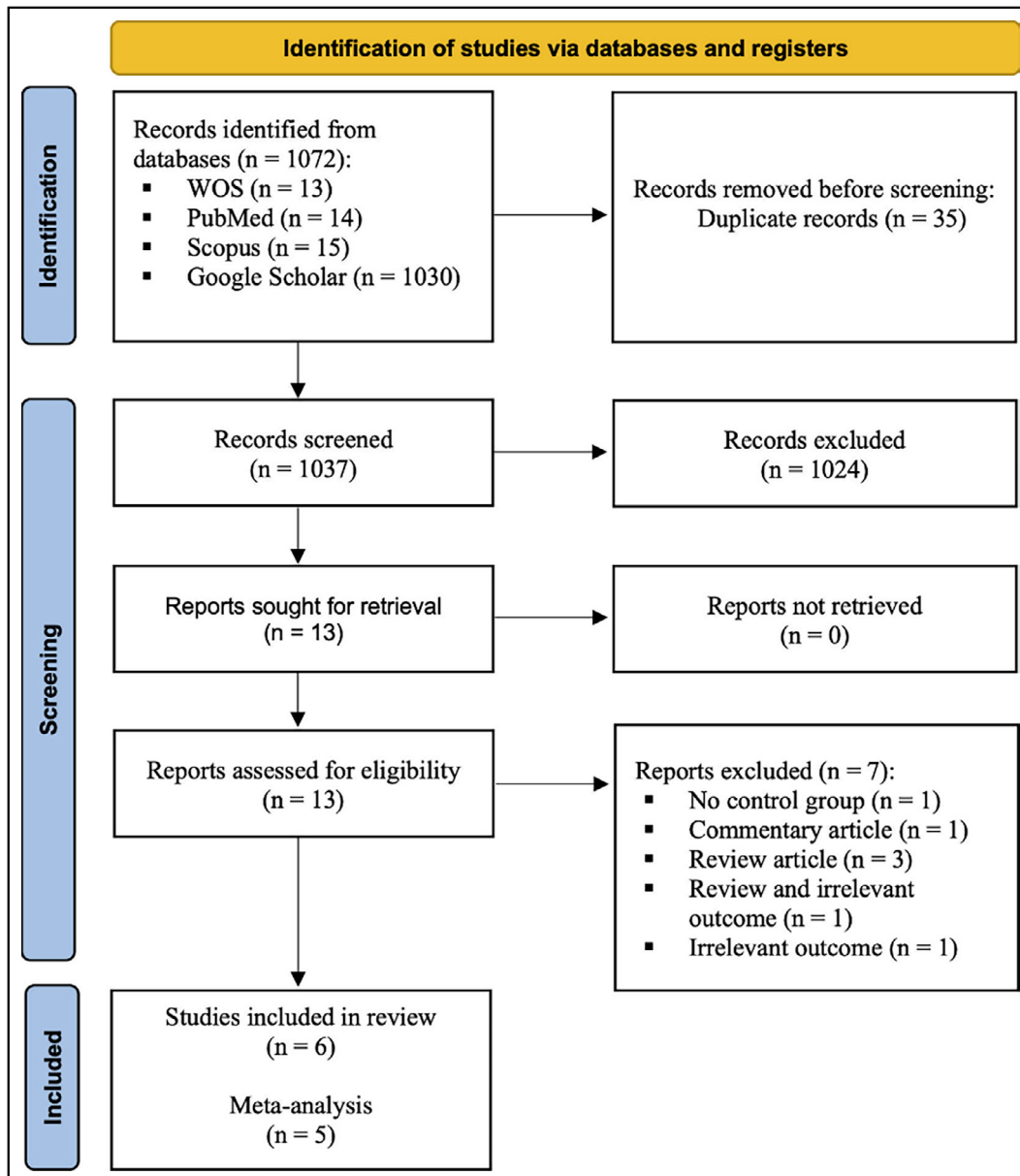


Figure 1. Flowchart of the study search strategy

were used to calculate the risk of AP and root-filled teeth with AP (RFT-AP) in IBD patients and control subjects. Heterogeneity was evaluated using the Chi-square test and the I^2 statistics. The “fixed-effects” model was used, given the low or moderate heterogeneity ($I^2 \leq 50\%$).

