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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/E-mail: arwa2008.dent@gmail.com

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 ABDULRAB7

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=10.33%, 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

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 interrelationship 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).

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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 I² statistics. The “fixed-effects” model was used, given the low or moderate heterogeneity (I² ≤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 Allihaibi 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). Heikkila 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, I²=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, I²=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>
<thead>
<tr>
<th>Author and date</th>
<th>Study design</th>
<th>Cases (IBD patients)</th>
<th>Control (normal subjects)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number (CD/UC)</td>
<td>Age range (mean±SD) M/F</td>
<td>Duration of disease (mean±SD year) (CD/UC)</td>
</tr>
<tr>
<td>Piras et al., 2017 (9) Italy</td>
<td>Case-control study</td>
<td>110 (NA)</td>
<td>18–70 (46±13.8) 49/61</td>
<td>12±7.5</td>
</tr>
<tr>
<td>Poyato-Borrego et al., 2020 (10) Spain</td>
<td>Case-control study</td>
<td>54 (28/26)</td>
<td>&gt;18 (43.1±14.0) 31/23</td>
<td>NA</td>
</tr>
<tr>
<td>Ideo et al., 2022 (7) Italy</td>
<td>Case-control study</td>
<td>69 (NA)</td>
<td>18–90 (47±13.2) 29/40</td>
<td>11.6±9</td>
</tr>
<tr>
<td>Segura-Sampedro et al., 2022 (28) Spain</td>
<td>Case-control study</td>
<td>28 (13/15)</td>
<td>&gt;18 (59.1±10.9) 8/20</td>
<td>(13.7±8.3/ 14.7±10.0)</td>
</tr>
<tr>
<td>Heikkila et al., 2022 (30) Finland</td>
<td>Cohort study</td>
<td>35740 with AP ≥29 (NA)</td>
<td>≥29 (NA)</td>
<td>NA</td>
</tr>
<tr>
<td>Allihaibi et al., 2023 (29) UK</td>
<td>Case-control study</td>
<td>16 (NA)</td>
<td>18–80 (49.5±14.7) NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Main results**

- 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.
- 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).
- 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.
- 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.

**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
Halboub et al. Association between Inflammatory Bowel Diseases and Apical Periodontitis

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 ($I^2=10.34\%, 21.82\%$, 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 tissues.

**TABLE 2.** NOS-based quality appraisal results

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Selection (4)</th>
<th>Comparability (2)</th>
<th>Exposure or Outcome (3)</th>
<th>Total Score (9)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piras et al., 2017 (9)</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>High</td>
</tr>
<tr>
<td>Poyato-Borrego et al., 2020 (10)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Ideo et al., 2022 (7)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>High</td>
</tr>
<tr>
<td>Segura-Sampedro et al., 2022 (28)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Heikkila et al., 2022* (30)</td>
<td>3</td>
<td>2*</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Allihaibi et al., 2023 (29)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*: 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

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 tissues.

**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
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 key-
stone 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 transmis-
ion 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 else-
where. Another, perhaps more powerful, yet related mecha-
nistic 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: Peri-
odontitis triggers the expansion of oral bacteria, which helps
to fasten ectopic colonisation of the gut and induction of col-
itis through IL-1β. 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 bacte-
rria (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 can-
not 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 feed-
bback mechanism and might end in a feedback 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 dimethy-
larginine, C3, and IgA, IgG, and IgM levels (63, 64). AP also
causes bacteraemia (40). Both contribute negatively to sys-
tem health (40, 63, 64) and vice versa (65). Accordingly, the
bidirectional association between AP and many systemic dis-
eases is not surprising; instead, it is increasingly gaining inter-
est 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 sam-
ple size in the meta-analysis is small. In addition, the presence
of confounding factors that may overestimate or underesti-
mate 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 alter-
nately are encouraged.

Disclosures

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

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REFERENCES

1. Nair PN. Apical periodontitis: a dynamic encounter between root canal
2. Tiburcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier
CA. The global prevalence of apical periodontitis: a systematic review
3. Bender IB, Seltzer S. Roentgenographic and direct observation of exper-
4. American Association of Endodontists; American Academy of Oral
Maxillofacial and Radiology. Use of cone-beam computed tomography
in endodontics Joint Position Statement of the American Association
of Endodontists and the American Academy of Oral and Maxillofacial
Association of endodontic lesions with coronary artery disease. J Dent
n-Gonzalez J, Velasco-Ortega E, et al. Diabetes mellitus, periapical in-
flammation and endodontic treatment outcome. Med Oral Patol Oral Cir
7. Ido F, Niazi S, Mezzena S, Mannocci F, Cotti E. Prevalence of apical peri-
odontitis in patients with autoimmune diseases under immunomodula-
MC, Cabanillas-Balsa D, Areal-Quecuty V, et al. Prevalence of endodon-
tic infection in patients with Crohn's disease and ulcerative colitis. Med
of apical periodontitis in patients with inflammatory bowel diseases: a
10. Poyato-Borrego M, Segura-Sampedro JJ, Martin-Gonzalez J, Torres-
Dominguez Y, Velasco-Ortega E, Segura-Egea JJ. High prevalence of apical
periodontitis in patients with inflammatory bowel disease: an age-
and gender-matched case-control study. Inflamm Bowel Dis 2020;
Prevalence of periodontitis and DMFT index in patients with Crohn's
12. Koutsoschristou V, Zellos A, Dimakou K, Panayotou I, Siahanidou S, Roma-
Giannikou E, et al. Dental caries and periodontal disease in children and
adolescents with inflammatory bowel disease: a case-control study. In-
J. Inflammatory bowel disease and oral health: systematic review and a
thelial-derived IL-33 and its receptor ST2 are dysregulated in ulcerative
colitis and in experimental TH1/TH2 driven enteritis. Proc Natl Acad Sci U
15. Cominelli F. Cytokine-based therapies for Crohn's disease—new para-
100(7):693–9.