<PE-AT>Incidence of Retrograde Peri-implantitis in Sites with Previous Apical Surgeries: A Retrospective Study.

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Summary: Implants placed in sites with previous apical surgery neither pose an increased risk of implant failure nor higher incidence of retrograde peri-implantitis.

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Abstract:

Background: Retrograde periimplantitis is a rapidly progressing periapical infection that forms around the implant apex. It is usually associated with sites adjacent to teeth with apical lesions; previous endodontic failures, retained root fragments etc. This study aimed to study the incidence of retrograde peri-implantitis in sites with history of apical surgeries.

Methods: Patients with sites treated for both apicoectomy and implant placement presenting to the University of Michigan School of Dentistry from 2001 to 2016 were screened**.** A total of 502 apicoectomies were performed, only 25 of these fit the predetermined eligibility criteria and were thus included in this retrospective analysis.

Results: Implants that were placed in sites with a previous apical surgery had a cumulative survival rate of 92%. The incidence of periimplantitis was 8%, while the incidence of retrograde peri-implantitis was 20%. There was an increased trend for retrograde peri-implantitis in cases where the cause of extraction was persistent apical periodontitis (35.7%), but this increase didn't reach the level of statistical significance (P=0.061).

Conclusions: Implants that are placed in sites with previous apical surgery are not at an increased risk of implant failure or retrograde peri-implantitis.

Keywords:

[Dental implants, Apicoectomy, Peri-implantitis, Complications**]**

<PE-FRONTEND>

INTRODUCTION

Implant-supported restorations have fairly high success and survival rates [1] and remain the primary choice of rehabilitation for partially and completely edentulous patients [2]. Despite this, peri-implant diseases present current clinical challenges with consistently increasing incidence [3, 4]. Apart from the classical presentation of peri-implant conditions (peri-implantitis and peri-implant mucositis), retrograde peri-implantitis (RPI) emerges as a distinct entity that originates at the apex of the involved implant. RPI was first defined as localized osteomyelitis and was believed to arise secondary to endodontic pathosis in adjacent teeth, among other reasons [5]. The definition has since been changed to any clinically symptomatic periapical lesion at a dental implant, sparing the coronal portion with undisturbed bone to implant interface [6].

For the etiology of RPI, some research groups have proposed that it results from either residual or active bacterial infection from previous endodontic therapy[7, 8]. Other reports concluded that determining a single causative factor is groundless, and might include, previous endodontic infection, apicoectomy, residual root fragments or previous periodontal infection [5, 9-14].

Based on that premise, the placement of implants in infected sites has since been cautiously approached. Multiple studies advocate against immediate or even early implant placement in such cases [7,15]. One study reported that if a periapical lesion at the apex of a tooth is present, a periapical implant lesion could be detected in 8.2–13.6% (OR 7.2) of the cases [15]. On the other hand, other studies showed remarkably high implant success rates, associated with immediate placement in similar situations, and a very low incidence of peri-implant disease [16-18]. A recent

quality assessment of systematic reviews concluded that this issue still remains controversial [19]. Others have suggested that a history of apical surgeries is the main predisposing factor for RPI [20], and that bacterial contamination of the implant body unequivocally remains a possibility after apical surgery [21].

When an infected tooth is extracted and pathogenic bacteria are left behind, these bacteria could undertake an inactive form, surrounding themselves with a singular coating which likely guards them from antibodies and antibiotics [22]. Later, when a dental implant is placed, the bacteria can be reactivated and colonize the implant surface (in this case, the apex). Furthermore, sites with a history of apical surgery will typically have a considerable apical defect [23] that may compromise the outcome of implant surgery. In addition, repeated flap reflection at these surgical sites leaves behind scar tissue and buccal bone loss [24, 25]. These conditions may discourage clinicians from placing dental implants in sites with previous periapical lesions and assume higher chances of developing peri-implantitis [26]. At this moment, only one study explored the potential correlation between failed apical surgeries and RPI [20]. Hence, the aim of this retrospective study was to evaluate the incidence of retrograde peri-implantitis in sites with history of apical surgeries. We hypothesized that implant placement in such sites would have an increased rate of retrograde peri-implantitis and failure.

MATERIALS AND METHODS

This study was approved by the University of Michigan School of Dentistry (UMSOD), Ann Arbor, USA Institutional Review Board for Human Studies (HUM00114382) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. The article was performed in concordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational/descriptive studies [27]. All patients who received dental implants between January 2001 and June 2016 at the UMSOD

were included in the screening process. The data was extracted from the patient records by two reviewers (MS and AR).