Certainty of Evidence

The certainty of evidence of the meta-analysis outcomes was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations tool [GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from <https://www.gradepro.org>]) (26). This grading tool assesses five domains (risk of bias, inconsistency, indirectness, imprecision, and other considerations), which can downgrade the certainty of the evidence. At the same time, the presence of other factors, such as the large magnitude of effect and dose-response gradient, can upgrade the certainty of the evidence (27).

RESULTS

Study Selection

The search strategy is depicted in Figure 1. A total of 1072 records were retrieved, 35 of which were duplicates. The remaining 1037 studies were screened independently by two investigators (SA and RB), and 1024 were excluded because they did not meet the eligibility criteria. The remaining 13 studies were evaluated independently by the two investigators. Of these, seven articles were excluded for various reasons (See the studies and reasons in Appendix 3). The remaining six studies were included and processed for data extraction.

General Characteristics of the Included Studies

Six studies (7, 9, 10, 28–30) were included. A total of 657 subjects (277 IBD) were included in 5 case-control studies (7, 9, 10, 28, 29), and 48,223 (35,740 and 12,483 were with and without AP, respectively) were included in the cohort study, where

188 of them (136 and 52, respectively) developed IBD after >9 years of follow-up (30) (Table 1). The six included studies were conducted in four different countries as follows: two studies in Italy (7, 9), two studies in Spain (10, 28), one study in the UK (29), and one study in Finland (30). The number of IBD participants in the case-control studies ranged from 16 (29) to 110 (9). The age of participants ranged from 18 to 90 years old. All studies included male and female participants (Table 1). Two studies confirmed the diagnosis of IBD cases by the international investigational protocols and Montreal classification of IBD (10, 28), one study by international investigational protocols alone (9), one study by records of drug reimbursement and International Classification of Diseases (30), and two studies relied on medical records without specifying the method of IBD confirmation (7, 29) (Appendix 4). The duration of IBD disease ranged from 2.6 to 24.7 years (Table 1).

AP Parameter

The parameter of AP (the main outcome) was the presence of periapical lesion measured by the periapical index (PAI) in four included studies (7, 9, 10, 28) and decayed, missing, and filled teeth (DMFT) index as a predictor of AP in two studies (29, 30) (Appendix 4). Ascertainment of AP status was assessed by either digital panoramic radiographs alone (10, 28–30) or panoramic and periapical radiographs (7, 9) (Appendix 4). The inter-observer agreement in all included case-control studies was high. The Kappa value ranged from 0.66 (29) to 0.89 (28). Similarly, the intra-observer agreement (Kappa) was also high, ranging from 0.66 (29) to 0.93 (10).

Qualitative Outcomes

Four studies (7, 10, 28, 29) demonstrated significant associations between AP and IBD (higher prevalence of AP in IBD patients). Meanwhile, one study reported an insignificant association between AP and IBD (9). In contrast, one large-scale cohort study reported no association between AP and the development of IBD (30). Taken individually, Poyato-Borrego et al. (10), in their case-control study, investigated the association between AP and IBD among 108 Spanish participants. The authors observed a significantly higher AP prevalence ($p=0.03$) but an insignificant higher number of RFT-AP in IBD participants ($p=0.39$). Another case-control study by Segura-Sampedro et al. (28) assessed the association between AP and IBD among 56 Spanish participants and showed a significantly higher number of RFT-AP in IBD patients ($p=0.001$). Although the prevalence of AP in IBD participants was higher, the difference was not statistically significant ($p=0.08$). In their case-control study of 198 Italian participants, Ideo et al. (7) assessed the association between AP and autoimmune (AI) diseases, including IBD, and found a significantly higher prevalence of AP in AI participants compared with the controls ($p=0.007$) and the highest prevalence of teeth with AP was recorded among IBD participants (113 out of 1758 teeth). A similar case-control study on 178 UK participants conducted by Allahaibi et al. (29) showed a significantly higher prevalence of AP in the autoimmune diseases (AI) group compared with the control group at the patient level ($p=0.015$) and at tooth level ($p=0.005$). However, IBD demonstrated the lowest risk among the tested AI diseases ($p=0.047$). In contrast, in another retrospective case-

control study on 220 Italians, Piras et al. (9) failed to find a significant association between AP and IBD ($p=0.489$). However, the authors found a significant difference in the mean number of teeth with AP in IBD female participants compared to healthy female participants ($p=0.042$). Surprisingly, the authors reported a significantly larger AP lesion size in IBD participants ($p=0.0001$). Heikkilä et al. (30) conducted a large-scale cohort study in Finland that included at baseline 48,223 participants; 35740 and 12483 were with and without AP, respectively. After > 9 years of follow up, 136 participants with AP and 52 participants without AP developed IBD. The incidence rate ratio of AP in IBD was 0.89, 95% CI: 0.61–1.31, suggestive of no association of the presence of AP at baseline with the incidence of IBD after over 9 years of follow-up.

