

Systematic Review Dental Implants

Histopathological and microbiological findings associated with retrograde peri-implantitis of extra-radicular endodontic origin: a systematic and critical review

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Abstract. The aim of this study was to systematically review the aetiology, in particular histopathological and microbiological factors, of retrograde peri-implantitis of endodontic origin. The review is registered in the PROSPERO database (CRD42017063898). An electronic search for publications was performed in two databases, from their inception up to October 2018. Subsequently a hand search of the reference lists was conducted. Articles in English and other languages using Latin characters were included. Two independent reviewers selected the studies, extracted and synthesized the data, and assessed the quality. The methodology of the included articles was evaluated using the relevant Joanna Briggs Institute tools. Six studies fulfilled the eligibility criteria and were included in the systematic review. Histopathological examination in the component studies reflected that the presentation of retrograde peri-implantitis involves cyst formation or chronic inflammation. Bacteria found in these lesions included *Porphyromonas gingivalis*, *Corynebacterium*, *Streptococcus*, and *Klebsiella pneumoniae*. Two studies were judged as having a low possibility of bias and four were judged as having a moderate possibility of bias. This review determined that endodontic complications associated with adjacent teeth, residual infection at the extraction site due to previous apical periodontitis, or refractory apical periodontitis might be considered likely aetiological factors, although the evidence is limited.

Key words: cyst; endodontics; extra-radicular; retrograde; root canal; peri-implantitis.

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Introduction

The growing popularity of dental implants as an alternative to fixed and removable prosthodontics for the treatment of edentulism is likely related to the fact that dental implants do not impact the integrity of adjacent teeth. Periodontal, as well as occlusal aspects, are more favourable when compared with other tooth replacement modalities^{1,2}. Apical periodontitis is a prevalent disease even in the presence of previous root canal treatment³. Therefore, due to the high number of people receiving dental implant and root canal treatment over their lifetimes, as well as the high prevalence of apical periodontitis, it is reasonable to expect that there is a segment of the population receiving, or who have received in the past, both treatment modalities and are experiencing implant-related and/or endodontic-related complications.

Failures do occur in any surgical procedure. Biological factors that lead to radiolucencies persisting after endodontic treatment include infection in the complex apical root canal system, extra-radicular infection, extruded root canal filling or other exogenous materials, accumulation of endogenous cholesterol crystals, true cystic lesions, and scar tissue healing of the lesion⁴. These may hinder the osseointegration of dental implants.

Endodontic failures and complications could be associated with implant issues and vice versa⁵⁻⁹, thus clinicians need to be aware of these potential issues.

Several terms have been used to describe such clinical scenarios, including peri-apical implant pathology⁵, retrograde peri-implantitis⁶, apical peri-implantitis⁷, and implant peri-apical lesion^{8,9}. A more exhaustive list of alternative terms used to describe retrograde peri-implantitis encountered during the study search is reported in Table 1. For the purpose of this study, these presentations were defined as 'retrograde peri-implantitis', a term previously suggested in the literature⁶.

Table 1. Alternative terms used to describe retrograde peri-implantitis encountered during the search (in alphabetical order).

Apical implantitis
Apical peri-implantitis
Apical (retrograde) peri-implantitis
Endodontic-implant pathology
Implant peri-apical lesion
Inflammatory implant peri-apical lesion
Peri-apical abscess adjacent to dental implant
Peri-apical implant lesion
Peri-apical lesion around implant
Peri-implant pathology
Retrograde peri-implant infection

Common features of retrograde peri-implantitis include clinical symptoms and a radiolucency developing in the apical part of the implant, with the coronal part having a normal osseointegration, occurring shortly after fixture insertion⁶. Lesions of endodontic origin may be timely consecutive (first apical periodontitis/lesion, then implant) or simultaneous (apical periodontitis/lesion of a neighbouring tooth extends to a dental implant) (Fig. 1). Aetiological possibilities for retrograde peri-implantitis of endodontic origin are summarized in Table 2. Although there is a large amount of literature available on this clinical scenario, most of the purported aetiological factors are not necessarily supported by histopathological and/or microbiological findings.

Specifically, the endodontic factors associated with retrograde peri-implantitis remain controversial, thus the present study focused solely on these. It appears that there has been no previous literature review specifically designed to assess the causes of dental implant complications associated with endodontics, based on histopathological and/or microbiological assessment of the retrograde peri-implantitis lesions. Therefore, a qualitative study was performed aiming to critically review the literature systematically in order to answer the following clinical question: 'What histopathological, aetiological or pathogenic factors are associated with retrograde peri-implantitis of endodontic origin?'

