# “Sapienza” Università di Roma

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**XXXV Ciclo**

***Coordinatore:*** Prof. Diego Ribuffo

# “RETROGRADE PERI-IMPLANTITIS: DIAGNOSTIC, CLINICAL AND HISTOPATHOLOGICAL FEATURES.”


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## Abstract

Dental implants are a predictable and successful option to replace missing teeth, however they are not free from biological complications. Peri-implantitis prevalence is consistently rising and is currently one of the most investigated conditions in dentistry. However, another pathological condition called retrograde/periapical peri-implantitis (RPI) might affect dental implants. The RPI involves only the peri-apical portion of the implant and is detected radiographically as a radiolucent area, without pathological probing and signs of marginal bone loss. A very low prevalence (0.26-1.86%) has been reported for RPI, therefore, also considering the few articles available in scientific literature on the topic, the pathology is still relatively unknown among clinicians. There is no consensus about RPI aetiology: the main possible causes hypothesized are implant insertion in a site with a pre-existing unhealed infection or inflammation, implant placement in a site that previously housed an endodontic treated tooth with further bacteria reactivation, pulpal/periapical endodontic lesions at adjacent teeth or bone overheating during implant drilling. Several treatment strategies have been reported: antibiotic therapy with/without endodontic treatment of the adjacent tooth or surgical/chemical debridement of the apical implant site with/without guided bone regeneration (GBR) procedures and with/without the resection of the implant apex. In a systematic review, our study group highlighted how surgical and mechanical debridement of the apical part of the implant associated with GBR was the most used surgical treatment option. After the publication of one cross-sectional and one retrospective study with the maximum follow-up available in literature, on the topic, our department was considered as a referral center for diagnosis and treatment of RPI by private practitioners based in Rome. The aims of this case series are to report prospective data and histopathological findings of RPI in a single center and to evaluate implant survival after a standardized surgical approach. During the observational period, a total of 4 patients were referred to our department for retrograde peri-implantitis treatment. Three male patients and one female, with a

mean age of 61.75±13.81 years, in all cases, prior to implant placement, teeth extracted had previous endodontic treatment. Patients reported symptoms of RPI after a mean period of 134.5±69.69 days (range: 34-192 days). All patients were treated with the same surgical approach: antibiotic therapy, mechanical curettage, chemical decontamination and guided bone regeneration. Furthermore, the periapical lesion was carefully enucleated and collected for histopathological examination. No implant was lost after treatment: a 100% survival rate was detected after a mean follow-up of 1.5±0.57 years (range: 1-2 years). The histopathological examination revealed, in all cases, the presence of a chronic inflammatory infiltrate with occasional multinucleated giant cells inglobating unidentified foreign particles and signs of bone remodeling. Based on the analysis of patients' characteristics and histopathological samples, it can be speculated that bacteria from teeth with failed endodontic treatment or residual lesions were reactivated by drilling for implant osteotomy, with subsequent colonization of the implant apex. Since in all cases previous teeth in implant sites were endodontically treated, foreign body particles incorporated in the inflammatory tissues might be derived from remains of previous root canal therapy.

Therefore, within the limitations of the study, it could be cautiously concluded that RPI can be predictably and successfully treated with surgical curettage and GBR. Further studies, with larger sample, are needed to confirm these clinical findings.

# Introduction

Implant supported prosthetic rehabilitation is considered a predictable and successful option for replacing missing teeth in partially and fully edentulous patients [1-3]. However, the widespread diffusion of dental implants has been associated, in the last 30 years, with the rise of mechanical [4-7] and biological complications [8,9], divided in peri-implant mucositis (fig.1) and peri-implantitis (fig.2) [10]. Peri-implantitis is an irreversible plaque-related inflammatory lesion and the first cause of late implant failure [11]. It is defined, by the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, as a pathological inflammation of peri-implant tissues with progressive loss of supporting bone detected radiographically [12].

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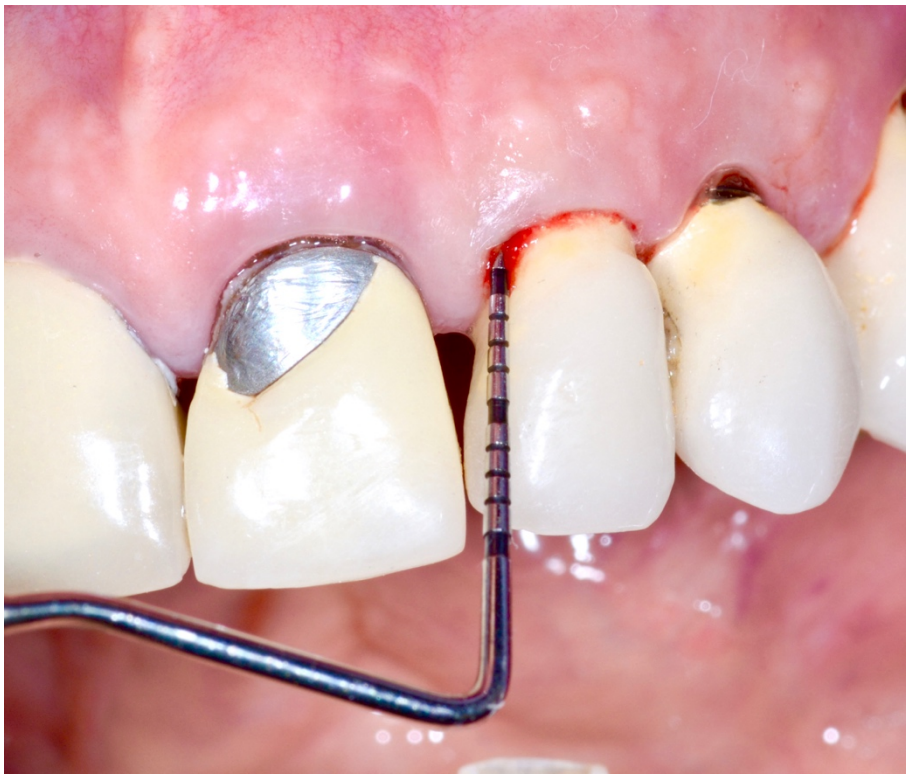


Fig. 1. Peri-implant Mucositis

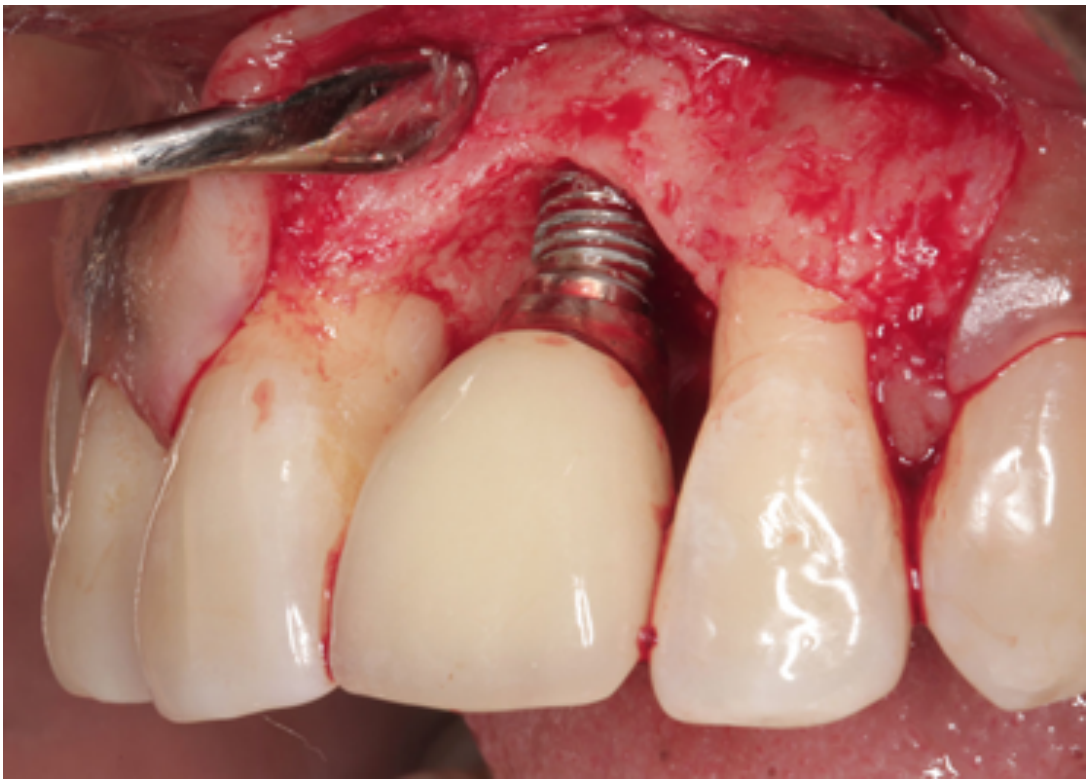


Fig. 2. Peri-implantitis

The prevalence of peri-implantitis is still controversial, depending primarily on case definition adopted: a recent systematic review found out that around 23% of dental implants are affected by peri-implantitis and 43% by mucositis [13]. At the same time, due to the heterogeneity of the case definition, recent systematic review [14] downgraded the peri-implantitis rate 18.5% at the patient level and 12.8% at the implant level.

Another disease, called retrograde/periapical peri-implantitis (RPI) [15], was firstly described in 1992. The RPI affects only the peri-apical portion of the implant and is detected radiographically as a radiolucent area (fig. 3), without pathological probing and signs of marginal bone loss (fig. 4-5) [16].