Quality of the Studies

NOS-based results demonstrated that the included studies were of moderate to high quality: one study was of moderate quality (29), and five studies were of high quality (7, 9, 10, 28, 30), with a total score ranging from 6 to 8 stars (Table 2). The results of the detailed assessment of the studies per each NOS domain have been demonstrated in Appendix 5a and b.

Meta-analysis

Five case-control studies (7, 9, 10, 28, 29) with 657 subjects (277 with IBD and 380 controls) were included in a meta-analysis regarding the prevalence of AP and showed that it was significantly more likely to occur in IBD (OR=1.71, 95% CI: 1.21 – 2.42, $p=0.002$) compared to the controls (fixed effect model, $I^2=10.337\%$, $p=0.347$) (Fig. 2). Moreover, three case-control studies (7, 10, 28) with 195 RFT in IBD patients and 218 RFT in controls revealed higher RFT-AP among IBD (OR=2.70, 95% CI: 1.77 – 4.12, $p<0.001$) compared to the controls (fixed effect model, $I^2=21.818\%$, $p=0.278$) (Fig. 3).

Certainty of the Evidence

The GRADE assessment demonstrated a moderate certainty of the evidence in the measured outcomes (Table 3). The overall quality of the evidence for association between IBD and AP or RFT-AP outcomes was downgraded due to the presence of confounding factors in the included studies. The initial quality of the evidence for association between IBD and RFT-AP outcome was also downgraded due to serious imprecision (see the footnote of Table 3), but the strong association between the RFT-AP and IBD (large effect: more than two) upgraded this outcome to become a moderate.

DISCUSSION

Converging and reproducible evidence on the association between oral and systemic diseases continues growing. IBD is not an exception. Indeed, many recent systematic reviews reported higher prevalence rates of caries (13, 31), periodontitis (13, 32, 33), and specific and nonspecific oral lesions (34, 35) among IBD patients. Similarly, many systematic reviews showed that AP is associated with cardiovascular diseases (36, 37), diabetes (30), adverse pregnancy outcomes (38), autoimmune diseases (39), and other systemic diseases (40). In particular, two systematic reviews (39, 41) have been published in 2021, suggesting a correlation between autoimmune diseases

TABLE 1. Characteristics of included studies

Author and date Country	Study design	Cases (IBD patients)			Control (normal subjects)			Main results
		Number (CD/UC)	Age range (mean±SD) M/F	Duration of disease (mean±SD year) (CD/UC)	Number	Age range (mean±SD) M/F		
Piras et al., 2017 (9) Italy	Case-control study	110 (NA)	18–70 (46±13.8) 49/61	12±7.5	110	18–70 (41±13.1) 53/57	There was an insignificant higher percentage of AP in the IBD group. However, a significantly higher number of teeth with AP (p<0.05) was observed in women with IBD.	
Poyato-Borrego et al., 2020 (10) Spain	Case-control study	54 (28/26)	>18 (43.1±14.0) 31/23	NA	54	>18 (43.1±13.8) 31/23	IBD disease was associated with a higher prevalence of AP compared to controls. However, no differences were found in the number of teeth with AP or the number of RFTs (p>0.05).	
Ideo et al., 2022 (7) Italy	Case-control study	69 (NA)	18–90 (47±13.2) 29/40	11.6±9	99	18–90 (48±15.8) 42/57	IBD showed a higher prevalence of AP than healthy controls. IBD patients had the highest prevalence of AP among all AI subgroups. Also, a significant higher number of teeth with AP (p<0.05) was observed in IBD patients.	
Segura-Sampedro et al., 2022 (28) Spain	Case-control study	28 (13/15)	>18 (59.1±10.9) 8/20	(13.7±8.3/ 14.7±10.0)	28	>18 (58.6±11.9) 8/20	IBD was associated with a higher prevalence of RFT and a higher percentage of RFT with periapical lesions. AP was not associated with the incidence of IBD.	
Heikkilä et al., 2022 (30) Finland	Cohort study	35740 with AP were followed for >9 years, and 52 of them developed IBD (4.27 per 1000 a year)	≥29 (NA)	NA	12483 without AP were followed for >9 years, and 136 of them developed IBD (3.85 per 1000 a year)	≥29 (NA)		
Allihaibi et al., 2023 (29) UK	Case-control study	16 (NA)	18–80 (49.5±14.7) NA	NA	89	18–80 (49.5±14.7) 37/52	Patients with IBD demonstrated a higher prevalence of AP than the control group, and DMFT was a predictor of AP prevalence.	