Methods

Protocol and registration

The protocol of this systematic review was registered a priori in the International Prospective Register of Systematic Reviews under CRD42017063898 (<http://www.crd.york.ac.uk/PROSPERO>).

Review question

The specific research question was as follows: "What histopathological, microbiological, aetiological or pathogenic factors are associated with retrograde peri-implantitis of endodontic origin in animals or humans?"

The PEO framework items were as follows: the population (P) comprised adult subjects or animals; the exposure (E) was retrograde peri-implantitis of endodontic origin, as explicitly stated by the authors and/or when it was concluded by the present review authors that this was the case; the outcome (O) was

histopathological and/or microbiological sampling findings.

Eligibility criteria

Articles were included in the systematic review if they met the following inclusion criteria: published in English or a language using Latin characters, included humans and/or animals, retrograde peri-implantitis caused by an endodontic pathosis as stated by the authors, findings were based on microbiological and/or histopathological sampling. Study designs could include experimental animal studies, case reports or case series, observational studies, and randomized or non-randomized clinical trials.

Studies in other languages or characters, systematic reviews, abstracts, personal opinion pieces, and in vitro studies were excluded. Studies without a discussion, aetiology, pathogenesis or histopathological assessment, and those without explicit mention of an endodontic pathosis origin were discarded. Studies were also excluded if endodontic complications were associated with mini-implants or if the endodontic pathosis was of implant origin.

Search strategy

Initially, PubMed was explored for screening of search terms pertinent to the research question using sentinel studies as a reference. The search strategy was developed from the appropriately identified key words and index terms and applied to PubMed and Embase from inception date to October 25, 2018. The search terms are summarized in Table 3. After duplicate records were removed, two authors (GM, GRF) independently and in duplicate screened the titles and abstracts of the articles. In the case of disagreement, consensus was reached through a discussion of the findings between the reviewers. A citation search of reference lists of all included articles was also conducted.

Quality assessment

Two reviewers (GM, GRF) independently assessed the possibility of bias the full-text articles by means of different critical appraisal tools, according to the study design.

For case series and case reports, the standard Joanna Briggs Institute (JBI) critical appraisal checklists were used^{10,11}. The two reviewers classified the articles on a percentage of positive criteria within the critical appraisal checklist. All studies that underwent