Inclusion criteria:

The inclusion criteria comprised: 1) Adult patients (≥18 years); 2) Implants placed in sites treated with apical surgeries due to root canal treatment failure; 3) Implant follow-up time of ≥3 years after prosthetic loading; 4) Radiographic follow-up with periapical radiographs that include the implant apex; 5) Complete clinical history.

Exclusion criteria:

Records were excluded from the study if they met one of the following criteria: 1) Patients taking medications that would influence bone metabolism; 2) Patients with uncontrolled diabetes mellitus (HbA1c≥8); 3) Teeth extracted due to reasons other than endodontic failure (i.e. trauma, strategic extractions, etc.) ; 4) Implants placed next to teeth with a periapical lesion 5) Implants placed but not restored; 6) Implants not placed at the UMSOD; 7) Patients with aggressive periodontitis; 8) Patient charts with inadequate data about peri-implant tissue health; 9) Implants placed before complete healing of periapical defect or before healing of guided bone regeneration (GBR) procedures.

Screening process:

A total of 9,317 implant cases and the corresponding 1,241 apical surgeries were screened, and only 41 cases were eligible for data analysis according to the aforementioned eligibility criteria. After a complete analysis of the included patient records, another 16 patients were excluded. Of the 16 cases excluded, 9 were due to a lack of sufficient documentation about the case and another 7 were excluded due to radiographs that a diagnosis was not discernable from.

Clinical procedures

All included patients were provided alternative treatment options before tooth extraction and implant placement, with written consent obtained before treatment. All cases had endodontic surgery performed after conventional endodontic treatment failed to relieve the symptoms. Only 20% of the involved teeth had a retrograde filling, which was in all cases done using a reinforced zinc oxide cement containing 32% eugenol and 68% ethoxy benzoic acid*. Eventually, all these surgeries failed for various reasons (Table 1).

Implant placement: After tooth extraction, the sites were thoroughly debrided and irrigated with saline. Forty four percent of sites had a ridge preservation procedure performed using cortico-cancellous allograft†. Patients who opted for implant placement were treated according to the standard protocol and were followed up regularly as part of a strict maintenance plan (at least 2 visits per year for periodontal maintenance therapy) after the implant was restored. Only in 3 cases (12%) was the clinical decision to place implants immediately. For the remaining 88%, the mean time between extraction and implant placement was 9.8 months (Table 2). As for implants that were diagnosed with RPI, treatment included either removing the implant or surgically treating the site through implant apical surgery (Table 2). The proposed guidelines for implant apical surgery were reported in a previous study [12]. Briefly, this consisted of making an incision at the mucogingival junction and reflecting a full thickness mucoperiosteal flap. The buccal plate was then removed to gain access to the periapical lesion, after which the lesion was collected for histopathologic examination and the residual defect was degranulated. Bone substitutes‡ and barrier membranes §were used to fill all these defects.

Clinical and radiographic evaluation:

The patient's age recorded was when the endodontic surgery took place. Smoking habits at the time of the surgery were also recorded, classifying them as non-smokers (0 cigarettes/day) or

smokers (≥1 cigarette/day). The history of periodontal disease was determined by checking the most recent periodontal chart, defining periodontal disease as the presence of at least 4 sites with clinical attachment loss (AL) ≥ 3 mm and a history of scaling and root planing [28]. Diabetic patients were verified by tracking full medical records.

Failure of apical surgery was considered when the treated teeth became symptomatic after a follow-up period of three months post-surgery. Eighteen out of the 25 teeth had apical lesions detectable radiographically at the time of extraction. The mean survival time of teeth after apical surgery was 2.4 years.

The resolution of a previous infection had to be achieved before a decision was made for implant placement. Implants were only placed when complete radiographic healing of sites was confirmed. As for the remaining defect after an extraction, most cases (83%) required either ridge preservation, GBR or both procedures before implant placement was considered possible. The average time between extraction and implant placement was approximately 10 months. A summary of the patient characteristics included in the study is provided in Table 1.

