


ORIGINAL ARTICLE

Periapical and endodontic status of patients with inflammatory bowel disease: Age- and sex-matched case-control study

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Abstract

Aim: Crohn's disease (CD) and ulcerative colitis (UC) are two chronic recurrent inflammatory processes of the gastrointestinal tract, grouped under the name inflammatory bowel disease (IBD), causing clinical episodes of intestinal inflammation. The aim of this study was to investigate the possible association between IBD and the prevalence of apical periodontitis (AP) and root canal treatment.

Methodology: A case-control study design matched to age and sex was used. The study group (SG) included 28 patients with IBD (13 with CD, 15 with UC). Another 28 healthy subjects, without IBD and age- and sex-matched, were included in the control group (CG). Radiographic records were analysed and AP was diagnosed as radiolucent periapical lesions (RPLs), using the periapical index score. Student's *t*-test, χ^2 test and multivariate logistic regression were used in the statistical analysis.

Results: In the CG, only 17 subjects (61%) had at least one tooth with AP, whilst in the SG group they were 23 patients (82%; OR = 2.98; 95% CI = 0.87–10.87; *p* = .08). The number of subjects with one or more root filled teeth (RFT) in the CG was 14 (50%), whilst in the SG they were 22 (79%; OR = 3.67; 95% CI = 1.14–11.79; *p* = .026). At least one RFT with AP was evident in three subjects (10.7%) in the CG, whilst in the SG 15 patients (53.6%) showed RFT with AP (OR = 9.60; 95% CI = 2.35–39.35; *p* = .001). In the multivariate logistic regression analysis, only endodontic status was found to be associated with IBD (OR = 1.86; 95% CI = 1.24–2.80; *p* = .003).

Conclusion: IBD, UC and Crohn's disease are associated with higher prevalence of RFT and higher percentage of RFT with periapical lesions. Dentists should consider these findings when caring for IBD patients by monitoring the evolution of periapical lesions of endodontically treated teeth.

KEYWORDS

apical periodontitis, Crohn's disease, inflammatory bowel disease, root canal treatment, ulcerative colitis

Correction added on 29th April 2022 after first online publication Corresponding author was added

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two chronic recurrent inflammatory processes of the gastrointestinal tract that are grouped under the name of inflammatory bowel diseases (IBD; Baumgart & Sandborn, 2012). In both diseases, there is diffuse inflammation of the intestinal mucosa, causing clinical episodes of intestinal inflammation. In CD, the terminal ileum is the most frequently affected site, although it can affect any segment of the gastrointestinal tract, from the mouth to the anus. In contrast, UC affects the large bowel, especially the distal colon (Papageorgiou et al., 2017). Oral manifestations are evident between 4% and 16% of patients with IBD, including mucosal oedema, linear ulceration, angular cheilitis and granulomatous gingivitis (Kalmar, 1994), also presenting a higher prevalence of caries (Brito et al., 2008) and periodontal disease (Koutsochristou et al., 2015). In the pathogenesis of IBD, host genetic factors, gut microbiota, environmental factors and, especially, abnormal inflammatory and immune responses are involved (Guan, 2019).

On the other hand, chronic apical periodontitis (AP) is radiographically characterized by a radiolucent image around the apex of the affected tooth resulting from inflammatory resorption of the alveolar bone (Liu et al., 2010). The prevalence of AP is high all over the world (Jiménez-Pinzón et al., 2004; López-López et al., 2011; Tibúrcio-Machado et al., 2021), being root canal treatment (RCT) the elective endodontic therapy for teeth affected by AP (Eriksen, 1998).

In recent years, numerous clinical studies and animal models focused on endodontic medicine (Segura-Egea et al., 2015) have been published, analysing the interrelationship between the pathological conditions of systemic and periapical tissues (Cintra et al., 2021). Moreover, several studies have reported statistical association between AP and systemic diseases in whose aetiology and pathogenesis the pro-inflammatory state of the patient is implicated, such as diabetes mellitus (Samuel et al., 2019; Segura-Egea et al., 2015, 2019) and cardiovascular disease (Liljestränd et al., 2016; Segura-Egea et al., 2011). Some epidemiological studies have also been published suggesting an association between endodontic status and diabetes (Limeira et al., 2020; Nagendrababu et al., 2020) or coronary heart disease (Lin et al., 2015; Sebring et al., 2021). However, in relation to IBD, in whose pathogenesis the pro-inflammatory status plays an important role, a limited number of studies (Piras et al., 2017; Poyato-Borrego et al., 2020) have investigated the possible association with AP or root canal treatment, with inconsistent results.

The purpose of this case-control study was to analyse the prevalence of AP and root canal treatment in

patients with IBD and healthy control patients. The null hypothesis was that there are no significant differences in these variables between control subjects and patients with IBD.

MATERIALS AND METHODS

Sample size calculation

The minimal sample size ($n = 28$) was calculated using the sample size calculator software of the National Center for Advancing Translational Sciences (NIH, UK; <http://www.sample-size.net/sample-size-proportions/>; National Center for Advancing Translational Sciences (NIH)) for comparison of proportions in two independent samples, with continuity correction. They were considered a two-sided significance level of 5% ($\alpha = 0.05$, $Z\alpha = 1.960$), and 80% power ($\beta = 0.20$, $Z\beta = 0.842$). The estimated prevalence of AP in the control group (CG) was 40% (Jiménez-Pinzón et al., 2004; López-López et al., 2012), whilst in the study group (SG) it was 75%.