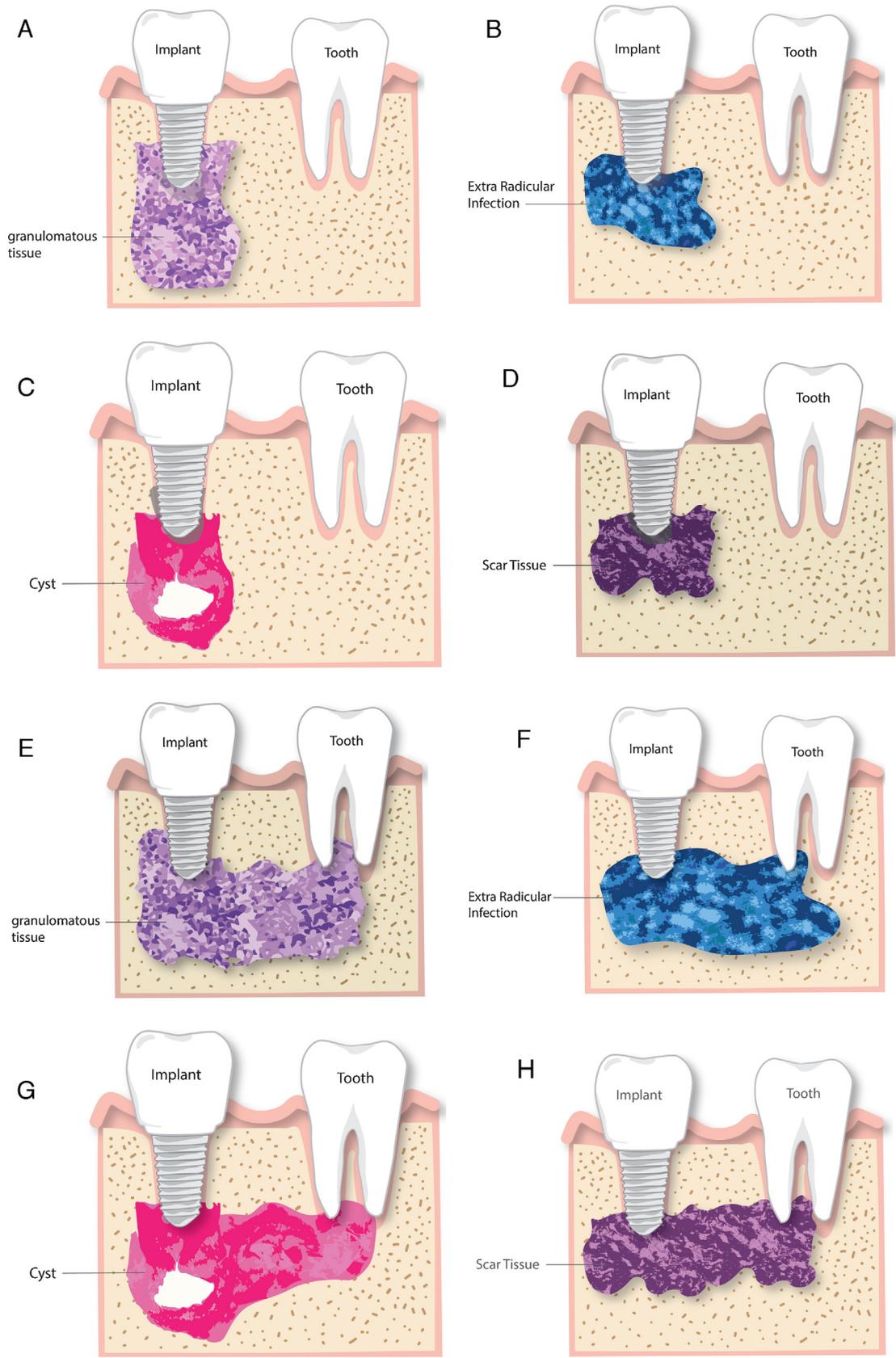


Fig. 1. Diagrammatic representation of the possible presentations of retrograde peri-implantitis of endodontic origin. (A) Timely consecutive lesion associated with granulomatous tissue. (B) Timely consecutive lesion associated with extra-radicular infection. (C) Timely consecutive lesion associated with cystic lesion. (D) Timely consecutive lesion associated with scar tissue healing. (E) Simultaneous lesion associated with granulomatous tissue. (F) Simultaneous lesion associated with extra-radicular infection. (G) Simultaneous lesion associated with cystic lesion. (H) Simultaneous lesion associated with scar tissue healing.

Table 2. Aetiology of retrograde peri-implantitis of endodontic origin (adapted from Nair 2006⁴ and Chan et al. 2011⁶).

Endodontic origin	Non endodontic origin
Root canal system infection	Violation of minimal distance from adjacent tooth
Extra-radicular infection	Overheating
Extruded root canal filling or other exogenous materials	Implant surface contamination
Accumulation of endogenous cholesterol crystals	Residual root particles or foreign bodies
True cystic lesions	Surgical drilling beyond the length of the implant
Scar tissue healing of the lesion	Fenestration of vestibular bone
	Bone compression
	Drainage of inflammation via marrow spaces
	Poor bone quality
	Premature loading
	Development of osteomyelitis
	Technique of the particular system used
	Bone loss caused by mucoperiosteal flap procedure

Table 3. Search terms.

Embase	Peri-implantitis OR periimplantitis OR Osseointegration/SYN OR 'Tooth implantation'/SYN OR 'Tooth implant*' OR 'Dental Implant*' OR Peri-implant* OR Implant OR 'Alveolar Bone loss'/SYN 'Tooth Periapical Disease'/SYN OR 'Periapical Abscesses' OR (Dental OR Periapical) Next/1 Granulomas OR (Periapical OR Apical OR Radicular) Next/2 Cyst* OR (Dental OR Root) Next/1 Canal* OR (Tooth OR Dental) Next/2 (Apex OR Apices) OR 'periapical pathology' OR Endodontic*
PubMed	((Periapical diseases[MH] OR Periapical disease*[TW] OR Periapical Periodontiti*[TW] OR Apical Periodontiti*[TW] OR Periapical Abscess*[TW] OR Dentoalveolar Abscess*[TW] OR Periapical Granuloma*[TW] OR Dental Granuloma*[TW] OR Radicular cyst*[TW] OR Periapical Cyst*[TW] OR apical Cyst*[TW] OR apical periodontal Cyst*[TW] OR dental fistula*[TW] OR Root canal*[TW] OR Tooth root*[TW] OR Tooth apex[TW] OR Tooth apices[TW] OR Apical foramen[TW] OR Periapical pathology[TW] OR Endodontic*[TW])) AND (Peri-implantitis[TW] OR periimplantitis[TW] OR Osseointegration[TW] OR Dental Implantation, Endosseous[MH] OR dental implant*[TW] OR Peri-implant*[TW] OR Bone loss[TW] OR Implant[TW])

