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ORIGINAL ARTICLE

Morphological evaluation of bone microdamage in medication-related osteonecrosis of the jaw using fluorescence microscopy

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Abstract:

Objective: The aim was to assess and classify bone microdamage (microcracks, microfractures, and diffuse damage) in MRONJ using fluorescence microscopy, a method that improves artefact discrimination compared to scanning electron microscopy. **Methods:** Patients diagnosed with MRONJ were selected, and during the surgery, bone fragments, including the sequestrum, were collected and then embedded in methylmethacrylate without decalcification. Bone microdamage was assessed in histological slides and classified as microcracks, microfracture, and diffuse damage, and bone morphology was also evaluated. **Results:** Ten patients were included in the study (mean age of 66.8±10.4 years, five female and five male). Bone microdamage was identified in 6 patients (60%), the microcracks being the most prevalent type, followed by microfractures (20%) and diffuse damage (20%). Eroded surfaces were present in all samples, both in the cortical and cancellous bone. Other findings included the presence of amorphous non-bone material, intracortical resorption areas, and non-circular Haversian canals. **Conclusion:** Bone microdamage was present in more than half of MRONJ patients, and the presence of bone microcracks suggests a potential compromise in the mechanical integrity of the bone tissue.

Keywords: Osteonecrosis; Oral medicine, Bone and bones.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is defined as a condition with an area of exposed and necrotic bone in the maxillofacial bone, associated with the use-current or previous of antiresorptive, antiangiogenic, or immunomodulatory therapies prescribed for some bone diseases and certain malignancies[1]. The precise pathophysiological mechanisms behind this osteonecrotic process remain poorly defined, mostly in the cases of an absence of a triggering factor. Unraveling the cascade of biological events that culminates in the development and progression of a MRONJ lesion still require further investigation, and the gap in the literature is mainly due to the variety of drug classes involved in the MRONJ etiopathogenesis and their distinct mechanisms of action[2,3].

Bone microdamage plays a critical role on bone health, mostly because of their impact on osteocytes and their response on an altered bone environment. It is known that the bone damage is repaired via targeted remodeling to preserve bone integrity, meaning that osteocytes start the process and then, osteoclasts and osteoblasts can take action on the bone that was damaged. In the presence of bisphosphonates or denosumab, one could suppose that this repair cascade is disrupted, and osteocyte apoptosis fails to trigger osteoclast recruitment, leading to progressive microdamage accumulation and necrosis, also in another way, even if osteoclasts are recruited, they will not perform their function[2,4].

Statement of Clinical Significance
Bone microdamage, present in 50% of MRONJ cases, can be related to the compromised bone mechanical integrity, contributing to the development and progression of the disease. Recognizing microdamage as a biomechanical factor may improve risk assessment and inform preventive strategies in patients receiving antiresorptive therapy.

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Bone microdamage can be classified considering their morphology as: linear (also known as microcracks), diffuse or microfractures. Microcracks appear when the bone 's capacity to dissipate mechanical loads is exceeded, leading to the crack formation and a sequential bone remodeling[5,6]. Experimental studies have demonstrated the presence of microcracks in MRONJ sites, indicating accumulation of unrepaired microcracks[7,8]. A study involving humans osteonecrosis samples reported that 54% of MRONJ samples exhibited microcracks, evaluated by scanning electron microscopy[8]. However, the studies found on the literature has some weakness, mostly considering the bone microdamage evaluation method. Further investigation is still needed to clarify the role of bone microdamage in the pathophysiology of MRONJ. There is limited evidence regarding the relationship between bone microdamage and the development of MRONJ. In this way, a question remains whether the application of appropriate methodologies to assess the morphological characteristics of bone microdamage could provide more comprehensive insights and improve our understanding of MRONJ pathogenesis.

This study aims to advance our understanding of bone microdamage presence in MRONJ, also to identify their most prevalent type, through a qualitative assessment using fluorescent microscopy, a method that improves artefact discrimination compared to scanning electron microscopy.