IBD: Inflammatory bowel disease, CD: Crohn's disease, UC: Ulcerative colitis, SD: Standard deviation, M: Male, F: Female, NA: Not available, AP: Apical periodontitis, RFT: Root-filled tooth or teeth, AI: Autoimmune diseases, DMFT: Decayed, missing, and filled teeth

TABLE 2. NOS-based quality appraisal results

Study	Selection (4)	Comparability (2)	Exposure or outcome (3)	Total score (9)	Quality
Piras et al., 2017 (9)	4	1	2	7	High
Poyato-Borrego et al., 2020 (10)	4	2	2	8	High
Ideo et al., 2022 (7)	3	2	2	7	High
Segura-Sampedro et al., 2022 (28)	4	2	2	8	High
Heikkila et al., 2022 [#] (30)	3	2 [†]	3	8	High
Allihaibi et al., 2023 (29)	2	2	2	6	Moderate

[#]: Assessed by the same NOS-based quality assessment scale but for cohort study, [†]: Patients with and without apical periodontitis were followed for >9 years, and the incident IBD cases were compared. NOS: Newcastle-Ottawa Scale, IBD: Inflammatory bowel diseases

(including IBD) and AP. In this context, since recent original studies (7, 28, 29) have been published in 2022 and 2023 and no meta-analysis on this issue has been conducted so far, to the best of our knowledge, and the presence of inconsistencies in the level of significance or the outcomes of the published studies (Table 1), the need for the current systematic review and meta-analysis is justified.

Based on the qualitative analysis of this systematic review, four studies (7, 10, 28, 29) out of the six included studies reported significant associations between AP and IBD and the other two studies showed either insignificant association (9) or no association (30) between AP and IBD, indicating little evidence for the association between AP and IBD. Such inconsistent results among the included studies may occur due to differences in sample size, the presence of confounding factors or both (42, 43). However, based on the quantitative analysis (meta-analysis), AP and IBD are correlated: IBD patients are significantly more likely to have AP (OR=1.71, 95% CI: 1.21 – 2.42, p<0.01)

compared to the healthy control and IBD patients have significantly more RFT-AP compared to the healthy control (OR=2.70, 95% CI: 1.77–4.12, p<0.001) with good or acceptable homogeneity across the included studies for AP and RFT-AP analyses (I²=10.34%, 21.82%, respectively). In addition, the assessment of the certainty of evidence revealed a moderate certainty, which emphasised the potential association between AP and IBD. However, interpretation of the results should be done with some caution, given the methodological limitations in the included studies discussed at the end of this section.

There is little evidence on the biological mechanism linking AP with IBD. It is a foregone conclusion that AP is the ultimate outcome of dental caries, and in many instances, AP develops at the expense of periodontal disease. Indeed, periodontitis has been reported as an independent factor for AP (44) and non-vital pulp (45). Although the treatments of AP and periodontitis are entirely different, they target the same aim: eradicating the causative microorganisms and the infected and necrotic

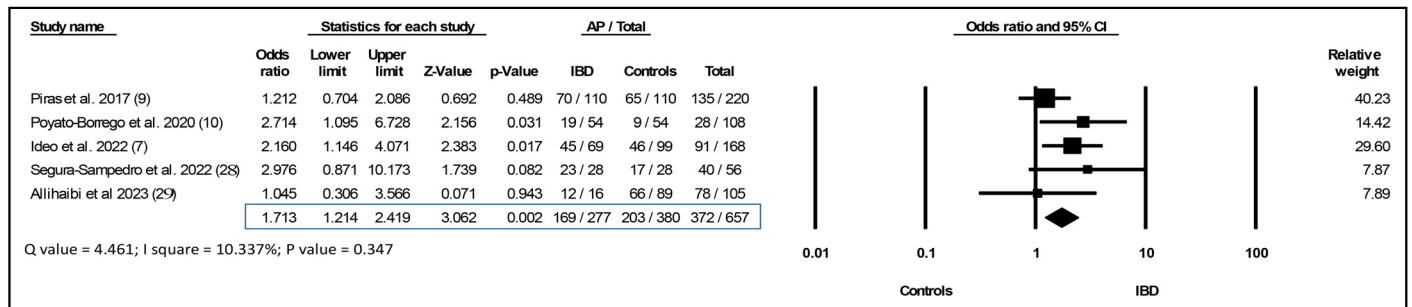


Figure 2. Meta-analysis of AP in IBD patients and controls

AP: Apical periodontitis, CI: Confidence interval, IBD: Inflammatory bowel diseases