assessment for the possibility of bias were included regardless of the score that they obtained, due to the low number of studies identified that fulfilled the eligibility criteria. In the case of disagreement, agreement was reached through a discussion of the findings between the reviewers.

To summarize the validity of the studies, they were grouped into the following categories: (1) low possibility of bias (i.e., studies that met at least 75% of the quality criteria); (2) moderate possibility of bias (i.e., studies that met between 50% and 75% of the quality criteria); (3) high possibility of bias (i.e., studies that met less than 50% of the quality criteria).

Data extraction

Two reviewers independently extracted data from the studies included in this review. Qualitative data were gathered from the studies to suggest aetiological factors and pathogenesis. The data extracted included author names, sex and age of the subjects, number of implants placed and instances of

retrograde peri-implantitis, and reason for previous tooth extraction. Data regarding the timing of post-implant placement complications, clinical presentation and radiographic assessment of the implant, and adjacent teeth, as well as the imaging methodology used, were extracted. In the case of disagreement, agreement was reached through a discussion of the findings between the reviewers.

Data synthesis

Textual data findings (verbatim extracts) were retrieved from the included studies and subsequently synthesized. The JBI methodology for systematic reviews was followed by two authors (GM and GRF, who is a trained JBI reviewer).

Results

Search strategy results

Electronic database searches identified 5400 records, of which 1287 were duplicates. Of the remaining 4113 records,

4039 were discarded after screening the titles and abstracts or summaries. Full-text assessment was completed for the remaining 74 records, following which 68 studies were excluded because they did not fulfil the inclusion criteria (Fig. 2). Six studies were included in this review^{6,12-16}. The citation search of the included articles did not reveal any additional records.

Included studies

Table 4 shows the main characteristics of the component studies^{6,12-16}. All studies were published in English and assessed humans. The number of instances of retrograde peri-implantitis ranged from 1 to 21, to produce a total of 30 occasions among 259 implants placed. With regard to the study design, five were case reports^{6,12-14,16} and one was a retrospective case-control study¹⁵.