MATERIAL AND METHODS

This observational and cross-sectional study was conducted using a qualitative and quantitative approach, which selected patients diagnosed with MRONJ. Samples were collected at two institutions under convenience sampling. The study was approved by the Research Ethics Committee. Patients diagnosed with active lesions of MRONJ (staging from 1 to 3 according to Ruggiero et al.[1]), and with an indication for a surgical procedure for MRONJ treatment were included. The inclusion criteria were patients older than 18 years old, and with a diagnosis of MRONJ. Exclusion criteria included: diagnosis of metastatic disease in the jaws, diagnosis of osteoradionecrosis, or other lesions in the jaws.

Bone fragments were collected during the surgical treatment, including the surgery for sequestrum removal and other osteotomy procedures. The bone samples were fixed in 70% alcohol and processed without demineralization. The fragments were stained with 5 mM Xylenol Orange (Xylenol Orange tetrasodiumsalt, Sigma-Aldrich) in ethanol solution for 7 days and then embedded in methyl methacrylate (MMA) (supplementary material 1). Two or three histological slides of around 100–150 μm were obtained from each block on a precision saw (EXAKT Diamond Band Saw) and followed by microscopy analysis (Supplementary material 1). All procedures were performed according to Rabelo et al.[9] and Francisquini et al.[10], and the bone microdamage was analyzed under the criteria proposed by Chapurlat and Delmas[6].

Analyses were performed using a BX41® vertical microscope (OLYMPUS®) equipped with Q-Capture Pro 5.1 image acquisition software (Q-Imaging®) and a 3.3-megapixel Q-Imaging® digital camera. The histological slides were analyzed under fluorescent light (green, excitation 460-490 nm, emission LP 520 nm) for all morphological parameters. To confirm bone microdamage, analysis was also performed in phase contrast and in the bright field. Two trained and experienced evaluators in bone histomorphometry jointly analyzed all histological slides. The entire slide was evaluated in the search for the bone microdamage.

Morphology evaluation focused on identifying all bone tissue present on the slide and characterizing its features, including:

a) Cortical bone: presence of osteons and Haversian canals composed of concentric lamellae; areas with indication of a previous bone resorptive process and eroded surfaces; areas of amorphous material and sequestrum features;

b) Trabecular bone: identification of trabeculae with parallel lamellae; amorphous regions suggestive of non-vital bone; eroded surfaces.

In addition, all samples were evaluated in its integrity (cortical and cancellous bone) for the presence of bone microdamage, which was classified into: linear damage or microcracks, microfractures and diffuse damage. Briefly, the damage was identified under fluorescence light and then confirmed under phase contrast and bright field with the micrometer adjustments according to the mentioned protocol of Rabelo et al.[9] and Francisquini et al.[10] All microcracks were measured in micrometers (microcrack length), using the "Segmented line" tool in ImageJ/Fiji software (1.54p, Wayne Rasband, National Institute of Health, USA). Artefactual cracks were not considered, i.e. cracks which were not brilliant and shiny under fluorescence, and not evidenced in phase contrast analysis,

as also the cracks which were found to be on the cutting-edge surfaces (these ones probably related to the surgical procedure on the cutting edges of the bone) (supplementary material 1).

In cases of MRONJ associated with dental implants, the bone between the implant threads was analyzed for characteristics indicative of osseointegration. All amorphous areas identified as non-vital bone were considered necrotic.

RESULTS

Ten patients were included in the study, with a mean age of 66.8±10.4 years. Five patients were female, and five were male. All participants were undergoing treatment with antiresorptive agents (AA) or monoclonal antibodies, isolated or with a previous history of intercalation between different types of AA. All data regarding the patients' conditions and MRONJ findings are available in Table 1. A total of 14 samples were analyzed because one patient was treated 3 times (in the same region, with one and two-year intervals), another presented two MRONJ sites (one in maxilla and the other in mandible), and a third individual had two surgical moments between six months. The two patients receiving oral bisphosphonates (alendronate) and the one patient treated with denosumab did not exhibit bone microdamage, whereas all seven patients on intravenous bisphosphonates showed bone microdamage in at least one sample (Table 1).