Patients' selection

Participants were recruited amongst patients with IBD receiving dental treatment at the Hospital Odontològic de Bellvitge, Universitat de Barcelona (Barcelona, Spain) between the years 2018 and 2021. Subjects who reported a history of CD and UC, diagnosed according to international investigational protocols (Satsangi et al., 2006), and following the Montreal classification of IBD (Silverberg et al., 2005), were asked to voluntarily participate. Inclusion criteria were as follows: patients older than 18 years, with no history of diabetes, metabolic syndrome, cardiovascular disease or smoking, and who agreed to a radiological examination. Exclusion criteria included patients younger than 18 years, patients with diabetes, metabolic syndrome, cardiovascular disease, or smoking, or patients who disagreed with a radiological examination. Only one patient refused to participate. Once the minimum sample size ($n = 28$) was achieved, recruitment was terminated. A total of 28 patients, eight men and 20 women (59.1 ± 10.9 years), who agreed and met the inclusion/exclusion criteria constituted the "study group". Table 1 shows the diagnoses and clinical characteristics of the patients with IBD included in the SG, according to the Montreal classification (Satsangi et al., 2006). The number of patients with CD was 13 (46.4%), being 61.5% of type L1 (ileal). The rest of the group, 15 patients (53.6%), suffered from UC, being 60.0% of E2 type (left side of the colon). The mean time from disease onset was 13.7 ± 8.3 years in

TABLE 1 Distribution of patients in the experimental group (IBD) according to the type of disease (UC, ulcerative colitis; CD, Crohn's disease) and location, according to the Montreal classification (Satsangi et al., 2006)

IBD (<i>n</i> = 28)	Number (%)
Crohn's disease (<i>n</i> = 13; 46.4%)	
Location	
L1: Ileal	8 (61.5%)
L2: Colonic	2 (15.4%)
L3: Ileocolonic	3 (23.1%)
L4: Ileal and upper disease	0 (0.0%)
Age at diagnosis	
A1: <16 years	1 (7.7%)
A2: 16–40 years	6 (46.2%)
A3: >40 years	6 (46.2%)
Mean time since onset of the disease	13.7 ± 8.3 years
Ulcerative colitis (<i>n</i> = 15; 53.6%)	
Location	
E1: Rectum and sigmoid colon	1 (6.7%)
E2: Left side of colon	9 (60.0%)
E3: All of colon	5 (33.3%)
Mean time since onset of the disease	14.7 ± 10.0 years

patients with Crohn's disease and 14.7 ± 10.0 years in patients with UC.

An additional 28 subjects, eight men and 20 women (58.6 ± 11.9 years), who agreed and met the same inclusion/exclusion criteria, healthy and who reported no history of IBD, were matched for age and sex, constituting the “control group”. Controls were recruited from patients in the same city and health district, seeking for the first time routine dental care (not emergency care) in the same hospital between 2018 and 2021.

Radiographic examination

The radiographic periapical status was diagnosed based on the examination of digital panoramic radiographs of the jaws. Two trained radiographic technicians, with over 10 years of experience, took the panoramic radiographs using a digital ortho-pantomograph machine (Promax[®], Planmeca, class 1, type B, 80 KHz, Planmeca).

Radiographic evaluation

Periapical status was assessed using the “Periapical Index” (PAI) score (Orstavik et al., 1986), as described previously (López-López et al., 2012; Segura-Egea et al., 2011). A score

greater than two (PAI ≥ 3) was considered to be a sign of periapical pathology. The worst score of all roots was taken to represent the PAI score for multi-rooted teeth. Teeth were classified as root filled teeth (RFT) if they had been filled with radiopaque material in the root canal(s).

The following information was recorded in structured form for each subject: (a) number of teeth present; (b) number of teeth that have identifiable radiolucent periapical lesions (AP); and (c) number of RFT.

For analytical purposes, both AP and RFT variables were dichotomized as absent or ≥1 AP or RFT.

The presence of periodontal disease was evaluated radiographically assessing alveolar bone loss. The height of the alveolar bone crest was measured from a fixed reference point (the cemento-enamel junction) proximal to all available teeth. Subjects with alveolar bone loss ≥4 mm were considered periodontal patients (Oettinger-Barak et al., 2007).

Observers' calibration

Three blinded observers with extensive clinical experience in endodontics examined the radiographs. Before evaluation, the observers participated in a calibration course for the PAI system, which consisted of 100 radiographic images of teeth, some root-filled and some not, kindly provided by Dr. Ørstavik. Each tooth was assigned to one of the PAI scores by using visual references (also provided by Dr. Ørstavik) for the five categories within the scale (Orstavik et al., 1986). After scoring the teeth, the results were compared to a “gold standard atlas”, and a Cohen *Kappa* was calculated.

Intra-observer reproducibility was evaluated for each examiner. Every observer scored the panoramic radiographs of 10 patients (five of each group, randomly selected). Then, 1 month after this first examination, the observer was re-calibrated in the PAI system and repeated the scoring of the radiographs of the same 10 patients. The intra-observer agreement test on PAI scores on the 10 patients produced a Cohen's *Kappa* ranging 0.87–0.92.

The Cohen's *Kappa* for inter-observer variability ranged 0.77–0.89. The consensus radiographic standard was the simultaneous interpretation by the three examiners of the panoramic radiograph of each patient (Flint et al., 1998; Rushton et al., 2002).

Statistical analysis

The prevalence of AP and the frequency of RCT were evaluated on the total number of individuals and the total number of teeth.

Raw data was entered into Excel (Microsoft Corporation). All analyses were performed in an SPSS environment (Version 11; SPSS, Inc). Student's *t*-test, χ^2 test, and logistic regression analysis were used to determine the significance of differences between groups. Multivariate logistic regression analysis was carried out in phases. In the first phase, all the variables analysed were included in the analysis: age, sex, number of teeth, periapical status, and endodontic status. The results of this first analysis showed, as expected, that neither sex nor age had an influence, since the study was carried out matched by sex and age. Therefore, the only independent variables that were included in the second stage of the multivariate logistic regression analysis were number of teeth, periapical status, and endodontic status.