Characteristics of exposure

All studies reported the number of implants placed and provided data for

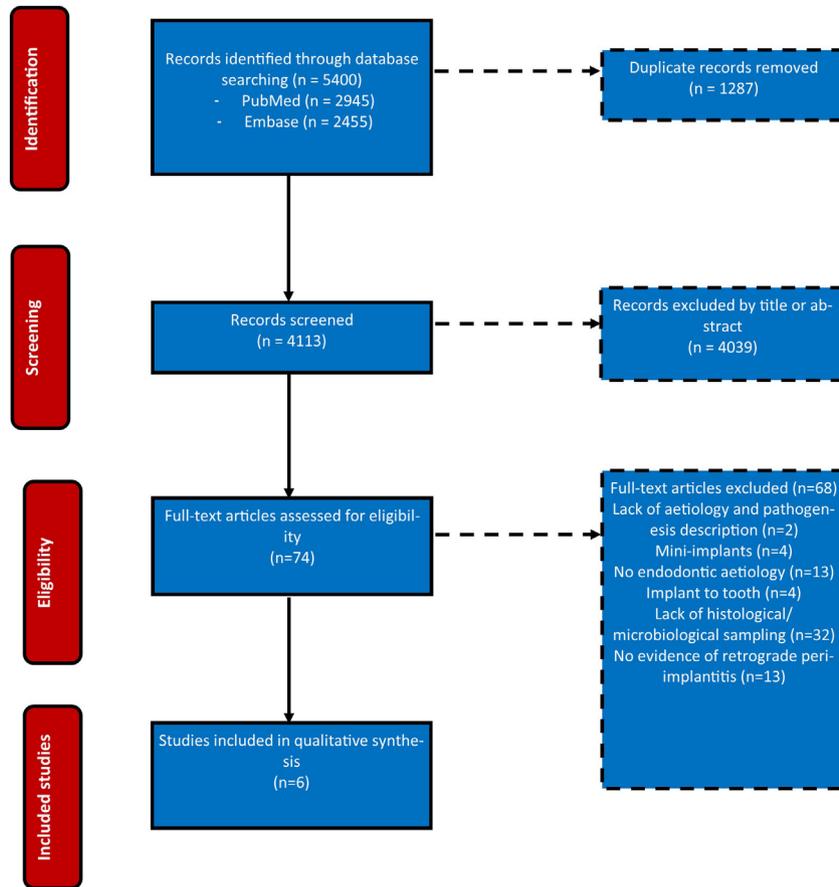


Fig. 2. Flowchart of the screening and study selection process (PRISMA).

the number of instances of retrograde peri-implantitis. Where reported, the age of the patients ranged from 28 years to 62 years. The five case reports indicated the timing of the initial post-implant placement complication, which ranged from 1 week¹³ to 6 months¹². In the case-control study, more than half of the implant failures occurred within the first 6 months¹⁵. The reason for previous tooth extraction was either due to caries¹⁶ or failed endodontic treatment^{6,15}; however three studies did not discuss the reason for tooth removal¹²⁻¹⁴.

Diagnostic methods and results

The following signs, symptoms, and findings developed as a result of retrograde peri-implantitis: abscess^{14,16}, swelling¹⁴, increased probing depths¹², sinus or fistula tract¹³, and pain in the form of tenderness to percussion¹³. Endodontic pathosis of adjacent teeth including acute pulpitis¹⁶, loss of vitality¹³, and acute/chronic peri-apical periodontitis occurred^{12,14}; however two studies did not report the status of all adjacent teeth^{6,15}. Radiographic assessment of

the implant and adjacent teeth was included for all studies, except for one case report¹⁴. These provided evidence of radiolucency associated with the implant. In nine out of 30 instances, a peri-apical radiolucency was related to an adjacent tooth¹²⁻¹⁵. Radiographic assessment was either performed using cone beam computed tomography (CBCT)^{6,16}, peri-apical radiography (PA)^{6,12-16}, or panoramic radiographs (dental panoramic tomogram, DPT)^{12,15}.

Microbiological and histopathological assessment

Following textual data extraction, microbiological and histopathological characteristics were summarized (Tables 5 and 6). It was found that microorganisms are not always present in retrograde peri-implantitis, as highlighted by one study⁶. Two studies reported bacteria, including *Klebsiella pneumoniae*¹⁴, *Streptococcus*¹⁴, *Porphyromonas gingivalis*¹⁵, *Corynebacterium*¹⁴, and *Prevotella intermedia*¹⁵. A chronic inflammatory infiltrate was reported by four stud-

ies^{6,12,13,16}, involving macrophages¹⁶, lymphocytes^{6,16}, and calcified tissues¹³. One study reported a radicular cyst¹².

Possibility of bias

Two studies displayed a low possibility of bias^{15,16} and four studies were deemed to have a moderate possibility of bias^{6,12-14} (Figs. 3 and 4).

Discussion

This systematic review is novel in assessing the histopathological and microbiological endodontic complications associated with retrograde peri-implantitis. Two-hundred and fifty-nine implants were included in this review and 30 implants developed retrograde peri-implantitis, with nine of those episodes associated with apical radiolucencies related to an adjacent tooth¹²⁻¹⁵. Other aetiological factors included existing infection at the extraction site associated with failed endodontic treatment^{6,15}, apical periodontitis^{6,15}, or remaining infected roots¹⁶.

Due to the lack of intracanal sampling in the component studies, it was not possible to assess the involvement of intraradicular infection in retrograde peri-implantitis. Similarly, non-microbial causes of persistent apical periodontitis, including scar tissue healing, were not reported in the component studies, although they may still occur. This review suggests that retrograde peri-implantitis is a symptomatic complication and commonly occurs within the first 6 months of placement, thus in agreement with the previous definition of the clinical entity⁶. It is worth noting that endodontic complications may occur before or after implant rehabilitation, thus timing may vary. Histopathologically this may involve chronic inflammation and/or cyst or microorganisms, including *Streptococcus*, *P. gingivalis*, and *Corynebacterium*.