Table 1. Patients included in the study and medication-related osteonecrosis of the jaw findings[1].

Patient	Age	Sex	Sample		Stage	Medicament (disease)	Treatment duration (months)	Bone Microdamage Type
			Region	Area				
1	77	F	Posterior mandible	PI	2	Alendronate (Osteoporosis)	12	No
2	77	F	NI	NI	2	Zoledronic acid (Breast cancer)	NI	Yes 1 diffuse damage
3	95	F	Posterior maxilla	PI	2	Alendronate (Osteoporosis)	NI	No
4	52	M	Posterior maxilla	Right residual ridge	1	Pamidronate + Zoledronic acid (Multiple myeloma)	NI	Yes 1 microcrack
5	56	M	Posterior mandible	Alveolar Ridge – 44/45	2	Denosumab (Giant cell tumor)	13	No
6 (MRONJ1)	62	F	Posterior maxilla	Left Alveolar Ridge	3	Pamidronate + Zoledronic acid (Breast cancer)	17	No
(MRONJ2)	63							No
(MRONJ3)	64							Yes 1 microcrack 1 diffuse damage
7 (MRONJ1)	66	M	Anterior maxilla	Left Alveolar Ridge – 27	2	Zoledronic acid (Multiple myeloma)	23	Yes 1 microfracture 1 microcrack
(MRONJ2)								Yes 1 microcrack
8	63	M	Posterior mandible	Lingual wall – 37	2	Zoledronic acid (Multiple myeloma)	9	Yes 1 microcrack
9	65	M	Posterior mandible	Left Alveolar Ridge – 35	1	Zoledronic acid (Multiple myeloma)	NI	Yes 1 microfracture
10 (MRONJ1)	65	F	Anterior maxilla	Left Maxillary Sinus Wall	3	Zoledronic acid (Breast cancer)	72	No
(MRONJ2)			Posterior mandible	Right Mandibular Body	3			Yes 1 microcrack

F: female; M: male; PI: peri-implant; NI: not informed; MRONJ: medication-related osteonecrosis of the jaw.

Bone microdamage was identified in 6 patients (60%). One patient had 3 samples from distinct MRONJ sites. Six patients had microcracks and among the 14 samples, two samples also revealed diffuse damage (14.3%) (Figure 1A-B), two revealed microfractures (14.3%) (Figure 1C-D), and the six samples with microcracks revealed the linear shiny crack under fluorescence (Figure 1E-F). Counting the 14 samples analyzed, the mean microdamage number per sample was 0.71±0.73. Regarding microcracks, the majority of them were found next to eroded surfaces (more then 90%), and some were found within the bone away from the outer surface (Figure 2A-F). These linear damages were either linked or unlinked to the outer bone surface. The mean microcrack length was 245 μm, with a range of 152–389 μm. In the cortex, some microcracks were not located on the cement line of the osteons but had a transversal orientation (Figure 2G-I). One patient revealed both microfracture and microcrack. One patient with two MRONJ sites revealed no microdamage in the maxilla but revealed microcracks in the mandible. All microcracks were found at the cortical bone, together with the two microfractures and one diffuse damage. Only one diffuse damage was found in the cancellous bone.

Regarding bone morphological aspects, eroded surfaces were found in 100% of the samples (Figure 3A), in more or less amounts, counting all external bone surface and intracortical surfaces in the resorption areas (Figure 3B). Amorphous areas (revealing no characteristics of a normal lamellar bone) were found in different amounts (Figure 3C). In the cortex, some bone areas showed normal structure whereas others displayed irregular and non-circular Haversian canals. In MRONJ associated with dental implants, it was noted that the bone between screws was sometimes integrated and sometimes revealing resorbed areas and a non-vital characteristic (Figure 3D-F). These areas of necrotic bone and others with the absence of bone between screws point to a lack of osseointegration.