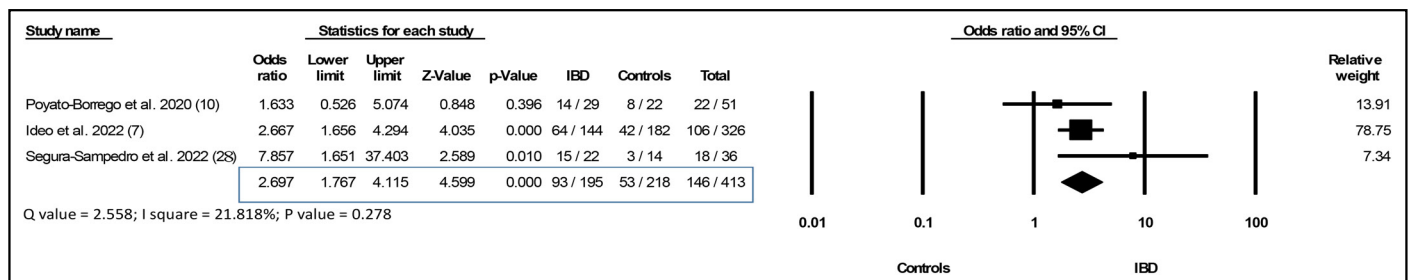


Figure 3. Meta-analysis of the RFT with AP out of all RFT among patients with IBD and controls

IBD: Inflammatory bowel diseases, CI: Confidence interval, RFT: Root-filled teeth, AP: Apical periodontitis

TABLE 3. The GRADE assessment results for the study outcomes

No of studies	Certainty assessment				No of patients	Effect		Certainty	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness		Imprecision	Other considerations			IBD
AP in IBD patients and controls (follow-up: range 2 years to 9 years; assessed with panoramic radiographs, intraoral radiographs, or both)										
5	Observational studies	Not serious	Not serious	Not serious	169/277 (61.0%)	203/380 (53.4%)	OR 1.71 (1.21 to 2.42)	128 more per 1,000 (from 47 more to 201 more)	⊕⊕○○ Moderate	Critical
RFT with AP in IBD and controls (follow-up: range 2 years to 4 years; assessed with panoramic radiographs, intraoral radiographs, or both)										
3	Observational studies	Not serious	Not serious	Serious ^{ab}	93/195 (47.7%)	53/218 (24.3%)	OR 2.70 (1.77 to 4.12)	221 more per 1,000 (from 119 more to 326 more)	⊕⊕○○ Moderate	Important

^a: Few events do not meet the optimal information size, suggesting weakness in the estimate. ^b: Wide confidence interval may cause uncertainty about the magnitude of the effect. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations, IBD: inflammatory bowel diseases, CI: Confidence interval, AP: Apical periodontitis, OR: odds ratio, RFT: Root-filled tooth or teeth

tissue, hoping to provide an ideal environment for healing. The etiopathogenesis mechanisms of both diseases overlap considerably: almost common microbial elements trigger a complex inflammatory immune response, ultimately resulting in bone destruction (46). Accordingly, it seems plausible that the proven and proposed mechanisms published so far in the context of the potential association of periodontitis and IBD also apply in the context of the potential association of AP and IBD.

The available evidence in the literature may not be sufficient to infer a causal relation between oral health (including AP) and IBD. Instead, a bidirectional correlation between them has been suggested, bringing a question into the scene: What comes first, the IBD or the AP? Hence, an unresolved question is whether AP is a cause, a consequence, or just a kind of coincident disease with IBD. Besides that, the results of the published follow-up studies were inconsistent. In a cohort study involving 20,162 individuals in Sweden who were followed for 40 years, the authors reported better oral health parameters (tooth loss, plaque) among 206 individuals who were diagnosed with IBD, suggesting unexpectedly a protective effect for poor oral health (47). On the contrary, the risk of developing periodontitis was higher among 6657 CD patients compared to 26,628 matched non-IBD controls (48). The results of animal studies were consistent with the latter study in which alveolar bone loss and even periodontitis have been reported to occur spontaneously in murine models of IBD (49) and Crohn's disease (50), respectively; the alveolar bone loss was proportional to intestinal inflammation rather than that of periodontium (49). In their turn, many studies, including the five studies included in this meta-analysis (7, 9, 10, 28, 29), almost consistently suggest an increased risk for poor oral health among IBD patients (13, 31).