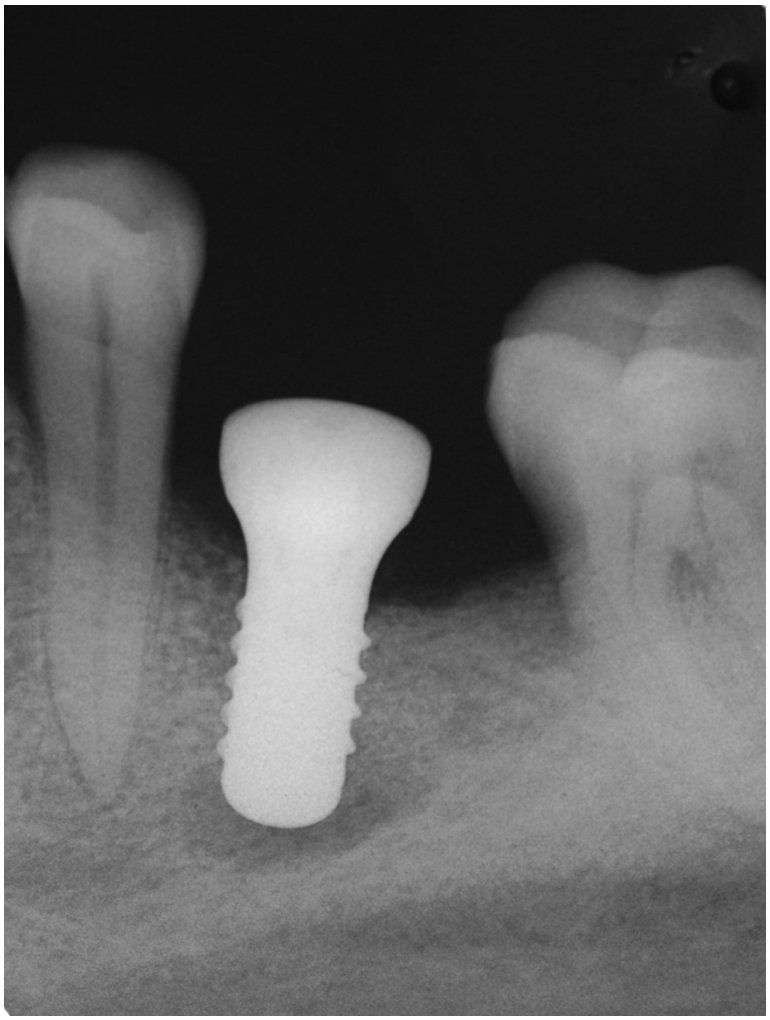


Fig. 3. The radiographic aspect of Retrograde Peri-implantitis (RPI)

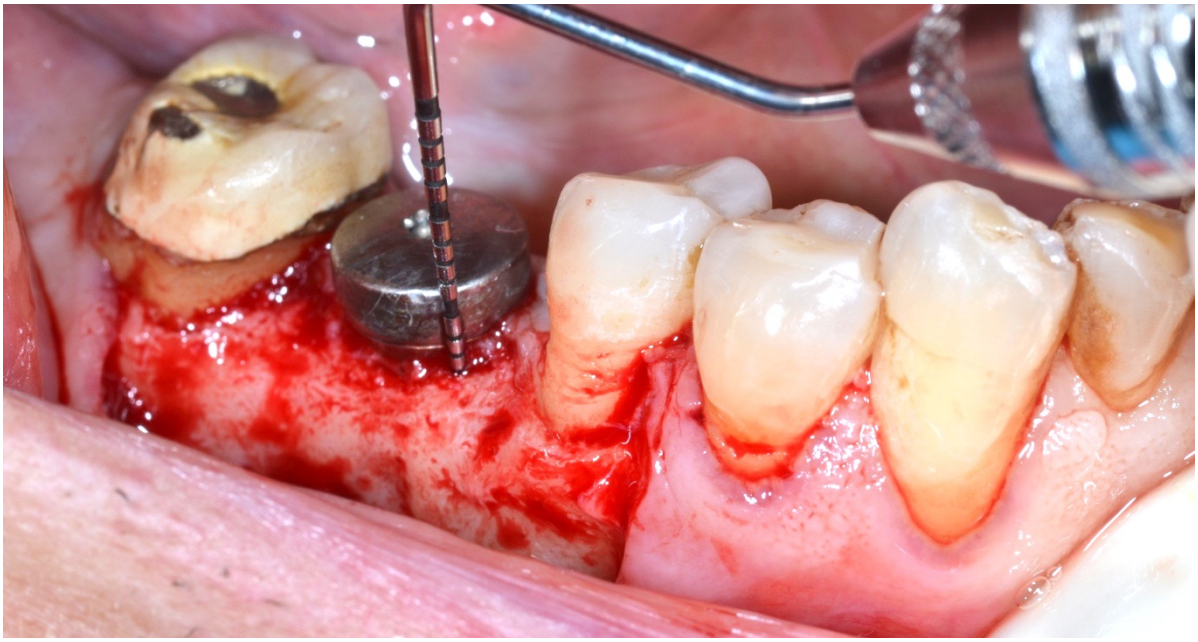


Fig. 4. An implant affected by RPI shows no pathological probing and signs of marginal bone loss

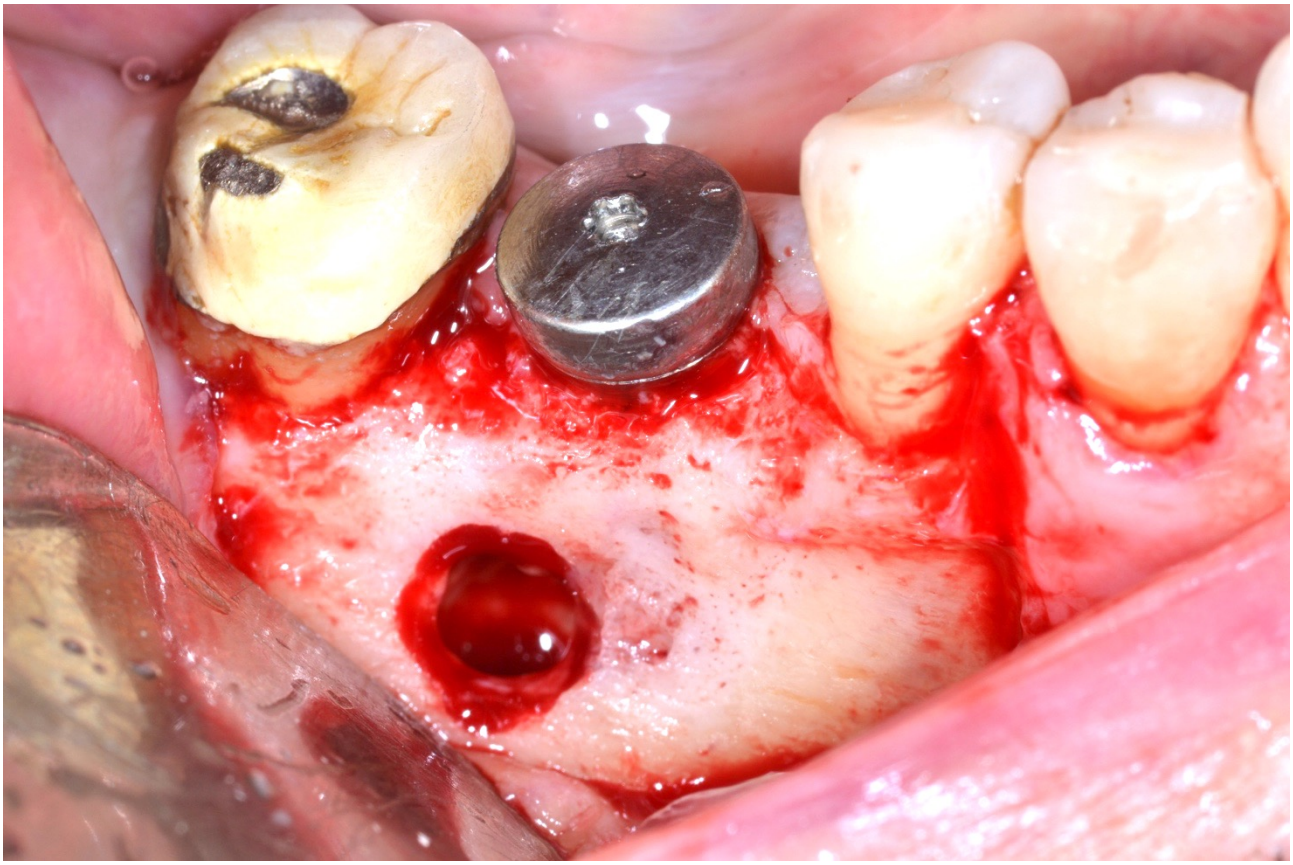


Fig. 5. An implant affected by RPI shows bone resorption only in periapical area

A very low prevalence (0.26-1.86%) has been reported for RPI [17], therefore, considering also the few articles available in scientific literature on the topic, the pathology is still relatively unknown among clinicians [18]. Zhou et al. reported a prevalence of RPI of 7.8% in cases of dental implants placed adjacent to teeth with endodontic periapical lesions [19], while Lefever et al. described Odds Ratio (OR) of developing RPI ranging from 7.2 to 8 in cases of endodontic pathology on the extracted or neighbouring tooth [20].

There is no consensus about RPI aetiology: the main possible causes hypothesized are implant insertion in a site with a pre-existing unhealed infection or inflammation [21], implant placement in a site that previously housed an endodontic treated tooth with further bacteria reactivation [22,23], pulpal/periapical endodontic lesions at adjacent teeth or bone overheating during implant drilling [24,25]. Furthermore, also implant placement in a longer prepared osteotomy site, has been reported as probable cause of asymptomatic periapical lesions at the implant site [16,21]. The RPI is characterized by progressive bone loss at the apical part of the implant, detected radiographically, in the first weeks up to four years after implant placement [15]; without radiological alterations of peri-implant marginal bone levels as well as pathological probing pocket depths [26].

Clinical findings are not always present and can include pain, dull percussion, swelling, tenderness, redness and a fistulous sinus tract site at the buccal apical part of the implant [17].

According to the classification proposed by Sussman and Moss in 1993, RPI is an endodontic implant pathology, divided in type 1 (implant to tooth lesion), which occurs when the implant placement results in the devitalization of an adjacent tooth, and type 2 (tooth to implant lesion), when an apical lesion from a neighbouring endodontically treated tooth contaminates the implant [25].

The original classification was implemented by Sarmast et al. in 2016 (fig.6), with the inclusion of two additional classes: type 3 and type 4 [27]. Type 3 is related to apical implant lesion developing in case of improper implant angulation (ie, outside the bone cortex). Type 4 is related to apical implant lesion developing for residual microorganisms (viruses or bacteria) or bone infection reactivation, with a non-osseointegration of the apical implant zone and its contamination.