In general, the eroded surfaces both on cortical and cancellous bone were evident in all samples from all patients, visualized in a shiny and brilliant halo on bone surface with the formation of concavities of different sizes characteristics of bone resorption (Figure 4).

DISCUSSION

Our study evaluated ten patients with MRONJ — nine receiving nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, or alendronate) and one treated with the monoclonal antibody Denosumab. All MRONJ sites were histologically evaluated, and more than half of them revealed the presence of bone microdamage. Only the patients in intravenous administration of bisphosphonates revealed microdamage. Besides microcracks, diffuse damage and microfractures were also found, although in less number. In addition, all samples revealed the presence of eroded surfaces indicating osteoclast activity. Surfaces with an active bone resorption process were found, as also the presence of other sites revealing linear surfaces (without the characteristics of the action of osteoclasts). These eroded surfaces were mostly around amorphous areas, which were found in all samples, suggesting the characteristics of a degraded non-vital material. The finding that 60% of MRONJ cases presented microdamage, predominantly microcracks, alongside universally observed eroded surfaces, raises important considerations regarding the persistence of osteoclastic activity even under antiresorptive treatment.

Due to their strong affinity for bone mineral, bisphosphonates (BPs) remain in the bone matrix for extended periods, leading to a prolonged half-life and preventing osteoclast "recycling". In contrast, Denosumab, whose effect is reversible, can provoke rebound bone resorption after it's discontinuation[11-13]. Both drugs interfere in bone resorption by inducing dysfunctional or apoptotic osteoclasts, although through different mechanisms: BPs inhibit the mevalonate pathway, while Denosumab acts by blocking RANKL[11,14]. Indeed, our findings suggest both the presence of bone microdamage and the eroded surfaces, which can be linked to osteoclast activity, meaning that osteoclasts were active at some point and maybe not all of them remain inactive when a necrotic process start. Studies already revealed that delayed osteoclast death, combined with suppressed bone turnover contributes to the accumulation of microdamage and long-term skeletal fragility[15]. This can indicate osteoclast activity, but probably not in all the bone sites where is needed. Osteocyte apoptosis induced by microdamage are thought to be one of the majors signaling that recruits new osteoclasts[6]. When this mechanism fails and the damage cannot be repaired (due to suppression of osteoclast activity related to BPs), the microcracks can grow and become microfractures[3,15].

Another important finding in our study was to evaluate the MRONJ associated with dental implants. With evidence of eroded surfaces and the presence of areas suggesting a lack of osseointegration, and areas of bone with no vital aspect, it can be supposed that