For establishing a diagnosis of peri-implantitis or retrograde peri-implantitis, intra-oral periapical radiographs were used. All radiographs were performed using a conventional standardized paralleling technique, utilizing position holders and a dedicated intra-oral radiographic unit**. Retrograde peri-implantitis was identified radiographically as a localized radiolucency 2 mm or more in size around the implant apex, in addition to the aforementioned clinical signs. The presence of peri-implantitis was confirmed when radiographic bone loss was found to be more than 2 mm from baseline of implant placement, and clinical records revealed bleeding on probing and exudate after ≥ 1 year(s) of implant prosthetic rehabilitation [29]. The amount of marginal bone loss around implants was measured after all radiographs were calibrated using an Imaging software†† [30]. Survival and success rates were calculated from the day of implant placement to the last patient visit with implant in situ, and without any complications, respectively. A diagnosis of RPI was deemed when progressive bone loss

confined to the apex of the implant [9, 31] was detected radiographically during follow-up visits by the Department of Endodontics, at the UMSOD.

Statistical analysis:

Each patient included in this study had only one implant placed after tooth extraction following the failure of a retrograde endodontic procedure. The following variables were retrieved for each patient: age, gender, smoking, presence of an apical lesion, performance of GBR, the occurrence of classical peri-implantitis, the occurrence of RPI and the reason for tooth extraction (apical periodontitis (EX-AP) vs other causes (EX-O)). Correlations among some of these variables were investigated using Pearson's correlation coefficient and chi-squared test. Setting the reasons for tooth extraction as the classification variable, differences in the parameters analyzed in patients who underwent extraction for apical periodontitis versus other reasons was also performed using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. All the analyses were performed using a dedicated software‡‡.

RESULTS

Our initial search yielded 502 apicoectomies performed during the 15-year observational period (2001 to 2016). Of these, only 25 cases fit the standard of being a failed apicoectomy, followed by implant placement, in addition to the other previously mentioned eligibility criteria. The average follow-up for these 25 was 70.3 months (5.9 years). After the cases were diagnosed with hopeless teeth that needed extraction by the Department of Endodontics, patients were referred to the Department of Periodontics department for extraction and implant placement. The causes of extraction varied, with 52% of the teeth extracted due to persistent apical

periodontitis and 34.7% because of vertical root fracture. Other causes of extraction included crown fracture, root resorption and endo-perio lesions (Table 1). About half (52%) of the cases in this study received ridge preservation, while 65.2% needed GBR at the time of implant placement. On average, the time between the extraction of failed teeth and implant placement was 9.8 months. The average survival time of teeth after apical surgery was 2.4 years and the mean follow-up time of implants placed was 6 years.

Five cases (20%) were diagnosed with RPI and another two (11.5%) had peri-implantitis. When comparing implants placed into sites where teeth were extracted due to persistent apical periodontitis (EX-AP) to those with teeth extracted due to other causes (EX-O) (Table 3), the prevalence of peri-implantitis observed was 14.3% in EX-AP and 0% in EX-O (p=0.5). The incidence of RPI was 35.7% in EX-AP sites and 0% in EX-O sites (p=0.061). The implant survival rate was 71.4% in EX-AP and 100% in EX-O. Of the 5 cases diagnosed with RPI, 3 were treated with implant apical surgery and 2 had to explanted. Details of treatment pertaining to the peri-implant surgery were reported in another study [12].

DISCUSSION

Peri-implantitis has been characterized as an inflammatory process around an implant, with both soft tissue inflammation and progressive loss of supporting marginal bone beyond biological bone remodeling [32]. The incidence of peri-implantitis in our cohort (8%) seems to corroborate the findings of studies investigating general implant populations, which implies that no added risk of peri-implantitis should be expected in a similar cohort [29]. The same can be held true for retrograde periimplantitis. Interestingly, the rate of RPI was found to be higher in EX-AP (35.7%) compared to patients EX-O (0%), with results close to the threshold of statistical significance (p-value = 0.061). We assume the lack of statistical significance to be probably due to the small sample size of the analyzed cohort (Table 3). Although our sample size is small, the

incidence of RPI in this patient population seems to be quite high, given that the incidence of RPI is generally rare; reportedly occurring in 10 of 3,800 cases [10].

In the present study, all EX-AP had a radiographic periapical lesion at the time of extraction. Recently, two systematic reviews concluded that debridement and grafting would improve the chances of success for implants placed in infected sites [33, 34]. In the current study, all sites were thoroughly debrided and irrigated after extraction, and systemic antibiotics were prescribed (when needed) at the time of extraction, GBR, and/or implant placement. Yet, the above-mentioned strategies did not appear to halt the progression of peri-implant disease or implant survival, particularly in the EX-AP sites (Table 2 & 3).