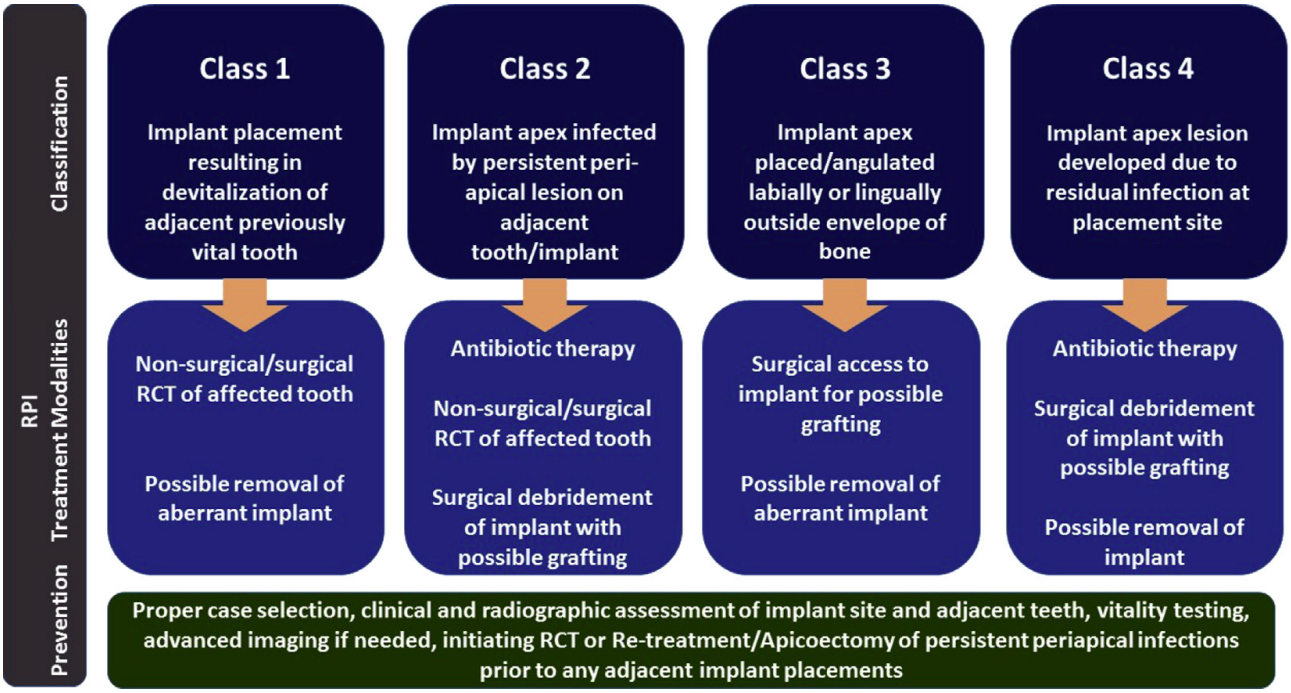



Fig. 6. The classification of retrograde peri-implantitis as published by Sarmast et al. in 2016. (Sarmast ND, Wang HH, Soldatos NK, Angelov N, Dorn S, Yukna R, Iacono VJ (2016) A novel treatment decision tree and literature review of retrograde peri-implantitis. J Periodontol 87:1458-1467)

According to Pennarrocha- Diago et al. [28], the evolution stage of the periapical lesion should be divided in three parts, promptly individuated and included in the diagnosis to determine the best suitable treatment strategy.

Acute periapical lesion staging can be divided into three parts:

1. Non-suppurated: there are no radiographically detectable changes in bone density around the apex of the implant, but a spontaneous and localized pain at the implant mucosa is present.

2. Suppurated: an appreciable radiolucency is present as a result of purulent collection around the apex of the implant, with an active process of bone reabsorption.

3. Suppurated-fistulized: there is a visible radiolucency, a fistulous tract from the apex of the implant is detectable in the buccal plate or in coronal direction. Diagnosis of retrograde peri-implantitis,

and therefore, its prevalence, may also be influenced by the limits of two-dimensional radiographic imaging systems, with an underestimation that can be solved by the use of three-dimensional cone beam. Regarding the treatment of RPI, there is no clear consensus in literature [20]: therapeutic modalities based only on antibiotic therapy with/without endodontic treatment of the adjacent tooth [29] have been described, together with surgical approaches with the aim to eliminate the inflammatory process and allow the re-osseointegration of the apical part of the implant [27]. The surgical treatment usually includes surgical/chemical debridement of the apical implant site with/without bone regeneration procedures and with/without the resection of the implant apex [30,31].

In a systematic review, our study group [32] highlighted how surgical and mechanical debridement of the apical part of the implant associated with GBR with allograft and absorbable membrane was the most used surgical treatment option. After the publication of several studies on the topic [32-35], our department was considered as a referral center for diagnosis and treatment of RPI by private practitioners based in Rome. The aims of this case series are to report prospective data and histopathological findings of RPI in a single center and to evaluate implant survival after a standardized surgical approach.

# Material and Methods

### *Study design*

A prospective case series was conducted enrolling patients with a diagnosis of retrograde peri-implantitis at the Department of Oral and Maxillo-Facial Sciences, "Sapienza" University of Rome between January the 1st 2020 and April 30th 2022. All patients agreed to be included in the study and signed the informed consent form according to the latest version of the World Medical Declaration of Helsinki (2013). The study was reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies.

### *Inclusion and Exclusion Criteria*

Patients were enrolled in this case series if they had one or more implants showing a radiolucency around the implant apex, without implant mobility.

### *Data Recording*

For each patient with a radiographic diagnosis of RPI the following variables were collected: sex, age, smoking habits, periodontal status (presence or absence of periodontitis), reason for tooth extraction and endodontic status prior to implant placement. Furthermore, clinical symptoms of RPI (pain, swelling, dull percussion or fistula presence) and days from symptoms' appearance after implant placement were also collected, as well as periodontal and endodontic status of adjacent teeth. Periapical x-rays taken with the long-cone parallel technique and a standardized film holder (Rinn Centratore XCP, Dentsply, Rome, Italy) at RPI diagnosis, three months after surgical treatment and at the latest follow-up available were collected for each patient included in the study.

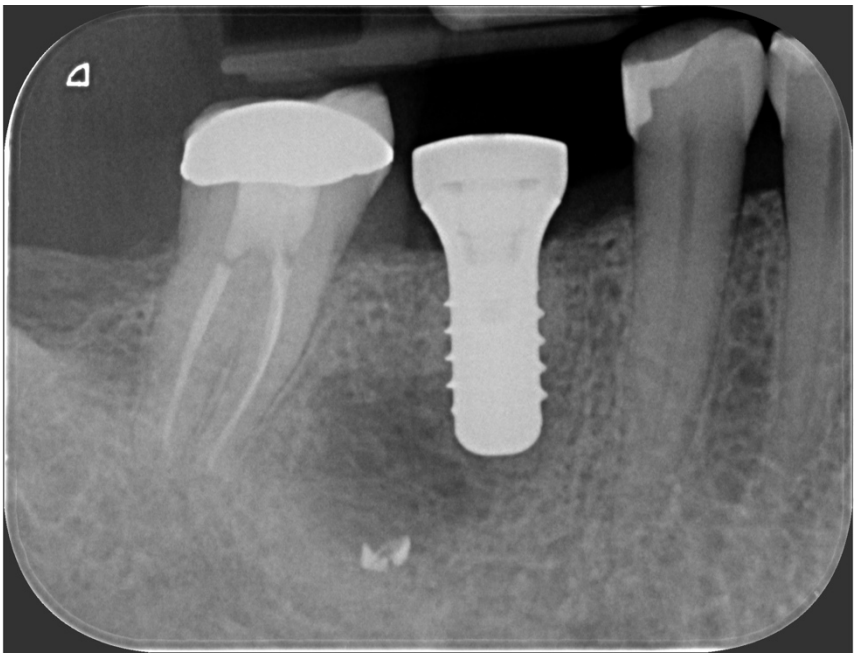
***Surgical Procedure***

After diagnosis of RPI through radiographic examination and symptoms presentation (fig. 7A-B), a sensibility test was performed at the adjacent teeth of implants involved to assess their vitality and, therefore, the possible endodontic origin of RPI. An antibiotic treatment was prescribed to all patients: a combination of amoxicillin 500mg (Zimox®, Pfizer, New York, USA) and metronidazole 250mg (Flagyl®, Pfizer, New York, USA) 3 times/ day for one week, starting one day before surgery. The same surgical approach was performed in all cases included by the same operator.

At the beginning of the procedure, patients were instructed to rinse for 1 minute with chlorhexidine gluconate 0.12%. Surgery was performed under local anaesthesia, with a sterile operating field. A mucoperiosteal flap was raised (fig. 7C-D) to gain access at the affected area by using a 15c scalpel blade (Hu-Friedy, Chicago, IL, USA), performing intrasulcular incisions at the implant and the distal tooth and a releasing incision at the mesial tooth. Meticulous mechanical debridement and degranulation of the bone in the periapical implant site were performed using Lucas spoon and Gracey curettes (fig. 7E-F). The periapical lesion was carefully enucleated and collected for histopathological examination (fig. 7G-H). The collected sample was conserved in a 10% neutral buffered formalin.