Data are reported as mean \pm standard deviation. According to the established significance level, a *p*-value $\leq .05$ was considered statistically significant.

RESULTS

Table 2 shows the distribution of the variables analysed in the two groups. No differences were found in the number of teeth between the SG (21.3 ± 5.7) and the CG (20.0 ± 5.1 ; $p > .05$). In the SG, the mean number of caries lesions was 2.4 ± 2.0 , whilst in the CG was 2.2 ± 1.7 ($p > .05$). In the SG, the number of teeth with AP was 2.3 ± 2.2 , whilst in the CG it was 1.4 ± 1.6 ($p = .086$). The number of RFT was higher in the SG (3.2 ± 2.6) compared to the CG (0.9 ± 1.3 ; $p = .0001$).

Taking the patient as a reference (Table 2), in the SG, 21.4% of the subjects had periodontal disease, whilst in the CG only 14.3% did ($p > .05$).

Twenty-three patients with IBD (82%) had at least one tooth with radiolucent periapical lesion (RPLs), whilst in the CG 17 subjects (61%) showed radiographic signs of AP (OR = 2.98; 95% CI = 0.87–10.17; $p = .076$).

The number of subjects with one or more RFT in the CG was 14 (50.0%) whilst in the SG they were 22 (78.6%; OR = 3.67; 95% CI = 1.14–11.79; $p = .026$). At least one RFT with AP was found in three subjects (10.7%) in the CG, whilst in the SG 15 patients (53.6%) showed RFT with AP (OR = 9.60; 95% CI = 2.35–39.35; $p = .001$).

To further analyse the possible association between endodontic variables and IBD, multivariate logistic regressions were run. In the multivariate analysis, including the number of teeth, number of carious teeth, periodontal status, periapical status, and endodontic status as independent variables, and taking as dependent variable the status of IBD (Table 3), only endodontic status was shown to be associated with IBD (OR = 1.86; 95% CI = 1.24–2.80; $p = .003$). Periapical status was not significantly associated

with IBD (OR = 1.03; 95% CI = 0.69–1.54; $p = .88$). Caries ($p = .89$) and periodontal disease ($p = .38$) were not associated with IBD.

DISCUSSION

This age- and sex-matched case-control study has investigated the relationship of periapical and endodontic status with IBD, a pathology that encompasses UC and CD, two highly prevalent chronic inflammatory intestinal diseases. The results show that in IBD patients, the number of RFT is significantly higher than in controls, being almost four times more likely to find a patient with an RFT in the group of patients with IBD.

This case-control study followed the STROBE guidelines for observational studies (Vandenbroucke et al., 2007; Von Elm et al., 2007). The sample size was determined according to the principles of theoretical sufficiency. Patients and controls were recruited using a method similar to that used in previous studies (Piras et al., 2017; Sánchez-Domínguez et al., 2015). Only one patient refused to participate; therefore, selection bias can be ruled out. As it was a study matched by age and sex, there were no significant differences in these variables between CG and SG. Moreover, the two groups also had a similar mean number of teeth, also ruling out the bias caused by this variable.

For the diagnosis of CD and UC the current criteria were carried out (Satsangi et al., 2006; Silverberg et al., 2005). The high percentage of patients with isolated ileal disease is striking, but has also been found in other studies carried out in the Spanish population (Rodríguez-Lago et al., 2018).

The "PAI" scoring system (Orstavik et al., 1986) has been used to assess the periapical status. PAI has been widely used in epidemiological and clinical studies (Kirkevang et al., 2017; Kumar et al., 2020; Tibúrcio-Machado et al., 2021). Although PAI was originally proposed to be applied using periapical radiographs, panoramic radiographs have been widely used to assess periapical status using PAI (Gomes et al., 2016; Liljestrand et al., 2021; López-López et al., 2012) or other indices (Liljestrand et al., 2016). Although panoramic radiographs have shown good diagnostic accuracy and high specificity in assessing AP (Nardi et al., 2018), the use of panoramic radiographs has been correlated with an underestimation of the number of periapical lesions (Eriksen & Bjertness, 1991). However, the difference between periapical and panoramic radiographs is not statistically significant (Molander et al., 1995; Ridao-Sacie et al., 2007). On the other hand, panoramic radiography has the advantages over periapical radiographs of showing all teeth, reducing the patient's

TABLE 2 Distribution of analysed variables amongst patients with IBD (SG) and normal subjects (CG)