The microbiology and histopathology involved in retrograde peri-implantitis of endodontic origin were assessed in this review using strict exclusion and inclusion criteria. As a result, the highest level of current evidence on this subject is provided by using a methodology that has been validated previously in the literature.

This review is limited by the low number of papers fulfilling the eligibility criteria. This is due to a lack of histopathological and microbiological analysis on the subject. Twenty-seven lesions were assessed for microbiology in the component study^{6,14,15}, and four for histopathological analysis^{6,12,13,16}. All studies that were assessed for the possibility of bias were included,

Table 4. Characteristics of the studies.

Author and year	Sex	Age (years)	Number of implants placed	Number of retrograde peri-implantitis lesions sampled	Reason for previous extraction	Time to initial onset of complications after implant insertion
Retrospective case-control study						
Lefever et al. ¹⁵ , 2013	NR	NR	248	21	Endodontic pathology/ no endodontic pathology	Between 0 and 90 months
Case reports						
Shaffer et al. ¹⁴ , 1998	M	62	3	3	NR	2 months
	M	59	2	2	NR	2 months
Chaffee et al. ¹³ , 2001	NR	NR	2	1	NR	1 week
Tseng et al. ¹² , 2005	F	33	2	1	NR	6 months
Chan et al. ⁶ , 2011	M	45	1	1	Apical periodontitis/failed RCT	3 months
Quet al. ¹⁶ , 2014	F	28	1	1	Caries and residual roots	5 months

Author and year	Abscess	Fistula/ sinus tract/ discharge	Swelling	Pain	Implant mobility	Probing depth	Adjacent teeth	Radiographic peri-apical radiolucency associated with implant	Number of adjacent teeth with peri-apical lesion	PA/DPT	CBCT
Retrospective case-control study											
Lefever et al. ¹⁵ , 2013	NR	NR	NR	NR	NR	NR	NR	Yes	5	Yes	No
Case reports											
Shaffer et al. ¹⁴ , 1998	NR	NR	Yes	NR	NR	NR	Chronic apical periodontitis	Yes	1	Yes	NR
	Yes	NR	NR	NR	NR	NR	Previous RCT, status questionable	NR	1	NR	NR
Chaffee et al. ¹³ , 2001	NR	Yes	NR	Yes	No	NR	Loss of vitality occurred	Yes	1	Yes	No
Tseng et al. ¹² , 2005	No	No	No	No	NR	9 mm	Peri-apical radiolucency present, RCT prior to implant placement	Yes	1	Yes	NR
Chan et al. ⁶ , 2011	NR	NR	NR	NR	No	NR	NR	Yes	0	Yes	Yes
Qu et al. ¹⁶ , 2014	Yes – “soft cystic mass”	No	NR	NR	NR	NR	Developed acute pulpitis	Yes	0	Yes	Yes

CBCT, cone-beam computed tomography; DPT, dental panoramic tomography; F, female; M, male; NR, not reported; PA, peri-apical radiograph; RCT, root canal treatment.

Table 5. Microbiological findings.

Textual data findings, "verbatim extracts"	Synthesized finding
"The culture revealed <i>Klebsiella pneumoniae</i> "; Shaffer et al., 1998 ¹⁴	Commensal and/or pathogenic microbiota of the oral cavity has been identified
"A culture demonstrated group D (<i>Enterococcus</i>) <i>Streptococcus</i> "; Shaffer et al., 1998 ¹⁴	
"The tissue around the implant showed gram-positive cocci, moderate growth of <i>Corynebacterium</i> species, and light growth of <i>alpha-hemolytic Streptococcus</i> "; Shaffer et al., 1998 ¹⁴	
"The microbial test of Case 1 failed to detect any examined bacterial species"; Chan et al., 201 ¹⁶	
"Bacteria were found in nearly all of the sites, but 9/21 in concentrations \geq log 4. The proportion of anaerobic species was always higher when compared with aerobic species. <i>P. gingivalis</i> and <i>P. intermedia</i> were detected in reasonable concentrations at six and four sites respectively"; Lefever et al., 2013 ¹⁵	

Table 6. Histopathological findings.