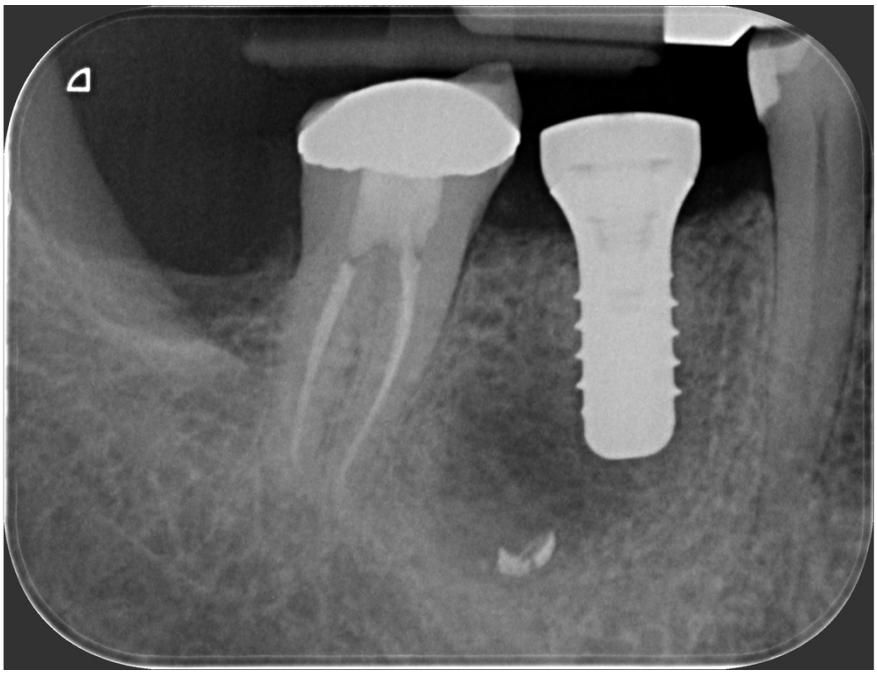
Ultrasonic devices and carborundum burs were used to polish the spiral convexity of the implant surface. A chemical detoxification was performed, by applying chlorhexidine gluconate 0.2% for 2 minutes on the titanium surface, and then, by rinsing abundantly the site with sterile saline solution 0.9%. Prior to flap closure with non-absorbable sutures, the cavity was filled by using small particles of deproteinized bovine bone material (Bio-oss, Geistlich AG, Wolhusen, Switzerland) (fig. 7I-L). A collagen membrane (Zimmer® Collagen Tape, Zimmer Biomet Dental, Okland, NJ, USA) was applied to cover the bone substitute in all patients (fig. 7M-N). The adjacent teeth remained untouched during the procedure. Standard postoperative instructions were prescribed together with rinsing with 0.2% chlorhexidine digluconate 2 times a day and to avoid tooth brushing in the area for 14 days, with ibuprofen 600 mg (Brufen, Abbott, Verona, Italy) prescribed to be taken as needed. Sutures removal was performed after 14 days (fig 7O).

Figures 7 (A-S). An RPI case treated:



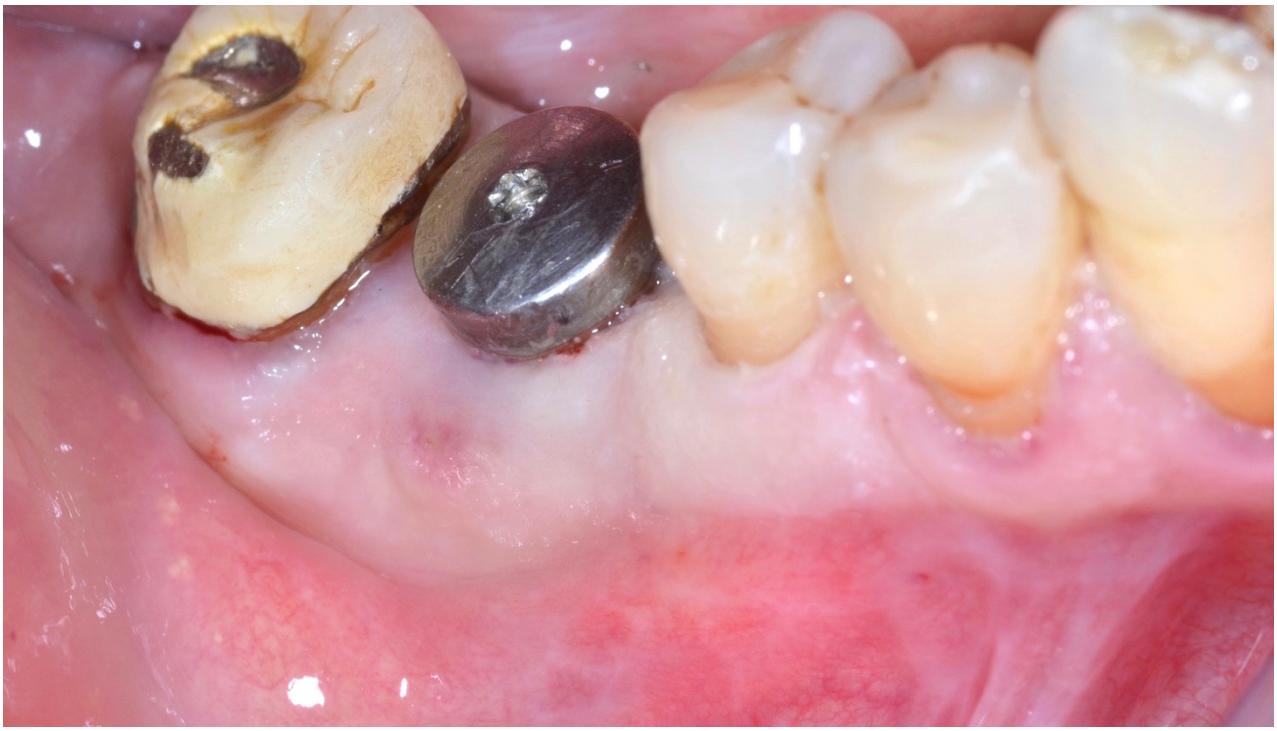
A. First periapical radiograph taken after symptoms occurrence.