	SG <i>n</i> = 28	CG <i>n</i> = 28	Total <i>n</i> = 56	<i>p</i> value/ OR
Age/years				<i>t</i> -test
Mean ± SD	59.1 ± 10.9	58.6 ± 11.9	58.8 ± 11.3	>0.05
Sex (<i>n</i> , %)				χ^2 test
Male	8 (28.6)	8 (28.6)	16 (28.6)	>0.05
Female	20 (71.4)	20 (71.4)	40 (71.4)	
No. of teeth				<i>t</i> -test
Mean ± SD	21.3 ± 5.7	20.0 ± 5.1	20.6 ± 5.4	>0.05
Median	23	20	21	
Carious teeth				<i>t</i> -test
Mean ± SD	2.4 ± 2.0	2.2 ± 1.7	2.3 ± 1.9	>0.05
Median	2	2	2	
Periodontal disease				χ^2 test
Any	6 (21.4)	4 (14.3)	10 (17.9)	>0.05
None	22 (78.6)	24 (85.7)	46 (82.1)	
OR				1.63
95% CI				0.41–6.58
Teeth with AP				χ^2 test
Any	23 (82.1)	17 (60.7)	40 (71.4)	= 0.076
None	5 (17.9)	11 (39.3)	16 (28.6)	
OR				2.98
95% CI				0.87–10.17
No. of teeth with AP				<i>t</i> -test
Mean ± SD	2.3 ± 2.2	1.4 ± 1.6	1.9 ± 2.0	= 0.086
Median	2	1	1	
RFT				χ^2 test
Any	22 (78.6)	14 (50.0)	36 (64.3)	= 0.026
None	6 (21.4)	14 (50.0)	20 (35.7)	
OR				3.67
95% CI				1.14–11.79
No. of RFT				<i>t</i> -test
Mean ± SD	3.2 ± 2.6	0.9 ± 1.3	2.1 ± 2.3	= 0.0001
Median	3	0.5	1	
RFT-AP				χ^2 test
Any	15 (53.6)	3 (10.7)	18 (32.1)	= 0.001
None	13 (46.4)	25 (89.3)	38 (67.9)	
OR				9.60
95% CI				2.35–39.35

Odds ratio (OR) values, and their 95% confidence interval (CI), have been estimated using χ^2 test.

Abbreviations: AP, apical periodontitis; OR, odds ratio; RFT, root filled teeth; RFT-AP, root filled teeth with AP.

exposure to ionizing radiation (Molander et al., 1995), faster acquisition, and convenience (Gulsahi et al., 2008).

The results of the present study show a significantly higher prevalence of RFT in patients with IBD (3.2 ± 2.6) compared to healthy control patients (0.9 ± 1.3 ; $p < .01$).

This finding could be explained, at least in part, by the higher incident of caries, the main cause of AP, in patients with IBD (Koutsochristou et al., 2015; Nijakowski et al., 2021; Tan et al., 2021; Zhang et al., 2020). A recent systematic review has highlighted a remarkably increased

TABLE 3 Multivariate logistic regression analyses of the association of IBD and the independent variables number of teeth, number of carious lesions, periodontal status (PD), periapical status (AP) and endodontic status (RFT)

Independent variables	<i>B</i>	<i>p</i>	Odds ratio	95% CI Inf. limit	95% CI Sup. limit.
No. teeth	0.0692	.2998	1.0717	0.9402	1.2216
No. caries	0.0260	.8890	1.0263	0.7127	1.4779
PD	0.8102	.3832	2.2485	0.3638	13.8954
AP	0.0308	.8797	1.0313	0.6918	1.5374
RFT	0.6223	.0027	1.8633	1.2400	2.7998

Note: Dependent variable: IBD (1 = present; 0 = absent).

Independent variables: periodontal disease (1 = present; 0 = absent), periapical status (1 = at least 1 tooth with AP; 0 = none) and endodontic status (1 = at least 1 RFT; 0 = none).

Overall model fit: Chi Square = 17.8270; df = 5; *p* = .0032.

past and present occurrence of dental caries in subjects with IBD, compared to healthy controls (Marruganti et al., 2021). However, in the present study, the difference in the number of carious teeth between the two groups was not significant.

Since periodontal disease can cause endodontic pathology and make RCT necessary, the higher prevalence of RFT in IBD patients demonstrated in the present study could also be explained by the higher prevalence of periodontal disease associated with IBD patients (Koutsochristou et al., 2015; Zhang et al., 2020). The coexistence of IBD and periodontal disease seems to be associated with a more responsive inflammatory reaction compared with individuals having one or the other (de Mello-Neto et al., 2021). Nevertheless, in the present study, the proportion of patients with periodontal disease was similar in the two groups compared.

In the multivariate logistic regression analysis, with IBD as dependent variable, the significant association between RFT and IBD stayed. RFT were shown to be significantly associated with IBD (OR = 1.86; 95% CI = 1.24–2.80; *p* = .027). This finding agrees with the higher frequency and need of RCT that have been shown in patients with IBD (Johannsen et al., 2015). Nevertheless, other studies that have also investigated the prevalence of RCT in patients with IBD have not shown it to be higher than that of the general population (Piras et al., 2017; Poyato-Borrego et al., 2020).

Although the mean of teeth with AP in the SG (2.3 ± 2.2) was higher than that of the CG (1.4 ± 1.6), the difference was not statistically significant (*p* = .086). Likewise, the proportion of patients with at least one periapical lesion was higher in the SG (82%) than in the CG (61%), but the difference was not statistically significant either (OR = 2.98; *p* = .076). Previous findings, such as those of the age- and sex-matched case-control study carried out by Poyato-Borrego et al. (2020), who demonstrated an OR = 5.7 (*p* = .05) for the association between AP and IBD, and those of Piras et al. (2017), have shown larger periapical lesions in IBD patients, higher PAI score,

and a significantly higher prevalence of AP in women with IBD. The lack of statistical significance of the results of this study regarding the prevalence of AP may probably be due to the small size of the sample, compared to that of previous studies (Piras et al., 2017; Poyato-Borrego et al., 2020).

A striking result of this study is the high proportion of IBD patients (54%) who have endodontically treated teeth with RPLs, compared to only 11% in the CG (OR = 9.6; *p* = .001). The periapical lesion in an RFT should be interpreted with caution, as it may be a healing lesion or an apical scar. In the orthograde endodontic treatment, as in periapical surgery, the lesion heals through tissue regeneration processes, but always involving some formation of periapical fibrotic tissue (Ricucci et al., 2009). The regeneration of the periapical tissues would never be complete, since it involves the repair of a postnatal injury, and in these cases, there is always scar formation (Bullard et al., 2003). Therefore, this finding could be explained, at least in part, by the high prevalence of low bone mass in IBD patients, together with changes in the OPG/RANKL/RANK system, and the effect of the medication they take to treat IBD (Miheller et al., 2007). The increased activation of the NLRP3 inflammasome could also be an explanation. The NLRP3 inflammasome participates in the pathogenesis of IBD (Zhen & Zhang, 2019), and in turn is involved in the loss of alveolar bone that occurs in AP (Ran et al., 2017). Patients with IBD may have delayed healing of the periapical osteolytic lesion.