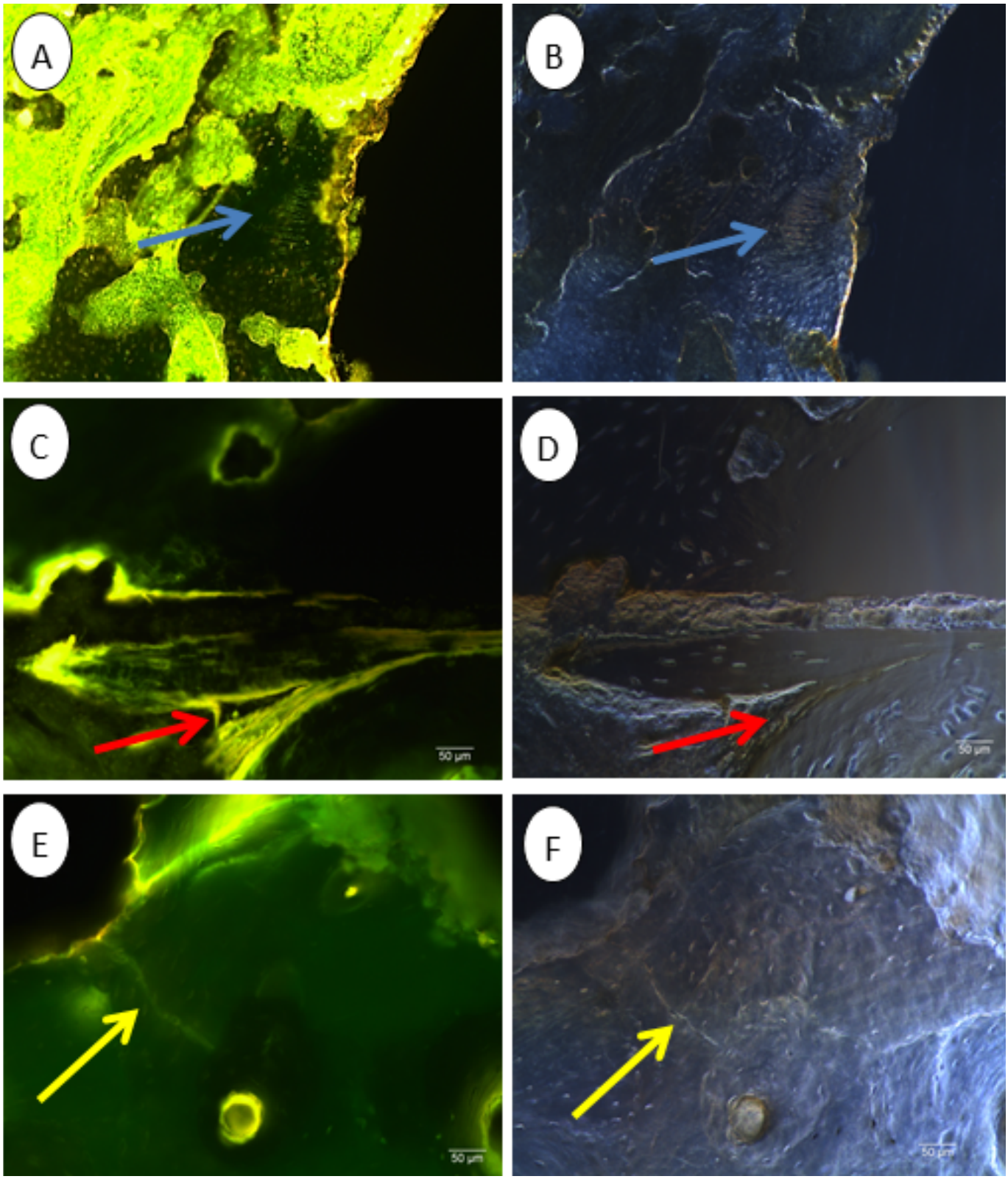

Figure 1. Types of microdamage in MRONJ (Xylenol Orange stained slides evaluated under polarized light (left) and fluorescence (right)). (**A–B**) Diffuse damage (blue arrows), characterized by multiple, predominantly parallel fissures throughout the bone matrix. (**C–D**) Micro-fractures (red arrows), identified as wider, discontinuous fracture lines. (**E–F**) Microcracks (yellow arrows), thin and well-defined, appearing as isolated linear defects in the examined region. Magnification: (**A–F**), 20 ×.

osteoclast activity can also be found in this specific situation, as the non-implant-related-MRONJ. A recent review showed that it is unclear if the material properties of peri-implant bone remain unaltered by antiresorptive agents[16]. In our study, which should be interpreted with caution because of the limited number of patients, we have shown that the bone properties are probably altered, mostly evidenced by the presence of intercalation of areas with or without morphological aspects of normality (meaning eroded surfaces, non-lamellar structure, and large areas of absence of bone-implant contact). In cases of MRONJ associated with dental implants, our findings suggest that biomechanical stress concentration at the implant threads may exacerbate microdamage. Our observations suggest that remodeling failure in these regions could be a direct consequence of microdamage, though further studies are required to confirm this association.