A radiolucency area affects the apical part of the implant

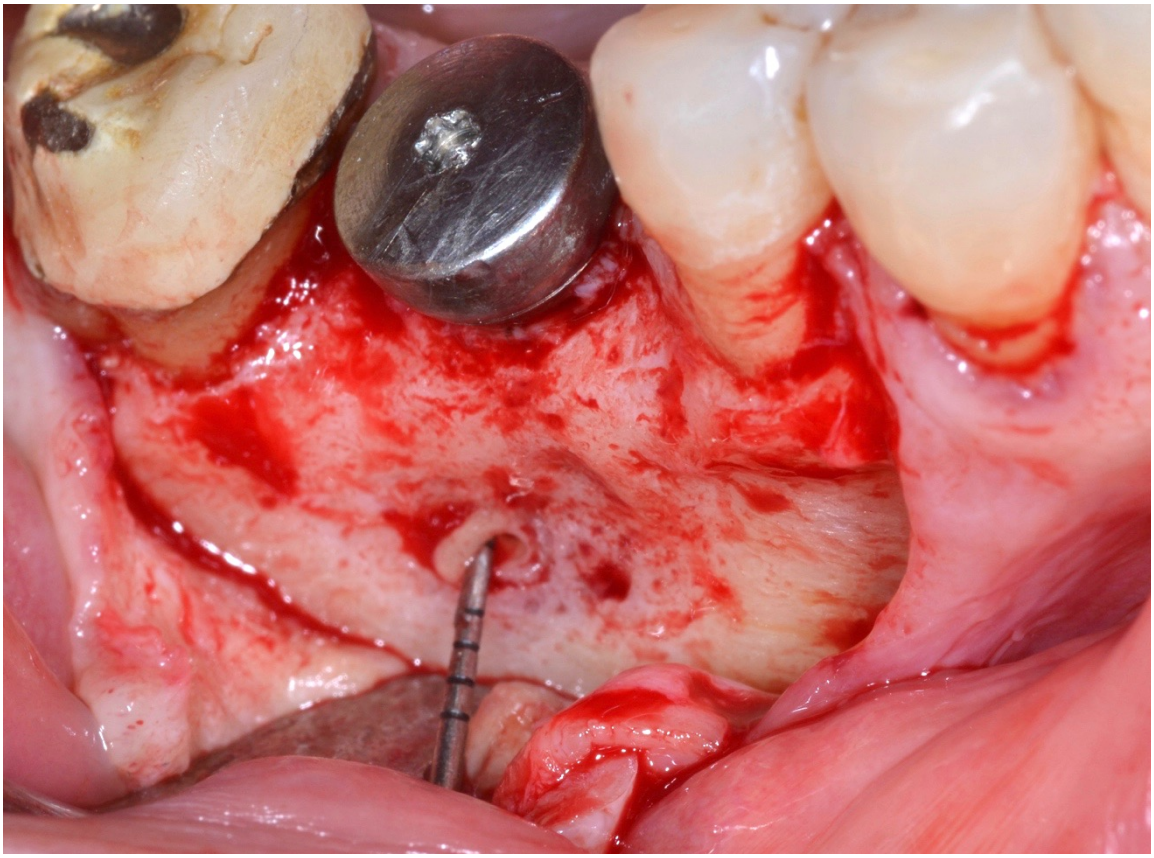


B. The periapical radiograph taken the day of the surgery (6 days after the first x-ray).

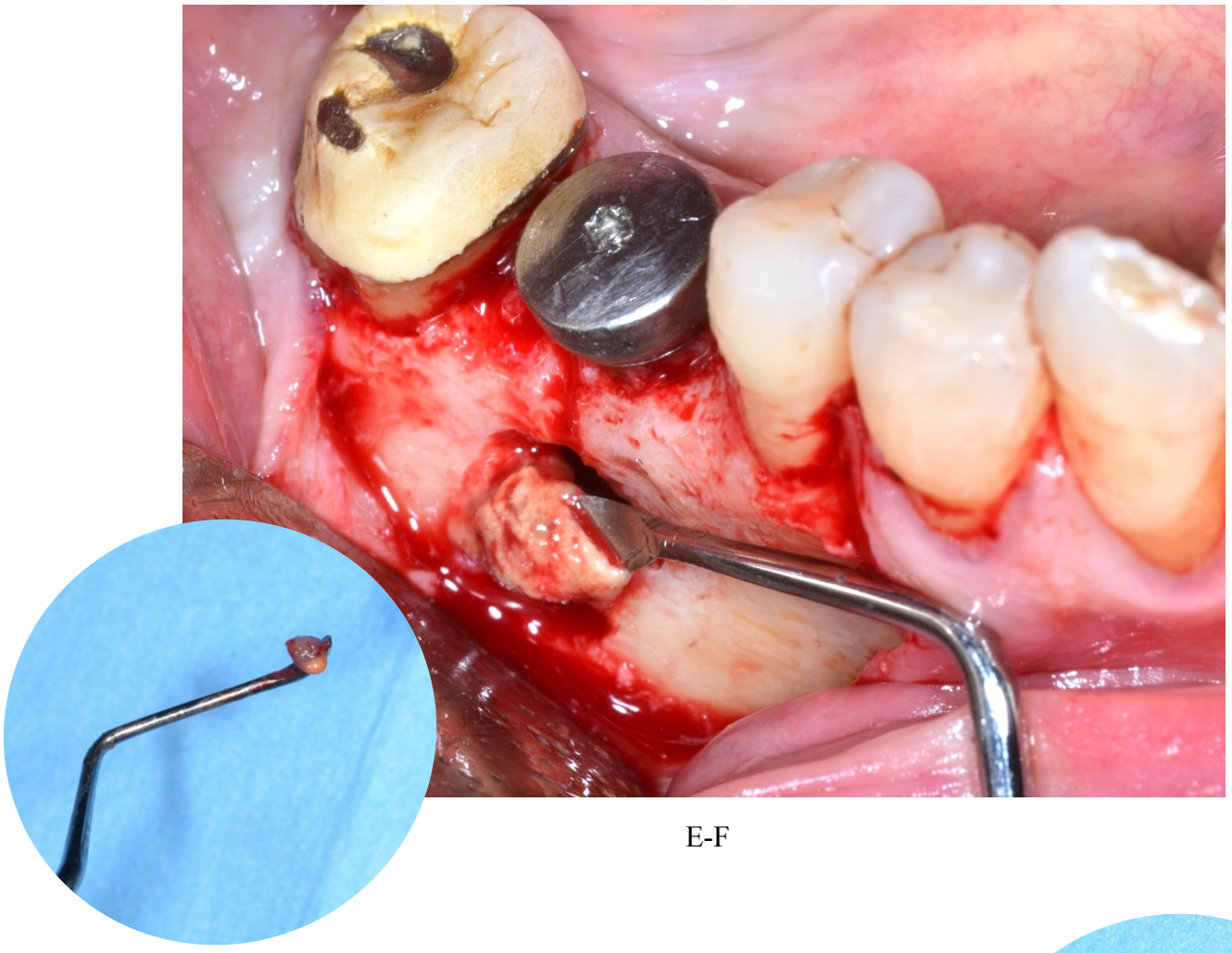
Rapid development of the lesion is shown



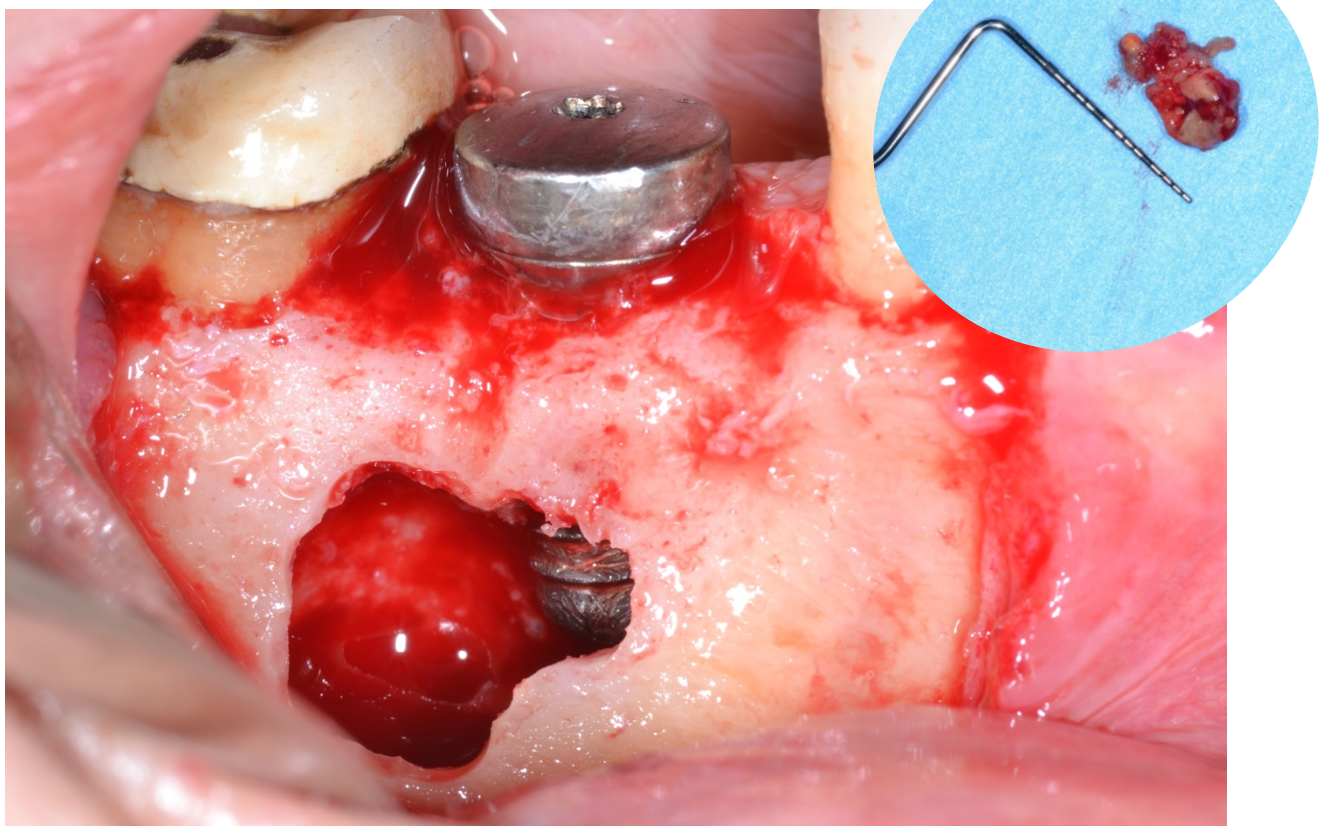
C.



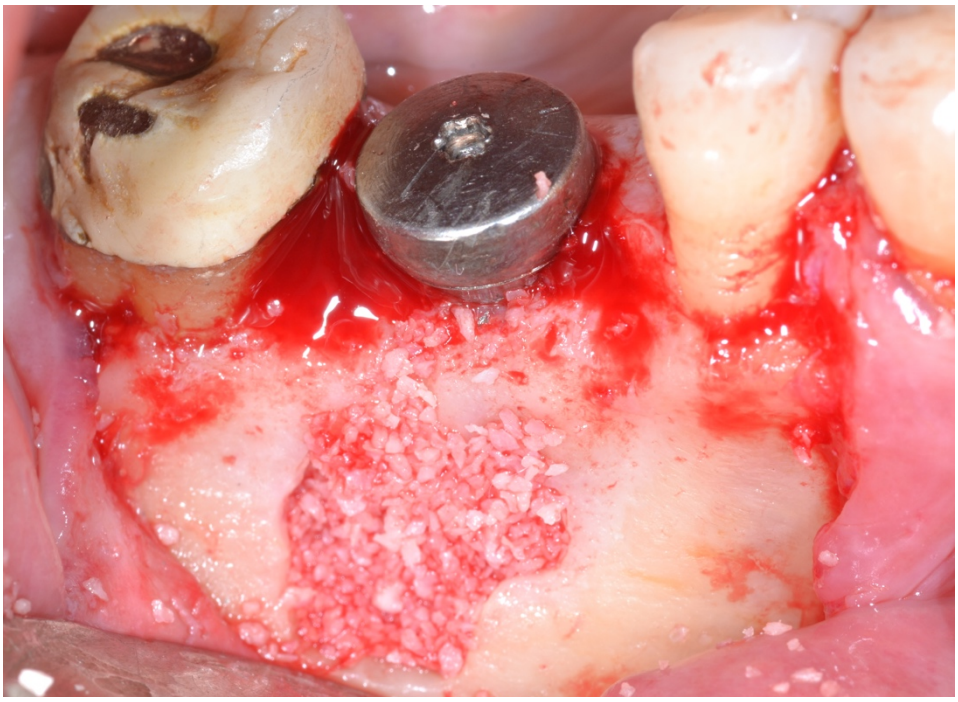
D.