The objectives of this study are part of the growing interest in research on the possible relationship of endodontic pathology with systemic diseases. The results of epidemiological studies carried out in the last years suggest a link between AP and some systemic diseases, such as diabetes mellitus (López-López et al., 2011; Sánchez-Domínguez et al., 2015), cardiovascular diseases (Cotti & Mercurio, 2015), atherosclerosis (Berlin-Broner et al., 2017), tobacco smoking (López-López et al., 2012; Pinto et al., 2020), metabolic syndrome (González-Navarro et al., 2020), osteoporosis (López-López et al., 2015),

inherited coagulation disorders (Castellanos-Cosano et al., 2013), and others (Segura-Egea et al., 2015). The results of these studies are already notable for the simple fact that they draw the attention of physicians and dentists to the interrelation between oral inflammatory pathology and systemic health status. These findings can help to promote greater attention to the oral health of these patients. Although many of these studies demonstrated a significant association of AP and/or RCT with the systemic pathology investigated, a causal relationship cannot be established (Segura-Egea et al., 2019). The vast majority are cross-sectional studies that cannot demonstrate time sequence or dose-response gradients. The relationship can be explained by shared risk factors and because they are all diseases with an inflammatory component (Segura-Egea et al., 2019). The lipopolysaccharide of Gram-negative bacteria causing AP is the main trigger of pro-inflammatory status (Garrido et al., 2019; Georgiou et al., 2021). Therefore, AP is associated with higher plasma levels of inflammatory markers such as CRP, IL-6, and fibrinogen (Gomes et al., 2013; Vidal et al., 2016), existing stronger evidence that AP contributes to low-grade systemic inflammation (Georgiou et al., 2019). Well-designed prospective longitudinal studies are needed to clarify whether there is a causal relationship between AP and RCT and IBD.

The results of this study should be carefully assessed, as some possible confounders have not been ruled out. Some relevant factors influencing periapical status and the prevalence of RCT have not been considered, such as educational level, socio-economic status, or history of trauma (Segura-Egea et al., 2004). These factors could be acting as confounding factors. On the contrary, having selected the sample with the absence of cardiovascular disease, smoking, diabetes and metabolic syndrome as inclusion criteria, these systemic factors are excluded as possible confounding variables. Nevertheless, the control of other possible confounding factors is difficult, particularly when any influence on AP is likely to be multifactorial.

According to translational research in dentistry, analytical epidemiological studies, of the type of the present case-control study, should have the ultimate goal of producing more meaningful and applicable results that serve to improve people's health (Faggion, 2020). Therefore, dentists should translate the results of this study, along with those of others previously published (Nijakowski et al., 2021; Piras et al., 2017; Poyato-Borrego et al., 2020, 2021), into the dental clinic. These patients should be explored for the presence of decayed teeth with asymptomatic initial or mild pulpitis (Wolters et al., 2017), and panoramic radiograph should be carefully analysed for asymptomatic periapical lesions.

CONCLUSION

IBD, UC and Crohn's disease are associated with higher prevalence of RFT and higher percentage of RFT with periapical lesions. Dentists should consider these findings when caring for IBD patients by monitoring the evolution of periapical lesions of endodontically treated teeth.

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CONFLICT OF INTEREST

The authors deny any conflicts of interest.

ETHICAL APPROVAL

This cross-sectional study was conducted following the Strengthening Reporting Observational Studies in Epidemiology (STROBE) guidelines. The Ethics Committee of the Odontologic Hospital of Bellvitge, Universitat de Barcelona (Spain), approved the protocol of this case-control study (number 3/2021). Each subject signed a consent form after being informed of the nature of the study.

AUTHOR CONTRIBUTIONS

JJS-E, JJS-S and JL-L designed the study and wrote the protocol. CJ-G, EJ-S and JL-L carried out the clinical explorations, recorded. JM-G, DC-B and JJS-E undertook the statistical analysis and performed the tables. JJS-S, JM-G, JL-L and JJS-E wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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REFERENCES

- Baumgart, D.C. & Sandborn, W.J. (2012) Crohn's disease. *The Lancet*, 380, 1590–1605.
- Berlin-Broner, Y., Febbraio, M. & Levin, L. (2017) Apical periodontitis and atherosclerosis: is there a link? Review of the