In the literature, microcracks have been reported in 54% of MRONJ specimens examined by scanning-electron microscopy (SEM)[8] and reproduced in animal models treated with BPs[7,17,18]. This type of microscopic damage occurs because suppressed bone remodeling prevents the repair of microcracks generated by masticatory forces and other mechanical loads, reinforcing the hypothesis that microcracks may represent an asymptomatic "first step" in MRONJ pathogenesis[8,15]. Our findings were in accordance with the studies mentioned, even evaluating the bone microdamage in a different method, which was considered a gold-standard method for microdamage once the stained cracks are indeed true damage, and not

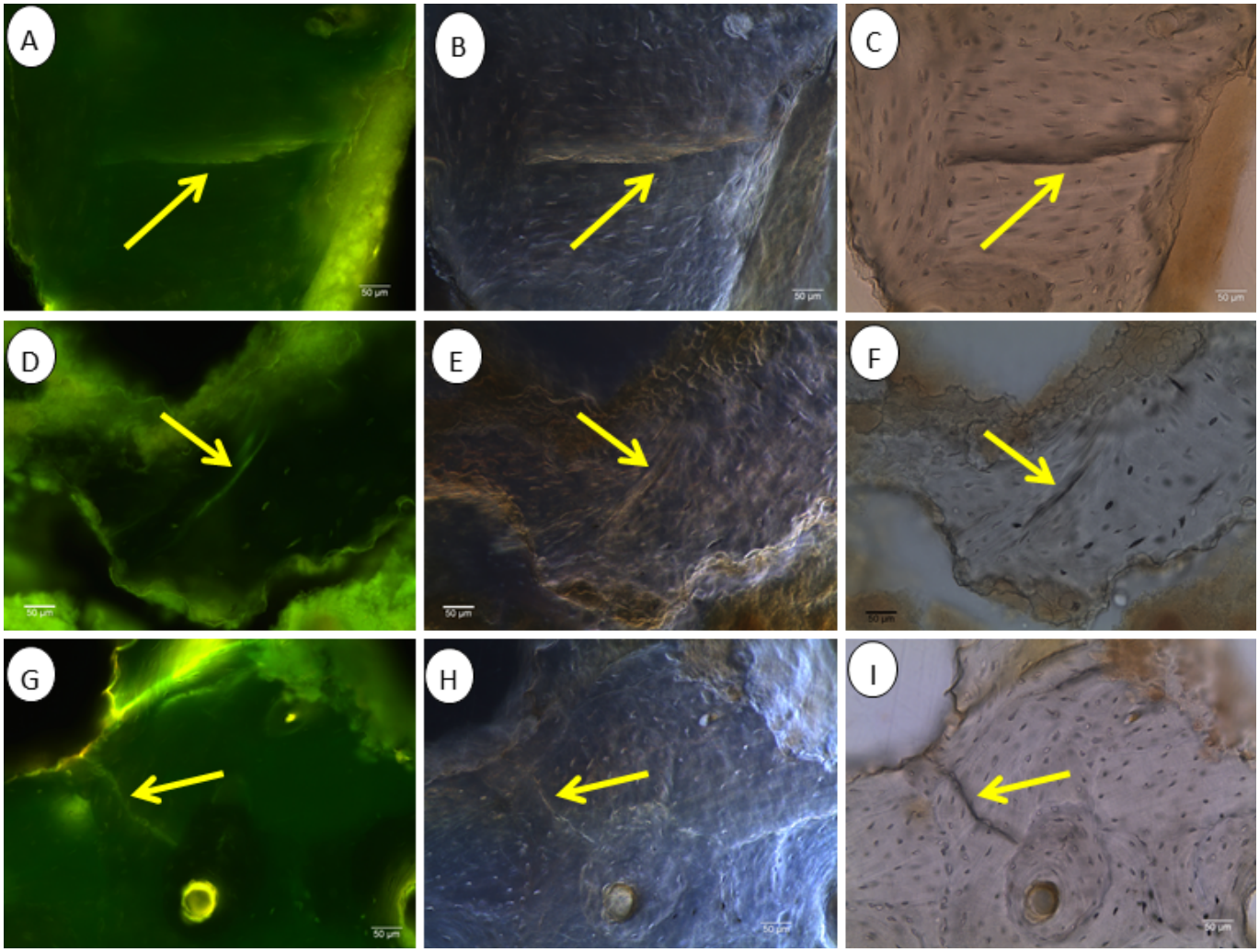

Figure 2. Histological images of undecalcified bone from MRONJ patients viewed with fluorescence, phase-contrast, and bright-field microscopy, respectively. (**A–B–C**) Microcracks located near eroded bone surfaces. (**D–E–F**) Microcracks situated deep within the cortical bone, away from the external surface. (**G–H–I**) Transversely oriented microcracks crossing an osteon with the Haversian canal visible. Magnification: (**A–I**) 20 ×.

artefactual. Microdamage evaluated under fluorescence microscopy and confirmed with phase contrast is more suitable, once the microcracks evidenced in electron microscopy could be confused with artefactual cracks. According with Allen[19] staining specimens before processing is essential to distinguish between microcracks that existed prior to processing and those generated during specimen preparation. Without this method, it is impossible to determine whether the damage is inherent to the sample or caused by the processing itself. In our study, we have used the most indicated method to observe real microcracks. Additionally, we excluded from our analysis any cracks located on bone cutting surfaces, as these were morphologically consistent with damage caused by surgical cutting procedures. While Hoefert et al.