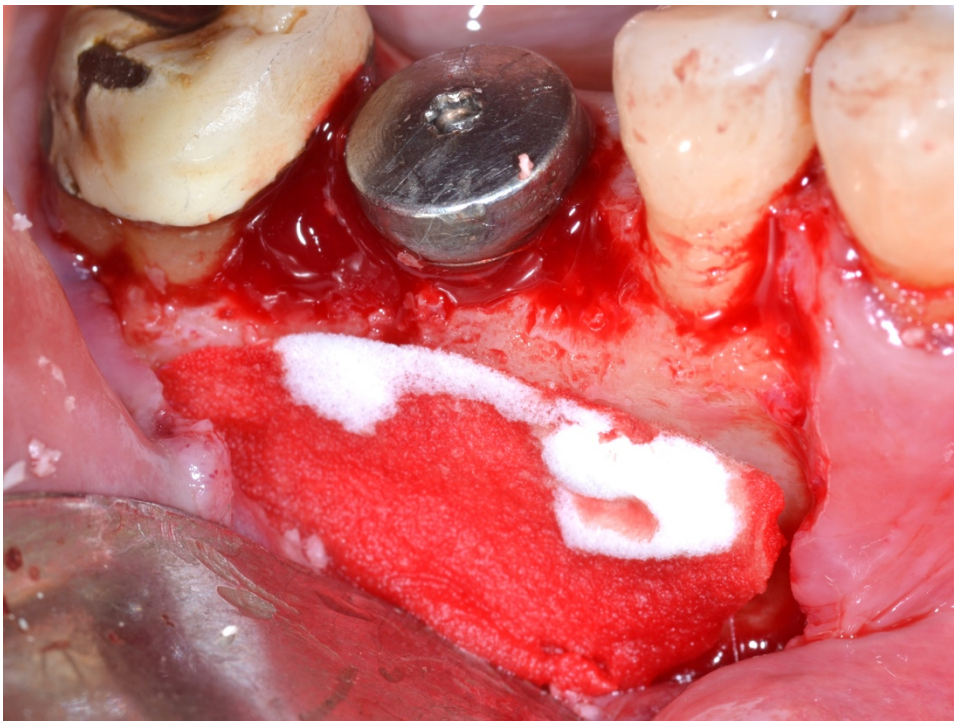
E-F



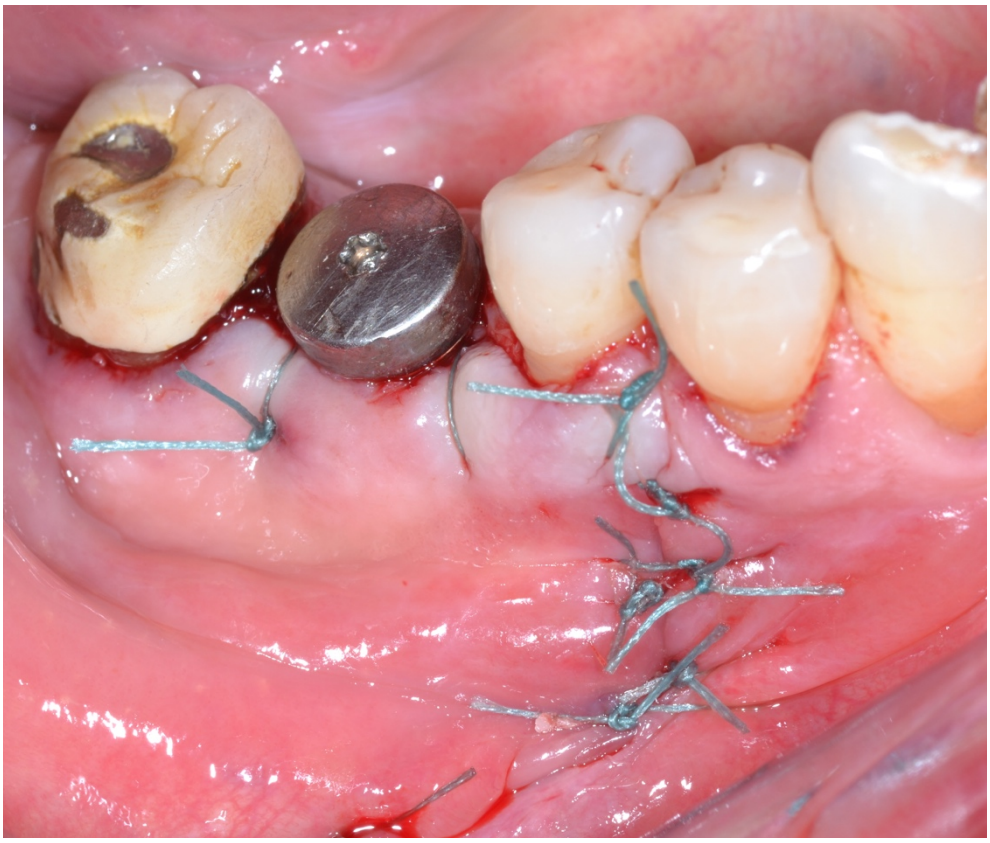
G-H



I-L



M-N.



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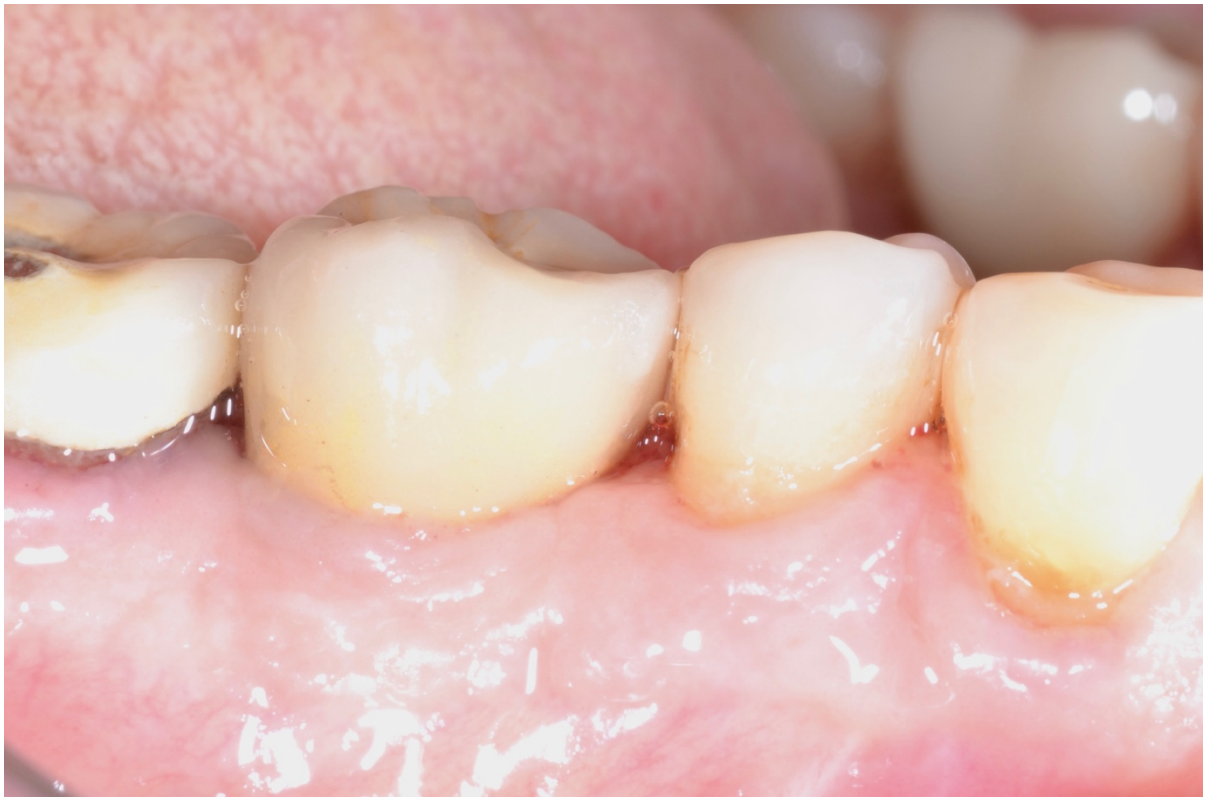

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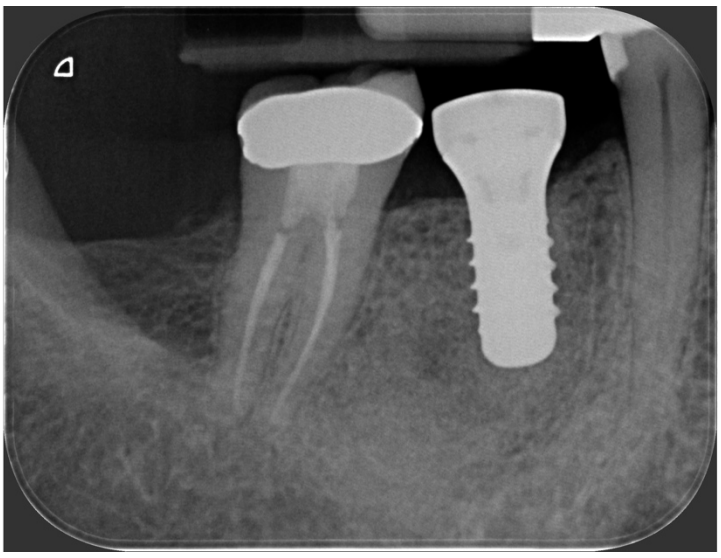
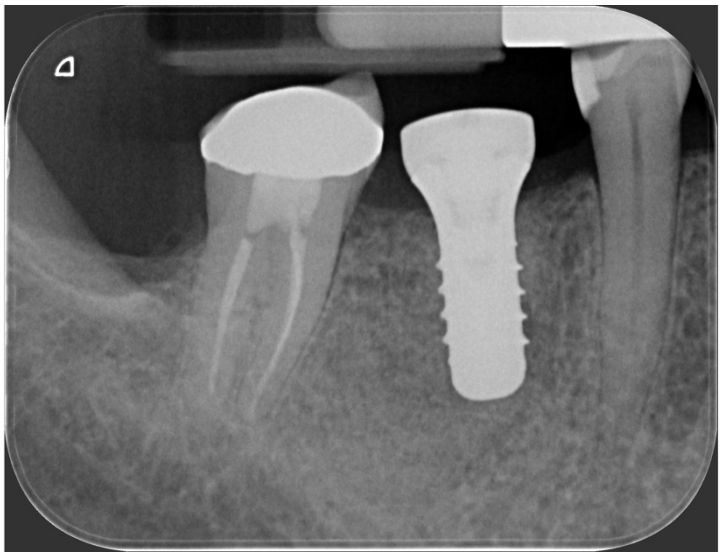
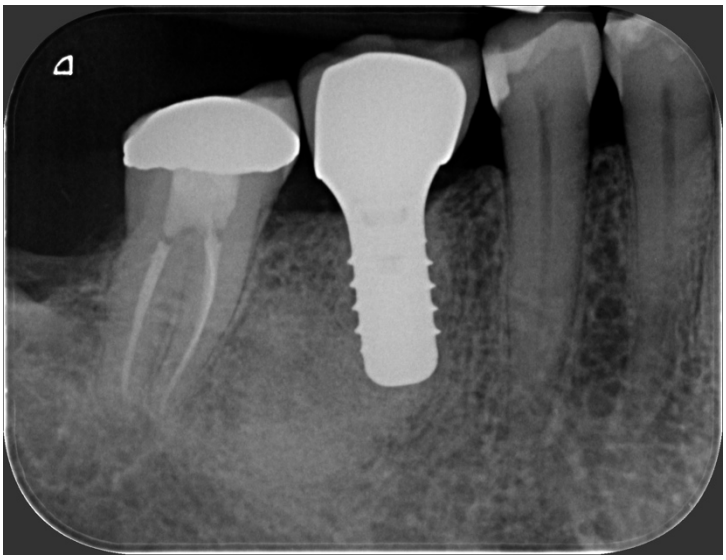


Q. Periapical x-ray taken immediately after surgical procedure



R. Periapical x-ray 3 months after surgery



S. Periapical x-ray 2 years after surgery

An implant in place at the respective follow-up visit was considered as surviving implant (fig.7P-S).