- literature and potential mechanism of linkage. *Quintessence International*, 48, 527–534.
- Brito, F., Barros, F.C.D., Zaltman, C., Pugas Carvalho, A.T., de Vasconcellos Carneiro, A.J., Fischer, R.G. et al. (2008) Prevalence of periodontitis and DMFT index in patients with Crohn's disease and ulcerative colitis. *Journal of Clinical Periodontology*, 35, 555–560.
- Bullard, K.M., Longaker, M.T. & Lorenz, H.P. (2003) Fetal wound healing: current biology. *World Journal of Surgery*, 27, 54–61.
- Castellanos-Cosano, L., Machuca-Portillo, G., Sánchez-Domínguez, B., Torrés-Lagares, D., López-López, J. & Segura-Egea, J.J. (2013) High prevalence of radiolucent periapical lesions amongst patients with inherited coagulation disorders. *Haemophilia*, 19, 110–115.
- Cintra, L.T.A., Gomes, M.S., da Silva, C.C., Faria, F.D., Benetti, F., Cosme-Silva, L. et al. (2021) Evolution of endodontic medicine: a critical narrative review of the interrelationship between endodontics and systemic pathological conditions. *Odontology*, 109, 741–769.
- Cotti, E. & Mercurio, G. (2015) Apical periodontitis and cardiovascular diseases: previous findings and ongoing research. *International Endodontic Journal*, 48, 926–932.
- Eriksen, H.M. (1998) Epidemiology of apical periodontitis. In: Orstavik, D. & Ford, T.P. (Eds.) *Essential endodontology: prevention and treatment of apical periodontitis*. Boston: Blackwell Science, pp. 179–191.
- Eriksen, H.M. & Bjertness, E. (1991) Prevalence of apical periodontitis and results of endodontic treatment in middle-aged adults in Norway. *Endodontics & Dental Traumatology*, 7, 1–4.
- Faggion, C.M. (2020) The (in)adequacy of translational research in dentistry. *European Journal of Oral Sciences*, 128, 103–109.
- Flint, D.J., Paunovich, E., Moore, W.S., Wofford, D.T. & Hermes, C.B. (1998) A diagnostic comparison of panoramic and intraoral radiographs. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 85, 731–735.
- Garrido, M., Cárdenas, A.M., Astorga, J., Quinlan, F., Valdés, M., Chaparro, A. et al. (2019) Elevated systemic inflammatory burden and cardiovascular risk in young adults with endodontic apical lesions. *Journal of Endodontics*, 45, 111–115.
- Georgiou, A.C., Crielaard, W., Armenis, I., de Vries, R. & van der Waal, S.V. (2019) Apical periodontitis is associated with elevated concentrations of inflammatory mediators in peripheral blood: a systematic review and meta-analysis. *Journal of Endodontics*, 45, 1279–1295.e3.
- Georgiou, A.C., Crielaard, W., Ouwering, P., McLean, W., Lappin, D.F. & van der Waal, S.V. (2021) The influence of apical periodontitis on the concentration of inflammatory mediators in peripheral blood plasma and the metagenomic profiling of endodontic infections: study design and protocol. *Contemporary Clinical Trials Communications*, 21, 100686.
- Gomes, M.S., Blattner, T.C., Sant'Ana Filho, M., Grecca, F.S., Hugo, F.N., Fouad, A.F. et al. (2013) Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. *Journal of Endodontics*, 39, 1205–1217.
- Gomes, M.S., Hugo, F.N., Hilgert, J.B., Sant'Ana Filho, M., Padilha, D.M.P., Simonsick, E.M. et al. (2016) Apical periodontitis and incident cardiovascular events in the Baltimore Longitudinal Study of Ageing. *International Endodontic Journal*, 49, 334–342.
- González-Navarro, B., Segura-Egea, J.J., Estrugo-Devesa, A., Pintó-Sala, X., Jane-Salas, E., Jiménez-Sánchez, M.C. et al. (2020) Relationship between apical periodontitis and metabolic syndrome and cardiovascular events: a cross-sectional study. *Journal of Clinical Medicine*, 9, 1–13.
- Guan, Q. (2019) A comprehensive review and update on the pathogenesis of inflammatory bowel disease. *Journal of Immunology Research*, 2019, 1–16.
- Gulsahi, K., Gulsahi, A., Ungor, M. & Genc, Y. (2008) Frequency of root-filled teeth and prevalence of apical periodontitis in an adult Turkish population. *International Endodontic Journal*, 41, 78–85.
- Jiménez-Pinzón, A., Segura-Egea, J.J., Poyato-Ferrera, M., Velasco-Ortega, E. & Ríos-Santos, J.V. (2004) Prevalence of apical periodontitis and frequency of root-filled teeth in an adult Spanish population. *International Endodontic Journal*, 37, 167–173.
- Johannsen, A., Fored, M.C., Håkansson, J., Ekbom, A. & Gustafsson, A. (2015) Consumption of dental treatment in patients with inflammatory bowel disease, a register study. *PLoS One*, 10, e0134001.
- Kalmar, J.R. (1994) Crohn's disease: orofacial considerations and disease pathogenesis. *Periodontology 2000*, 6, 101–115.
- Kirkevang, L.L., Ørstavik, D., Bahrami, G., Wenzel, A. & Væth, M. (2017) Prediction of periapical status and tooth extraction. *International Endodontic Journal*, 50, 5–14.
- Koutsochristou, V., Zellos, A., Dimakou, K., Panayotou, I., Sihanidou, S., Roma-Giannikou, E. et al. (2015) Dental caries and periodontal disease in children and adolescents with inflammatory bowel disease: a case-control study. *Inflammatory Bowel Diseases*, 21, 1839–1846.
- Kumar, G., Tewari, S., Sangwan, P., Tewari, S., Duhan, J. & Mittal, S. (2020) The effect of an intraorifice barrier and base under coronal restorations on the healing of apical periodontitis: a randomized controlled trial. *International Endodontic Journal*, 53(3), 298–307.
- Liljestrand, J.M., Mäntylä, P., Paju, S., Buhlin, K., Kopra, K., Persson, G.R. et al. (2016) Association of endodontic lesions with coronary artery disease. *Journal of Dental Research*, 95, 1358–1365.
- Liljestrand, J.M., Salminen, A., Lahdentausta, L., Paju, S., Mäntylä, P., Buhlin, K. et al. (2021) Association between dental factors and mortality. *International Endodontic Journal*, 54, 672–681.
- Limeira, F.I.R., Arantes, D.C., de Souza, O.C., de Melo, D.P., Magalhães, C.S. & Bento, P.M. (2020) Root canal treatment and apical periodontitis in a Brazilian population with type 1 diabetes mellitus: a cross-sectional paired study. *Journal of Endodontics*, 46, 756–762.
- Lin, P.-Y., Chien, K.-L., Chang, H.-J. & Chi, L.-Y. (2015) Unfinished root canal treatments and the risk of cardiovascular disease. *Journal of Endodontics*, 41, 1991–1996.
- Liu, S., Cheng, Y., Xu, W. & Bian, Z. (2010) Protective effects of follicle-stimulating hormone inhibitor on alveolar bone loss resulting from experimental periapical lesions in ovariectomized rats. *Journal of Endodontics*, 36, 658–663.
- López-López, J., Castellanos-Cosano, L., Estrugo-Devesa, A., Gómez-Vaquero, C., Velasco-Ortega, E. & Segura-Egea, J.J. (2015) Radiolucent periapical lesions and bone mineral density in post-menopausal women. *Gerodontology*, 32, 195–201.
- López-López, J., Jané-Salas, E., Estrugo-Devesa, A., Velasco-Ortega, E., Martín-González, J. & Segura-Egea, J.J. (2011) Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. *Journal of Endodontics*, 37, 598–601.