Textual data findings, "verbatim extracts"	Synthesized finding
"granulation tissue containing acute inflammatory cells, necrotic debris, and abundant hemorrhage bound by fibrous connective tissue infiltrated with chronic inflammatory cells (Fig. 3). Calcified debris was present in the granulation tissue in 1 area"; Chaffee et al., 2001 ¹³	Chronic inflammation is commonly present
"... a radicular cyst was subsequently diagnosed"; Tseng et al., 2005 ¹²	Cystic presentations have been reported
"Histopathologically (Fig. 3A), the specimen consisted of fibrous connective tissue with a mild chronic mixed inflammatory cell infiltrate. Viable bone was noted at the periphery of the specimen. At higher magnification (Fig. 3B), clusters of inflammatory cells, primarily lymphocytes, were noted in a background of relatively dense connective tissue"; Chan et al., 2011 ⁶	
"... inflammatory cyst wall-like lesion, with the infiltration of macrophage and lymphocytes, but the epithelial lining was undetected"; Qu et al., 2014 ¹⁶	

with four papers deemed as having a moderate possibility of bias^{6,12-14}. All case reports failed to clearly describe the patient's history and provide reasons for tooth extraction, and no study reported the response to all diagnostic tests (Table 4). Five component studies were case reports, making it difficult to generate precise overall conclusions^{6,12-14,16}. Nevertheless, it was decided to include the case reports and studies with a high possibility of bias due to the scarcity of studies assessing the endodontic complications causing retrograde peri-implantitis. Furthermore, systematic reviews of aetiology have a limitation regarding the study design of the included studies, considering that it would be unethical to carry out a randomized controlled trial, for example. This review used two databases and included studies written in English and in languages using Latin characters, and did not include the grey literature. These may be considered as limitations in the study selection process. However, the search strategy was designed

with the assistance of a research librarian with expertise in systematic reviews and was tailored to each separate database.

It should be highlighted that the inclusion of studies relied on the authors explicitly stating the cause and/or the present review authors concluding that this was the case, when full-texts of the potentially eligible studies were assessed for eligibility. For example, a study mentioned 'caries and residual roots'¹⁶ as the cause of previous tooth extraction; however this may not necessarily be related to endodontic issues. Similarly, a case report, part of one the component studies, was not included in the present systematic review, as it was considered that this particular case was not a retrograde peri-implantitis of endodontic origin based on the description⁶. Finally, in the retrospective case-control study¹⁵, only 21 out of 59 lesions were microbiologically tested and no histopathological assessment was conducted. Furthermore, it was not specified whether these were associated to previously

extracted or neighbouring teeth. Thus, the precise aetiology of these lesions needs further understanding.

This systematic review differs from a previously published review with regards to the outcome evaluated, as the previous publication reviewed the symptoms, risk factors, and treatment methods of retrograde peri-implantitis¹⁷. Unsurprisingly, some of the studies included coincided^{6,12,14}.

Based on the findings of this study, it can be summarized that the microbiota found in retrograde peri-implantitis of endodontic origin, periodontitis, and peri-implantitis have a degree of similarity^{18,19}; however this remains controversial in the literature²⁰. There has been evidence of *P. gingivalis* and *P. intermedia*, gram-positive rods and uncultivable gram-negative rods present, and occasionally fungi such as *Candida albicans* have been found at these sites¹⁸. Some of the above bacteria were reported in the component studies, including *P.*

	Lefever et al., 2013 ¹⁵
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Green
Were the participants included in any similar comparisons?	Red
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Green
Was there a control group?	Red
Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Green
Was follow up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Green
Were the outcomes of participants included in any comparisons measured in the same way?	Green
Were outcomes measured in a reliable way?	Green
Was appropriate statistical analysis used?	Green

Fig. 3. Possibility of bias for the case series studies: JBI critical appraisal for QUASI experimental studies (adapted).

	Shaffer et al., 1998 ¹⁴	Chaffee et al., 2001 ¹³	Tseng et al., 2005 ¹²	Chan et al., 2011 ⁶	Qu et al., 2014 ¹⁶
Were the patient's demographic characteristics clearly described?	Green	Red	Green	Green	Green
Was the patient's history clearly described and presented as a timeline?	Red	Red	Red	Red	Red
Was the current clinical condition of the patient on presentation clearly described?	Yellow	Red	Red	Green	Green
Were the diagnostic tests of assessment methods and the results clearly described?	Yellow	Green	Red	Red	Green
Was the intervention(s) or treatment procedure clearly described?	Green	Green	Green	Green	Green
Were the advanced events (harms) or unanticipated events identified and described?	Green	Green	Green	Green	Green
Does the case report provide takeaway lessons?	Green	Green	Green	Green	Green