***Peri-implant parameters***

For each implant affected by RPI, the following clinical measurements were also recorded at six sites per implant by using a periodontal probe (PCP-Unc 15, Hu-Friedy®, Chicago, Illinois, USA) with a light force (approximately 0.15 N), without anaesthesia by the same trained calibrated operator:

• Probing Pocket Depth (PPD). Measured in millimetres, is the distance from the mucosal margin to the bottom of the probable pocket

• Plaque Index (PI) recorded with dichotomic values (present/absent)

• Bleeding on probing (BOP) recorded with dichotomic values (present/absent)

Furthermore, Full Mouth Plaque Score (FMPS) and Full Mouth Bleeding Score (FMBS) were recorded at baseline and at the latest follow-up available.

***Histopathological examination***

Histopathological examination (hematoxylin and eosin stain) of collected samples was performed at the Department of Anatomical, Histological, Forensic Medicine and Orthopedic Science at "Sapienza" University of Rome.

***Statistical analysis***

Data were evaluated using standard statistical analysis software (version 20.0, Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). A database was created using Excel (Microsoft, Redmond, WA, USA). Descriptive statistics (mean, standard deviations and range) were computed for each continuous variable collected, while frequency was reported for categorical variables.

# Results

During the observational period, a total of 4 patients were referred to our department for retrograde peri-implantitis treatment. Patients were three male and one female, with a mean age of 61.75±13.81 years (range: 48- 80 years) and implants affected constituted 30.76% of the total implants placed in these patients (n= 4/13), with every subject having all the other dental implants classified as clinically healthy. Demographic data and detailed implant-related characteristics of patients enrolled are reported in Table 1.

**Table 1.** Detailed characteristics of dental implants with retrograde peri-implantitis

| **Variable** | **Case 1** | **Case 2** | **Case 3** | **Case 4** |
|---|---|---|---|---|
| Sex | M | M | M | F |
| Age | 80 | 48 | 55 | 64 |
| Smoking habits | no | yes | no | yes |
| Periodontitis | no | yes (stage 3, grade B) | no | yes (stage 3, grade B) |
| Implant position | 4.6 | 1.2 | 3.6 | 3.6 |
| Implant brand | Straumann | Straumann | Straumann | Zimmer |
| *Reason for tooth loss* | endodontic failure | fracture | fracture | periodontitis |
| *Endodontic status of previous tooth* | endo-treated | endo-treated | endo-treated | endo-treated |
| Implant length | 10 | 12 | 10 | 10 |
| Implant diameter | 4.8 | 3.3 | 4.8 | 4.1 |
| *Symptoms* | | | | |
| Days until appearance following implant insertion | 34 | 145 | 167 | 192 |
| Constant pain | yes | yes | yes | no |
| Dull percussion | no | no | yes | yes |
| Swelling | no | yes | no | yes |
| Fistulous tract | no | no | yes | no |
| Mesial neighbour | vital | endo-treated | vital | vital |
| Distal neighbour | endo-treated | vital | implant | vital |
| Total implants (n) | 3 | 3 | 3 | 4 |
| Follow up (years) | 2 | 1 | 2 | 1 |

The referring dentists reported that all dental implants were placed adopting a delayed approach several months after teeth extractions, following proper manufacturers' instructions and checking intraoperatively correct buccal-oral position of the implant and integrity of the facial bone wall. No immediate loading procedures were attempted in any case.

Reasons for extraction prior to implant placement were root fracture (2 teeth), endodontic treatment failure (1 tooth) and periodontitis (1 tooth). All teeth extracted had previous endodontic treatment. Two implants were placed adjacent to endodontically treated teeth, while two patients were classified as periodontitis cases based on the latest 2017 World Workshop classification [36]. Patients reported symptoms after a mean period of 134.5±69.69 days (range: 34-192 days) from implant placement.

***Rpi Treatment***

Following RPI surgical treatment, the inflammatory process was eliminated, and no adverse reactions or complications were recorded.

No implant was lost after treatment: a 100% survival rate was detected after a mean follow-up of 1.5±0.57 years (range: 1-2 years). Healing was uneventful in all cases treated, no adverse reactions were reported, and peri-implant clinical parameters collected throughout the follow-up period are reported in Table 2.

Adjacent teeth remained untreated in all cases.

**Table 2:** Clinical parameters of dental implants with retrograde peri-implantitis

| Variable | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| ***Probing pocket depths (PPD)*** *Implant site* | | | | |
| PPD-baseline | 3.33±0.51 | 3.8±1.16 | 3.8±0.75 | 3.33±0.51 |
| PPD-latest follow-up | 3.8±0.75 | 3.33±0.51 | 4±0 | 4.16±0.98 |
| ***Bleeding on Probing (BOP)*** *Implant site* | | | | |
| BOP-baseline | - | + | - | + |
| BOP- latest follow-up | - | - | + | - |
| ***Plaque Index (PI)*** *Implant site* | | | | |
| PI-baseline | - | - | - | - |
| PI- latest follow-up | - | + | - | - |
| ***Full Mouth Bleeding Score (FMBS)*** | | | | |
| FMBS-baseline | 18% | 22% | 18% | 24% |
| FMBS- latest follow-up | 16% | 24% | 14% | 22% |
| ***Full Mouth Plaque Score (FMPS)*** | | | | |
| FMPS- baseline | 16% | 23% | 14% | 22% |
| FMPS- latest follow-up | 18% | 22% | 12% | 22% |

The histopathological examination (fig. 8) revealed, in all cases, the presence of a chronic inflammatory infiltrate with occasional multinucleated giant cells inglobating unidentified foreign particles and signs of bone remodeling.

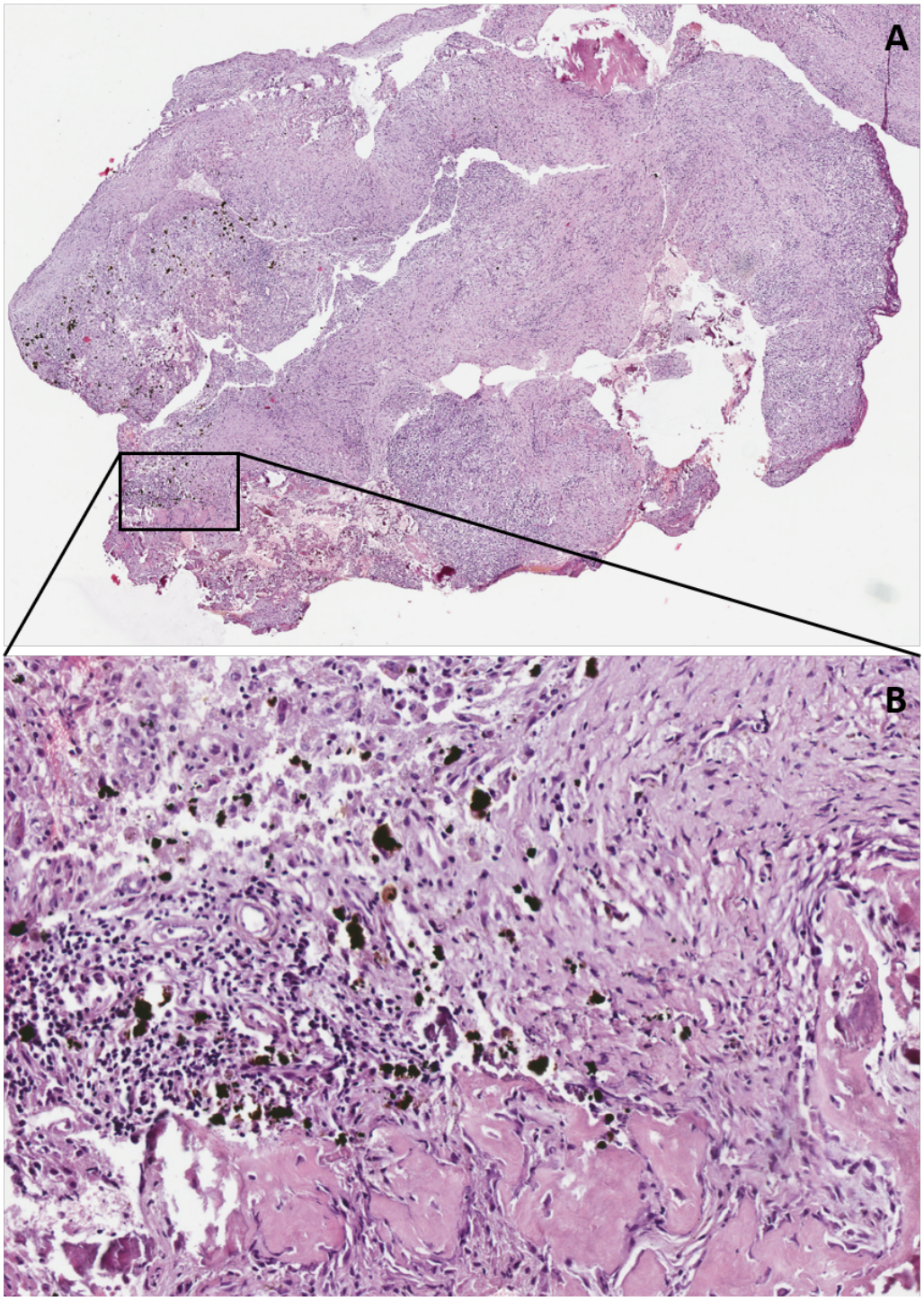



Fig. 8. A: (EE-5x magnification) low power shows fibrous connective tissue with bone fragments B: (EE-20x magnification) at high power granulation tissue is noted, associated with chronic inflammatory infiltrate, a rich xanthomatous macrophagic population and occasional multinucleated giant cells inglobating exogenous material. Bone trabeculae show remodelling

## Discussion

The aims of this case series were to report prospective data on the treatment and histopathological findings of RPI in a single center and to evaluate implant survival after surgical approach. After the publication of several studies on the topic [32-35], our department was considered as a referral center for diagnosis and treatment of RPI by private practitioners based in Rome.

Based on the results of the study, all implants affected by RPI were successfully treated with surgical curettage of the periapical lesion and GBR with deproteinized bovine bone material and a collagen membrane after a mean follow-up of 1.5±0.57 years.

RPI is quite an unknown pathology: in a previous study, the authors [35] evaluated the knowledge and attitude of Italian implantologists regarding retrograde peri-implantitis. Four hundred seventy-five randomly selected implantologists completed an anonymous questionnaire sent via email (fig. 9), including a section about demographic information and questions related to RPI origin, radiographic representation, symptoms and treatment options. All questions were multiple answer and close-ended.