- López-López, J., Jané-Salas, E., Estrugo-Devesa, A., Castellanos-Cosano, L., Martín-González, J., Velasco-Ortega, E. et al. (2012) Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. *International Dental Journal*, 62, 40–46.
- López-López, J., Jané-Salas, E., Martín-González, J., Castellanos-Cosano, L., Llamas-Carreras, J.M., Velasco-Ortega, E. et al. (2012) Tobacco smoking and radiographic periapical status: a retrospective case-control study. *Journal of Endodontics*, 38, 584–588.
- Marruganti, C., Discepoli, N., Gaeta, C., Franciosi, G., Ferrari, M. & Grandini, S. (2021) Dental caries occurrence in inflammatory bowel disease patients: a systematic review and meta-analysis. *Caries Research*, 55, 485–495.
- de Mello-Neto, J.M., Nunes, J.G.R., Tadakamadla, S.K. & da Silva Figueredo, C.M. (2021) Immunological traits of patients with coexistent inflammatory bowel disease and periodontal disease: a systematic review. *International Journal of Environmental Research and Public Health*, 18(17), 8958.
- Miheller, P., Muzes, G., Rácz, K., Blázovits, A., Lakatos, P., Herszényi, L. et al. (2007) Changes of OPG and RANKL concentrations in Crohn's disease after infliximab therapy. *Inflammatory Bowel Diseases*, 13, 1379–1384.
- Molander, B., Ahlqvist, M. & Gröndahl, H.G. (1995) Panoramic and restrictive intraoral radiography in comprehensive oral radiographic diagnosis. *European Journal of Oral Sciences*, 103, 191–198.
- Nagendrababu, V., Segura-Egea, J.J., Fouad, A.F., Pulikkotil, S.J. & Dummer, P.M.H. (2020) Association between diabetes and the outcome of root canal treatment in adults: an umbrella review. *International Endodontic Journal*, 53, 455–466.
- Nardi, C., Calistri, L., Grazzini, G., Desideri, I., Lorini, C., Occhipinti, M. et al. (2018) Is panoramic radiography an accurate imaging technique for the detection of endodontically treated asymptomatic apical periodontitis? *Journal of Endodontics*, 44, 1500–1508.
- Nijkowski, K., Gruszczyński, D. & Surdacka, A. (2021) Oral health status in patients with inflammatory bowel diseases: a systematic review. *International Journal of Environmental Research and Public Health*, 18, 11521.
- Oettinger-Barak, O., Segal, E., MacHtei, E.E., Barak, S., Baruch, Y. & Ish-Shalom, S. (2007) Alveolar bone loss in liver transplantation patients: relationship with prolonged steroid treatment and parathyroid hormone levels. *Journal of Clinical Periodontology*, 34, 1039–1045.
- Orstavik, D., Kerekes, K., Eriksen, H.M., Ørstavik, D., Kerekes, K. & Eriksen, H.M. (1986) The periapical index: a scoring system for radiographic assessment of apical periodontitis. *Dental Traumatology*, 2, 20–34.
- Papageorgiou, S.N., Hagner, M., Nogueira, A.V.B., Franke, A., Jäger, A. & Deschner, J. (2017) Inflammatory bowel disease and oral health: systematic review and a meta-analysis. *Journal of Clinical Periodontology*, 44, 382–393.
- Pinto, K.P., Ferreira, C.M., Maia, L.C., Sassone, L.M., Fidalgo, T.K.S. & Silva, E.J.N.L. (2020) Does tobacco smoking predispose to apical periodontitis and endodontic treatment need? A systematic review and meta-analysis. *International Endodontic Journal*, 53, 1068–1083.
- Piras, V., Usai, P., Mezzena, S., Susnik, M., Ideo, F., Schirru, E. et al. (2017) Prevalence of apical periodontitis in patients with inflammatory bowel diseases: a retrospective clinical study. *Journal of Endodontics*, 43, 389–394.
- Poyato-Borrego, M., Segura-Egea, J.J., Martín-González, J., Jiménez-Sánchez, M.C., Cabanillas-Balsera, D., Areal-Quecuty, V. et al. (2021) Prevalence of endodontic infection in patients with Crohn's disease and ulcerative colitis. *Medicina Oral Patología Oral Y Cirugía Bucal*, 26, e208–e215.
- Poyato-Borrego, M., Segura-Sampedro, J.J., Martín-González, J., Torres-Domínguez, Y., Velasco-Ortega, E. & Segura-Egea, J.J. (2020) High prevalence of apical periodontitis in patients with inflammatory bowel disease: an age- and gender- matched case-control study. *Inflammatory Bowel Diseases*, 26(2), 273–279.
- Ran, S., Liu, B., Gu, S., Sun, Z. & Liang, J. (2017) Analysis of the expression of NLRP3 and AIM2 in periapical lesions with apical periodontitis and microbial analysis outside the apical segment of teeth. *Archives of Oral Biology*, 78, 39–47.
- Ricucci, D., Lin, L.M. & Spångberg, L.S.W. (2009) Wound healing of apical tissues after root canal therapy: a long-term clinical, radiographic, and histopathologic observation study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 108, 609–621.
- Ridao-Sacie, C., Segura-Egea, J.J., Fernández-Palacín, A., Bullón-Fernández, P. & Ríos-Santos, J.V. (2007) Radiological assessment of periapical status using the periapical index: comparison of periapical radiography and digital panoramic radiography. *International Endodontic Journal*, 40, 433–440.
- Rodríguez-Lago, I., Merino, O., Azagra, I., Maiz, A., Zapata, E., Higuera, R. et al. (2018) Characteristics and progression of pre-clinical inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*, 16, 1459–1466.
- Rushton, V.E., Horner, K. & Worthington, H.V. (2002) Screening panoramic radiography of new adult patients: diagnostic yield when combined with bitewing radiography and identification of selection criteria. *British Dental Journal*, 192, 275–279.
- Samuel, R.O., Ervolino, E., de Azevedo Queiroz, Í.O., Azuma, M.M., Ferreira, G.T. & Cintra, L.T.A. (2019) Th1/Th2/Th17/Treg balance in apical periodontitis of normoglycemic and diabetic rats. *Journal of Endodontics*, 45, 1009–1015.
- Sánchez-Domínguez, B., López-López, J., Jané-Salas, E., Castellanos-Cosano, L., Velasco-Ortega, E. & Segura-Egea, J.J. (2015) Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. *Journal of Endodontics*, 41, 601–606.
- Satsangi, J., Silverberg, M.S., Vermeire, S. & Colombel, J.F. (2006) The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*, 55, 749–753.
- Sebring, D., Buhlin, K., Norhammar, A., Rydén, L., Jonasson, P., EndoReCo et al. (2021) Endodontic inflammatory disease: a risk indicator for a first myocardial infarction. *International Endodontic Journal*, 55, 6–17.
- Segura-Egea, J.J., Cabanillas-Balsera, D., Jiménez-Sánchez, M.C. & Martín-González, J. (2019) Endodontics and diabetes: association versus causation. *International Endodontic Journal*, 52, 790–802.
- Segura-Egea, J.J., Castellanos-Cosano, L., Velasco-Ortega, E., Ríos-Santos, J.V., Llamas-Carreras, J.M., Machuca, G. et al. (2011) Relationship between smoking and endodontic variables in hypertensive patients. *Journal of Endodontics*, 37, 764–767.
- Segura-Egea, J.J., Jiménez-Pinzón, A., Poyato-Ferrera, M., Velasco-Ortega, E. & Ríos-Santos, J.V. (2004) Periapical status and