The present study shows that compared to sites with previous endodontic failures, sites with a history of apical surgery pose no additional risk. In the current study, the total implant survival rate was 92%. Lindeboom and co-workers reported a similar implant survival-rate of 92% when rough-surface implants were placed immediately in previously infected sites [35]. However, if only EX-AP results are considered, the survival rate would considerably drop to 85.7%. Previous studies reported an incidence of 0.26% for RPI [36], increasing to 7.8% if adjacent teeth had previous root canal therapy [7] and 13.6% if the tooth extracted had a periapical lesion [15]. Other studies showed the chance of RPI occurring in an implant adjacent to a tooth with an apical lesion to be about 25% (OR = 8.0) [37].

It has been suggested that delayed/late implant placement in previously infected sites would drastically decrease the expected complications [33, 34]. On the contrary, Quirynen and co-workers reported that 40% of their initial implant failures were associated with periapical lesions regardless of whether the implants were placed within an immediate or delayed protocol [6]. In the current study, in cases of delayed placement, implants were placed only after complete radiographic resolution was achieved. The mean time between extraction and implant placement was 8.9 and 10.3 months in EX-O and EX-AP, respectively. This suggests that in the

latter group, protracted healing times had no impact on decreasing the rate of biological complications.

Early studies reported an increased incidence of RPI after implant placement in sites with history periodontal disease [9], which emphasizes the role of bacterial biofilm in the development of RPI. Moreover, a study by Nelson and Thomas in 2010 found that bacterial biofilm persists in otherwise apparently healed alveolar bone after teeth with apical pathoses had been extracted [38]. Moreover, even after using their prescription debridement technique, around 50% of the bacteria lingered in the study sites [38]. These findings were verified by another group [39], which reported that 24 (15.6%) of their 154 patients had infected bone with bacterial colonies persisting in the alveolar bone one year after extraction and full mucosal healing. They concluded that this may represent a significant risk factor for early implant failure [39].

Some studies hypothesized that implant placement may activate the rather dormant bacteria in previously infected sites [22], which could be due to a foreign body reaction via titanium leakage due to corrosion [40, 41]. Others speculated that the bacteria itself might be responsible for modifying the rate and nature of corrosion of such metallic devices, thus predisposing the site to infection [42]. It is also worth noting that not only the bacteria are the culprit in this process; a few studies have linked viruses such as the Epstein-Barr virus with the incidence of RPI [8, 43]. Epstein-Barr virus is occasionally associated with the pathogenesis of symptomatic periapical lesions in endodontically involved teeth and should likewise be expected to play a role when implants are placed in the same sites [44]. Additionally, an HIV-related infection had been described as an etiological factor for RPI as well [37].

Quirynen and coworkers suggested that rough surface implants had a higher incidence of RPI than machined surface implants [6]. When a machined surface comes in contact with a granuloma or endodontic pathosis, it will rapidly be surrounded by granulation tissue and subsequently fail. Alternatively, due to their increased bone affinity, rough implant surfaces will have a crestal portion that is fully integrated before the defect-laden apical portion does. If the apical part also

has residual bacteria, the implants will exhibit RPI [6]. In our study, one out of 2 machined surface implants had retrograde peri-implantitis and eventually failed. In disagreement with previous theories, Alsaadi in a retrospective study involving 720 implants found failure rates in the moderately rough surface implants to be 20% when placed in sites with a history of apical lesions versus 1.82% when placed in apparently healthy sites [45]. Unfortunately, our cohort is too small to make conclusions regarding the role of implant surface on RPI incidence. Finally, it appears that residual defects usually remain for an extended period of time after failed apicoectomy procedures. One study found that the residual bony defects ranged in size between 0.3mm^2 and 21.1mm^2 in 83% of sites one year after apical surgeries [46]. In our study, this did not affect the success of implants placed in the EX-O group (Table 3).

The nature of the current study did not allow us to justify our management of the RPI cases, which were either managed by apical surgery or implant removal (Table 2). In a recent systematic review, it was reported that 35.7% of RPI cases will eventually lead to implant removal [47]. Other groups have provided detailed classifications and decision-trees to aid in deciding whether surgical intervention or implant removal is recommended, which the readers are encouraged to review [47, 48].

The circumstances addressed in the current study are quite particular but not uncommon in daily practice. Due to the small sample size included, it was hard to demonstrate any statistical significance in the results, yet this does not necessarily mean a lack of clinical significance [49]. That being said, the incidence of RPI in patients who had extractions due to apical periodontitis compared to other reasons nearly reached statistical significance (p-value = 0.061). Since this study lacked a control group (of patients who did not undergo apical surgery), our results cannot suggest that implants placed in such sites have an inferior survival rate compared to implants placed in healed sites. Another important limiting factor ascribed to the current study was our dependence on two-dimensional radiographs to aid in diagnosing the healing of sites with previous apical lesions.