Only 23.6% of the sample answered “yes” to the question “Have you have ever treated a RPI case?”, interestingly 76.5% of them were > 45 years. Even if all clinicians enrolled in this survey practiced implant dentistry, 26.7% of them ignored the radiographic representation of RPI (“a radiolucent area at the apical aspect of the implant”), selecting the wrong answers: “a radio-opaque area at the apical aspect of the implant” and “a radiolucent line at the lateral side of the implant”.

Regarding the origins of RPI, only 17.1% of participants included in their answers “marginal peri-implantitis becoming retrograde”, which is obviously incorrect. RPI is a disease entity affecting only the apical part of the implant and can destroy the circumferential bone [15]. As the exact etiology of RPI remains still controversial, all other answers (bone overheating during implant placement, presence of residual cystic cells, residual infection/inflammation of the tooth replaced by the implant or the endodontic lesion of neighboring teeth) were considered right.

**KNOWLEDGE AND ATTITUDE TOWARDS RETROGRADE PERI-IMPLANTITIS AMONG ITALIAN IMPLANTOLOGISTS**

Age: ≤30 31-44 ≥45
Sex: M F
Years of experience in dentistry: < 5 5-9 10-19 >19
Do you perform implant dentistry on a regular basis? YES NO
Number of dental implants placed per year <20 20- 80 >80

1 Where did you learn about retrograde peri-implantitis?
   a) at the University
   b) From scientific papers
   c) From direct experience
   d) For colleagues' experience
   e) I've never heard of it

2) What are the causes of RPI? (more than one answer is allowed)
   a) Bone overheating during implant drilling
   b) presence of residual cystic cells
   c) residual infection/inflammation of the tooth replaced by the implant
   d) marginal peri-implantitis becoming retrograde
   e) periapical endodontic lesions of neighbouring teeth

3) Which is the radiographic representation of RPI?
   a) a radio-opaque area at the apical aspect of the implant
   b) a radiolucent area at the apical aspect of the implant
   c) a radiolucent line at the lateral side of the implant

4) What are the symptoms of RPI? (more than one answer is allowed)
   a) Dull percussion
   b) Persistent pain
   c) Implant mobility
   d) Suppuration and/or presence of fistula
   e) None

5) How would you treat an implant affected by RPI? (more than one answer is allowed)
   a) surgical debridement
   b) surgical debridement + bone substitute/GBR
   c) surgical debridement + bone substitute/GBR + apicoectomy of the implant
   d) implant removal

6) Have you have ever treated a RPI case?
   a) yes
   b) no

Fig. 9. The anonymous questionnaire about the knowledge of RPI sent to four hundred seventy-five randomly selected implantologists

As for treatment, 64.5% of the respondents selected the following options: surgical debridement, surgical debridement + bone substitute/GBR, surgical debridement + bone substitute/GBR + apicoectomy of the implant; while implant removal was considered the wrong answer, and was

chosen by 35.5% of clinicians, showing a very limited knowledge of available management strategies and high survival rate after RPI surgical treatment.

It is notable that for the question "Where did you learn about RPI?", more than a quarter of the sample enrolled (26%) answered that they had never heard of RPI; 48.2% had > 45 years while 35.7% had more than 19 years of working experience; only 21.4% were <30 years. Only 9.8% answered "at the university", and the majority of them were <30 years. The vast majority of participants (89.7%) who answered "for direct experience" were >45 years, with 72.4% of them with more than 19 years of working experience.

Based on the results of the study, incorrect answers were associated with the less experienced participants (<80 implants/year) for all questions evaluated, with the exception of treatment strategies. Therefore, age and experience were associated with a higher number of correct answers and this could be explained by either their direct involvement in the diagnosis or treatment of RPI and their better knowledge of implant dentistry. Hence, more experienced and older implantologists have placed a greater number of dental implants throughout their career, compared to less experienced and younger clinicians, and faced, therefore, more complications. In contrast, as for the question on RPI treatment, survey takers > 45 years of age showed the worst results and this could probably be explained by their lower propensity for continuing education and scientific literature update.

In another retrospective study [34], the authors reported data on the prevalence of RPI in a single center during a twenty-years observational period (1999-2019) and evaluated implant survival following a standardized surgical procedure. Among the 1749 dental implants placed in the study period, only six were affected by RPI, with a prevalence of 0.34%. All the implants were surgically treated with curettage and xenograft application and they are still in place up to date, with a survival rate of 100% after a mean follow-up of 8.83±5.34 years (range 3-20 years). Speculating on the possible aetiology of RPI in implants included in the study, a common finding was that there were no implants with adjacent endodontically treated teeth and the 6 cases reported might all be ascribed to class 4 of the Sarmast classification [27]. In four cases, implants were placed in sites with previously

endodontically treated teeth, with two teeth affected also by apical periodontitis and one with a periapical lesion. In the remaining two cases, patients' teeth were extracted for severe periodontitis more than 3 years prior to implant placement. An association between endodontic therapy and RPI was present in four cases included, however, RPI was diagnosed also in two cases of dental implants placed in sites without a previous endodontic treatment or endodontically treated adjacent teeth. Another possible explanation for implant apex contamination could be the presence of residual lesions (granulomas, residual apical cysts, root remnants) of the extracted teeth [20,23], or bone overheating during implant drilling [25]. Even in cases of appropriate curettage of the alveolar cavity, bacteria could remain encapsulated and be reactivated by implant drilling [37]. In the retrospective study, patients had teeth extracted from four months to several years prior to implant placement and pre-operative periapical radiographs did not show any radiolucent lesion. All patients came to observation with symptoms, therefore periapical x-rays were taken, and lesions diagnosed. Asymptomatic RPI lesions diagnosed by routine radiographic examinations have been also reported: this might be an explanation on the relatively low prevalence and knowledge of RPI compared to marginal peri-implantitis [30]. Hence, RPI generally occurs in the first weeks after placement and asymptomatic untreated lesions could lead to implant mobility and lack of osseointegration, with early implant failure before prosthetic loading and an underestimation of the disease. Therefore, it might be recommended to take a periapical x-ray at implant placement and after 6-8 weeks before prostheses delivery in order to intercept and to early detect signs of RPI [18]: a radiolucent lesion surrounding the implant apex should always alert the clinician, with the exception of implant overdrilling. All patients were treated with the same surgical approach: antibiotic therapy, curettage and removal of the lesions, chemical decontamination and bone regeneration. To the best of the authors' knowledge, only four studies [20,26,31,38] reported data on the implant survival rate and follow-up after treatment: cumulative survival rate (CSR) ranged from 67.5 to 97.4%, with a mean follow-up from 72 months to 4.54 years. Reported results for the first time a CSR of 100%, with the maximum follow-up available in literature, with a mean observation period of 8.83±5.34 years (range

3-20 years). Even if the management of RPI is still unclear, removal of all granulation tissue, with a careful decontamination of the implant apex and following bone graft seemed to arrest bone loss progression.

To the best of the author's knowledge, this is the first study reporting presence of foreign body cells in the histopathological examination. A recent systematic review [39] evaluated the histopathological and microbiological findings associated with RPI. As for the histopathological results, only four studies were included [40-43], with two studies [40,41] describing lesions with chronic inflammation with granulation tissue and two studies [42,43] reporting a cystic presentation of the periapical lesions.

Therefore, different histopathological features were reported by Marshall et al. [39], however, contrary to our observations, no mention of foreign particles/fragments was reported in any article.

In the six studies included in the review, 21/30 dental implants with a RPI diagnosis were associated with failed endodontic treatment, apical periodontitis or remaining infected roots at the implant site. In these cases, microbiological analysis of samples collected revealed the following bacteria: Porphyromonas gingivalis, Corynebacterium, Streptococcus and Klebsiella pneumoniae. Siqueira et al. [44] reported that Enterococcus faecalis is the most common bacteria found at the apex of endodontically treated teeth, furthermore also Prevotella intermedia, Fusobacterium Nucleatum and Porphyromonas gingivalis have been discovered after endodontic therapy [45]. These bacteria might remain encapsulated in cancellous bone after the extraction of teeth with failed endodontic treatment and might be reactivated by drilling for implant osteotomy, with subsequent colonization of the implant apex [37]. In a retrospective study [20], an Odds Ratio (OR) of 7.2 was reported for a tooth with an endodontic history to develop RPI, even in absence of periapical lesions.

In a recent retrospective cohort study, Saleh et al. [46] evaluated the incidence of RPI in patients who underwent previous apical surgeries. The incidence of RPI was quite high (20%) and an increased trend of RPI was reported for teeth extracted for persistent apical periodontitis, however the small sample size enrolled (n=25) could not lead to statistically significant results.

Pistilli et al. [47] reported three cases of RPI associated with infected residual cystic lesions and complete resolution of the pathology after surgical treatment with curettage and GBR. In another recent retrospective case-control study, Solomonov et al. [48] described 23 cases of RPI, with an OR of 6.67 (95% CI 2.7-16.5) of developing RPI in cases of adjacent teeth previously endodontically treated with a periapical radiolucency.

Main limitations of this study are the limited sample enrolled and the small follow-up available. However, research on this topic is generally composed by case reports and there are just few retrospective cohort or case-control studies. To the best of the author's knowledge, this is the first study to report prospective data on RPI, evaluating histopathological features and treatment success after a standardized surgical approach.

## Conclusions

Prevalence of retrograde peri-implantitis is extremely low ranging from 0.26 to 1.86%, is a relatively unknown pathology, also among experienced implantologists, and research on the field is mainly composed by case reports. In our prospective case series, all the implants affected by RPI were surgically treated with curettage and GBR and they are still in place, with a survival rate of 100% after a mean follow-up of 1.5±0.57 years. Based on the analysis of patients' characteristics and histopathological samples, it can be speculated that bacteria from teeth with failed endodontic treatment or residual lesions were reactivated by drilling for implant osteotomy, with subsequent colonization of the implant apex. Since in all cases previous teeth in implant sites were endodontically treated, foreign body particles incorporated in the inflammatory tissues might be derived from remains of previous root canal therapy.

Therefore, within the limitations of the study, it could be cautiously concluded that RPI can be predictably and successfully treated with surgical curettage and GBR. Further studies, with larger sample, are needed to confirm these clinical findings.

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