Oral-gut microbiome axis is a new concept where oral-to-gut and gut-to-oral microbial transmissions or translocation contribute to shaping or reshaping both microbial ecosystems, modulating eventually the pathogenesis of diseases in these habitats (51, 52) and even diseases in distant sites (52). Although the acidic medium of the stomach and the highly competitive gut microbiome render the gut resistant to colonisation, some microbiological studies detected oral bacteria in the intestinal biopsies or stools of IBD patients (53, 54). More specifically, paediatric patients with UC showed depletion of core gut microbes at the expense of the expansion of bacteria, which is typical of the oral cavity (55). The chance of colonisation of the gut by oral bacteria increases in cases of chronic oral infections (oral dysbiosis) (56), such as AP, particularly in susceptible hosts (57). In a mouse experimental model,

infection of dental pulp by *Porphyromonas gingivalis*, a keystone oral bacterium, induced chronic AP, which in turn led to dysbiosis of the gut microbiome, along with aggravating experimentally-induced atherosclerosis (58). Colonisation of the gut by oral bacteria, irrespective of the route of transmission or translocation, oral-gut, lymphatic or haematogenous, and the release of their toxins are not the sole mechanisms through which oral dysbiosis induces disease processes elsewhere. Another, perhaps more powerful, yet related mechanism is through instigating both arms of immunity (innate and adaptive) with the subsequent firing of inflammation (59). Kitamoto et al. (59) provided a murine model to investigate the pathogenesis of periodontitis and colitis as follows: Periodontitis triggers the expansion of oral bacteria, which helps to fasten ectopic colonisation of the gut and induction of colitis through IL-1 β . T helper 17 cells are activated in periodontal inflammation; these cells migrate to the gut, contributing to colitis through interaction mainly with the ectopic oral bacteria (59). Worth mentioning is that T helper cells are activated through almost similar pathways in the context of AP (60, 61). Gut innate and adaptive immune responses to ectopic oral bacteria and the resultant outcompeted gut microbiome cannot be overlooked. Indeed, ectopic colonisation of the gut by bacteria of oral origin causes the expansion of colitogenic T cell-promoting colitis in susceptible hosts (62).

Based on the argument above, the association between IBD and oral conditions, including AP, probably starts in a feedback mechanism and might end in a feedforward one, causing a vicious cycle. Similar to periodontitis, AP causes low-grade systemic inflammation and increases the systemic levels of inflammatory markers (40, 63) mainly through elevation of C-reactive protein, interleukins 1, 2 and 6, asymmetric dimethylarginine, C3, and IgA, IgG, and IgM levels (63, 64). AP also causes bacteraemia (40). Both contribute negatively to systemic health (40, 63, 64) and vice versa (65). Accordingly, the bidirectional association between AP and many systemic diseases is not surprising; instead, it is increasingly gaining interest among dental and medical researchers.

Although it is the first systematic review with meta-analysis that sought to elucidate the potential association between IBD and AP, the evidence provided must be dealt with cautiously given the following limitations that must be accounted for. The number of the included studies is few, irrespective of the homogeneity of the main outcome. Similarly, the pooled sample size in the meta-analysis is small. In addition, the presence of confounding factors that may overestimate or underestimate the effect magnitude (43). Thus, these limitations may reduce the overall strength of the evidence for the association between IBD disease and AP prevalence.

CONCLUSION

To sum up, the available evidence indicates that IBD may be associated with AP. However, further, well-designed, large-scale, prospective cohort studies are highly warranted to stand on conclusive evidence. Studies on animal models where AP is considered as exposure and outcome alternately are encouraged.

Disclosures

Online Appendix Files: [https://jag.journalagent.com/eurendodj/abs_files/EEJ-74507/EEJ-74507_\(0\)_FINAL_EEJ-2023-05-057_\(2\)_edit_appendix.pdf](https://jag.journalagent.com/eurendodj/abs_files/EEJ-74507/EEJ-74507_(0)_FINAL_EEJ-2023-05-057_(2)_edit_appendix.pdf)

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