- quality of root fillings and coronal restorations in an adult Spanish population. *International Endodontic Journal*, 37, 525–530.
- Segura-Egea, J.J., Martín-González, J. & Castellanos-Cosano, L. (2015) Endodontic medicine: connections between apical periodontitis and systemic diseases. *International Endodontic Journal*, 48, 933–951.
- Silverberg, M.S., Satsangi, J., Ahmad, T., Arnott, I.D.R., Bernstein, C.N., Brant, S.R. et al. (2005) Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Canadian Journal of Gastroenterology*, 19(Suppl A), 5A–36A.
- Tan, C.X.W., Brand, H.S., Kalender, B., De Boer, N.K.H., Forouzanfar, T. & de Visscher, J.G.A.M. (2021) Dental and periodontal disease in patients with inflammatory bowel disease. *Clinical Oral Investigations*, 25, 5273–5280.
- Tibúrcio-Machado, C.S., Michelon, C., Zanatta, F.B., Gomes, M.S., Marin, J.A. & Bier, C.A. (2021) The global prevalence of apical periodontitis: a systematic review and meta-analysis. *International Endodontic Journal*, 54(5), 712–735.
- Vandenbroucke, J.P., Von Elm, E., Altman, D.G., Gøtzsche, P.C., Mulrow, C.D., Pocock, S.J. et al. (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Annals of Internal Medicine*, 12, 1500–1524.
- Vidal, F., Fontes, T.V., Marques, T.V.F. & Gonc, L.S. (2016) Association between apical periodontitis lesions and plasmatic levels of C-reactive protein, interleukin 6 and fibrinogen in hypertensive patients. *International Endodontic Journal*, 49, 1107–1115.
- Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C. & Vandenbroucke, J.P. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Medicine*, 4, 1623–1627.
- Wolters, W.J., Duncan, H.F., Tomson, P.L., Karim, I.E., McKenna, G., Dorri, M. et al. (2017) Minimally invasive endodontics: a new diagnostic system for assessing pulpitis and subsequent treatment needs. *International Endodontic Journal*, 50, 825–829.
- Zhang, L., Gao, X., Zhou, J., Chen, S., Zhang, J., Zhang, Y. et al. (2020) Increased risks of dental caries and periodontal disease in Chinese patients with inflammatory bowel disease. *International Dental Journal*, 70, 227–236.
- Zhen, Y. & Zhang, H. (2019) NLRP3 inflammasome and inflammatory bowel disease. *Frontiers in Immunology*, 10, 276.

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