[8] reported microcracks in 54% of SEM samples, our study showed 60% using fluorescence microscopy. Unlike SEM, our method allowed visualization of true microdamage via Xylenol Orange staining, as validated by Allen[19]. An interesting finding concerned the length of the microcracks, which showed a mean of 245 μm. This value is higher than that reported in a previous study from our group[9], in which microcracks in the mandibular bone of patients with a mean age of 58±11 years had a mean length of 68.22±25.85 μm. These results suggest that microcracks in MRONJ may be larger, and as expected, in the absence of effective remodeling they may progress into microfractures, which were also observed in our samples.

Despite providing relevant insights, the present study has limitations. The sample is small and clinically heterogeneous, preventing refined comparisons across different drugs, doses, or MRONJ stages. Although the sample was limited, stratifying damage patterns by drug class (zoledronic acid vs. denosumab) or lesion location (maxilla vs. mandible) could yield important insights in larger cohorts. All specimens were obtained during debridement, tooth or sequestrum removal, making it difficult to compare distinct anatomic sites under identical conditions. Nevertheless, it is known that most existing knowledge on microdamage comes from animal studies, and our study in humans with the most appropriate method of microdamage assessment was important on giving these biomechanical insights into the MRONJ condition. Also, collecting bone samples from MRONJ patients (or at risk) is a difficult task, because we cannot increase morbidity of the surgical procedure by collecting more material than the one that was already supposed to be removed.