It is important to emphasize that while peri-implantitis occurs circumferentially in the coronal portion of the implant and is associated with clinical signs of bleeding and/or suppuration, RPI occurs at the apex of the implant and commonly without early symptoms. Thus, peri-implantitis can be clinically detected more readily via probing. Meanwhile, RPI relies on patient compliance and careful radiographic assessment of the clinician. Furthermore, when a decision is made to treat the RPI lesion surgically, access is usually restricted, rendering a more unpredictable infection removal process [12, 50].

CONCLUSIONS

Implants that are placed in sites with previous apical surgery pose neither an increased risk of implant failure nor a higher incidence of retrograde peri-implantitis. A larger sample size in a controlled prospective study design is required to further validate the findings of this study.

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Table 1: Characteristics of included patients

	Characteristics of included patients
Number of screened patients	9317
Number of patients included in the study	25
Age(years), mean	58.7
Females (%)	17 (68%)
Males (%)	8 (32%)
Smokers(n), (%)	4 (16%)
Maxillary teeth(n), (%)	20 (80%)
Mandibular teeth(n), (%)	5 (20%)
History of periodontitis	6 (24%)
Causes of extraction	**persistent apical periodontitis** 14 (52%)
	Vertical root fractures 8 (34.7%)
	Non-restorable crown fracture 1 (4.3%)
	External root resorption 1 (4.3%)
	Endo-Perio lesion 1 (4.3%)
Type of restorations placed	**Single crown** 20 (80%)
	Bridges 5 (20%)

Table 2: Summary of outcomes of clinical interventions

	Summary of interventions and clinical characteristics
Opposing occlusion composed of natural teeth	25 (100%)
Number of apical surgeries with retrograde filling	20 (76%)
Presence of apical lesion at time of tooth extraction	19 (76%)
Survival time of tooth from apicoectomy to extraction (mean in years)	2.4 y
Ridge preservation after extraction	11 (44%)
Time between extraction and implant placement (mean in months)	9.8 months
Immediate implant placement	3 (12%)
GBR performed before or with implant placement	15 (60%)
Patients who performed both ridge preservation and GBR	10 (40%)
Systemic antibiotics prescribed with implant surgery	15 (60%)
Follow up time after implant placement (mean)	6 y

Peri-implantitis	2 (8%)
Retrograde Peri-implantitis (RPI)	5 (20%)
Implant survival	23 (92%)
Treatment of the 5 RPI cases	2 Implant removal
	3 Implant apical surgery

Table 3: Comparison of outcomes when cause of tooth extraction was considered

	(EX-AP) Teeth extracted due to persistent apical periodontitis (n=14)	(EX-O) Teeth extracted due to other causes (n=11)	*p-value*
Smokers	2	2	1.00
Survival time of tooth from apicoectomy to extraction (mean in years)	2.73 y	2.05 y	0.378
Ridge preservation/GBR after extraction	5 (35.7%)	5 (38.4%)	0.680
Time between extraction and implant placement (mean in months)	10.3 months (2.6-19.3)	8.9 months (0-11.6)	0.095
GBR performed before or with implant placement	9 (64.2%)	5 (38.4%)	0.624
Systemic antibiotics prescribed with implant surgery	9 (64.3%)	4 (36%)	0.657
Peri-implantitis	2 (14.3%)	0 (0%)	0.500
Retrograde peri-implantitis	5 (35.7%)	0 (0%)	0.061

Footnotes:

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* Super EBA (Harry J Bosworth Co, Skokie, IL, USA)
† Puros Cortical Particulate Allograft, Zimmer dental, Carlsbad, CA, USA.
‡ Puros Cortical Particulate Allograft, Zimmer dental, Carlsbad, CA, USA.
§ Biomend, Zimmer dental, Carlsbad, CA, USA.
** Rinn XCP film holder, Dentsply, USA.
†† ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA.
‡‡ STATA 16.0. (StataCorp 4905 Lakeway Drive, College Station, Texas 77845 USA).

Table Legends:

Table 1: Characteristics of included patients

Table 2: Summary of outcomes of clinical interventions

Table 3: Comparison of outcomes when cause of tooth extraction was considered