Fig. 4. Possibility of bias for the case reports: critical appraisal for case reports (adapted).

gingivalis¹⁵, *P. intermedia*¹⁵, and *Streptococcus*¹⁴ species. Furthermore, the quantitative characteristics of the bacteria have been suggested as the determi-

nant of the disease course²⁰. It appears that the commensal and/or pathogenic microbiota of the oral cavity may be involved in peri-implantitis irrespective

of whether the origin is endodontic or periodontal. Thus further investigation is required in order to assess the effects of implants and the quality and quantity of microbiota in the development of retrograde peri-implantitis.

The role of extra-radicular infection in relation to endodontic failure remains controversial, although it is generally accepted that microorganisms are present in cases of exacerbation, apical abscess, and draining sinus tract⁴. Otherwise, it has been suggested that extra-radicular infections are rare and that they can be caused by *Actinomyces* and *Propionibacterium*⁴. It has also been suggested that an extra-radicular infection can be contaminated by bacteria involved in intra-radicular infection, which is seen in refractory apical periodontitis⁴. However, a different group has highlighted that extra-radicular infections are relatively more common and involve *Candida* and gram-positive bacteria including *Staphylococcus*, *Enterococcus*, and *Enterobacter*, but *Actinomyces* is not always present^{21,22}.

An important issue is the potential for contamination during sampling procedures, as no component study described the sampling protocol implemented. A seminal study highlighted that, despite a sterile operation field, there is a high risk of contamination when undertaking samples of peri-apical regions²³. In fact sterility was only achieved consistently when isolation with acrylic shields and sterility of the apical region was tested via the root canal²³. Therefore, future studies implementing stringent sterilization procedures are required to determine the microorganisms involved in retrograde peri-implantitis. Furthermore, it should be highlighted that the presence of sinus tracts/fistulas was reported inconsistently in the component studies. This is of relevance, as these may constitute portals of entry for microorganisms from the oral cavity into the lesion, and therefore the microbiota detected may not necessarily be related to the aetiology of retrograde peri-implantitis. Similarly, further details regarding the overall oral health status (e.g., hygiene and other teeth) of the subjects may help to better understand the reported clinical observations.

There is currently no sound method for detecting a peri-apical pathosis radiographically. Amongst the component studies, all utilized PA^{6,12-16}, two studies used DPT^{12,15}, and two utilized CBCT^{6,16}. One study reported that the use of PA and DPT for diagnosis should be done with great care due to the risk of false-negatives²⁴. One study reflected the limitations of PA

and DPT, including the fact that a lesion positioned buccally or lingually will be impossible to distinguish and a lesion will not be detected until perforation of the cortex has occurred²⁵. However, CBCT has been proven to be more accurate and will more readily detect peri-apical lesions²⁴. In contrast, CBCT has also been associated with false-positives in endodontic diagnosis²⁶.

Clinicians need to be aware that radiographic diagnostic tools should be interpreted with caution. Thorough history-taking and clinical examination is paramount, and the integration of all knowledge prior to implant placement will allow for increased awareness of a pathosis occurring at the implant site. A true diagnosis can only be achieved with a histopathological and microbiological examination, which can be difficult prior to implant placement and also presents limitations related to potential sample contamination. Also, sampling and subsequent assessment are not necessarily applicable to routine clinical practice in implantology.

Finally, it should be highlighted that, although there is a trend suggesting an increased risk when placing implants in relation to an endodontic pathosis, the overall outcomes for implant rehabilitation appear not to be affected as long as adequate local measures and/or endodontic treatment of neighbouring teeth are considered before implant placement^{15,27–30}. Similarly, due to the limitations of diagnostic procedures mentioned above, implant placement will occur in the presence of extra-radicular infections and/or inflammation without the knowledge of the operator.

In conclusion, retrograde peri-implantitis of endodontic origin may involve the commensal and/or pathogenic microbiota of the oral cavity and/or a chronic inflammatory infiltrate, and can be associated with adjacent teeth and/or residual infection at the extraction site. The literature assessing the topic is scarce; therefore further confirmatory evidence is necessary for the proposed diagnostic entity and to elucidate its pathogenesis.

Patient consent

Not applicable.

Funding

None.

Ethical approval

Not applicable.

Competing interests

None.

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