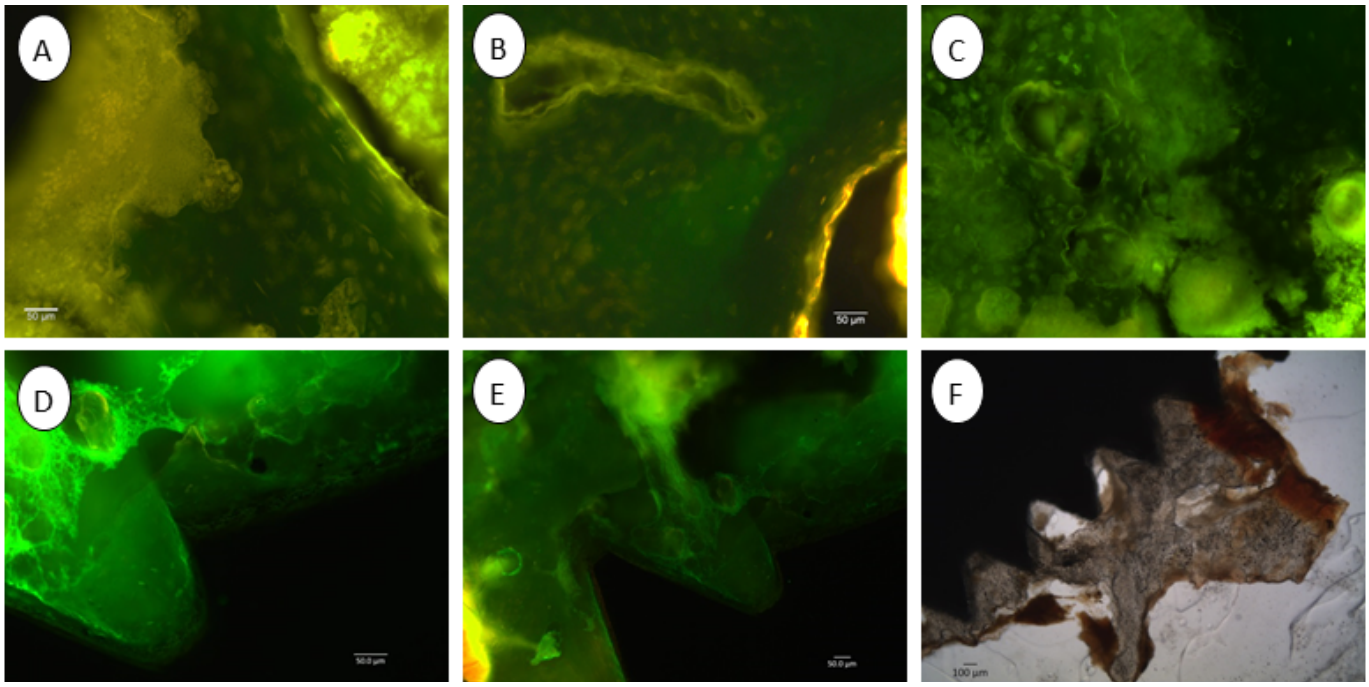

Figure 3. Histological aspects of bone and peri-implant bone in resin sections stained with fluorescence. (**A–B**) Eroded bone surfaces, osteocyte lacunae, and amorphous matrix areas suggestive of active inflammation. (**C**) Disorganized trabecular tissue with amorphous matrix interspersed by typical resorption zones. (**D–E**): Deposition of disorganized, amorphous bone matrix directly adherent to the implant surface. F: Bone with normal morphology interposed among implant threads, with an adjacent resorption focus. Magnification: (**A–E**), 20 ×; F, 10 ×.

Collectively, these results might support the idea that inhibited turnover, unrepaired microdamage, structural fragility, and other factors such as microbial colonization form a central axis in MRONJ pathogenesis, over half of the patients exhibited microdamage in MRONJ sites, they probably contribute to disease installation, progression and recurrence.

CONCLUSION

Sixty percent of the MRONJ patients showed bone microdamage, majorly microcracks, confirming that target remodeling at MRONJ sites may have an impact on bone mechanical properties at the jaws contributing to the development and progression of the disease. The presence of eroded surfaces suggests an ongoing bone resorption process with osteoclast activity. In cases of MRONJ associated with dental implants, the evidence of well-integrated surfaces between threads and necrotic areas in other regions reveals that loss of osseointegration can occur and can be site specific.

AUTHORS' CONTRIBUTIONS

LB: Conceptualization, Data curation, Formal analysis, Writing – original draft. ACSC: Data curation, Formal analysis, Methodology, Writing – original draft. RES: Formal analysis, Methodology, Writing – original draft. HFS: Methodology, Validation, Writing – original draft. AMBS: Methodology, Validation, Writing – original draft. LJG: Methodology, Resources, Writing – original draft. ROG: Methodology, Formal analysis, Validation, Writing – review & editing. MCM: Methodology, Validation, Resources, Writing – original draft.

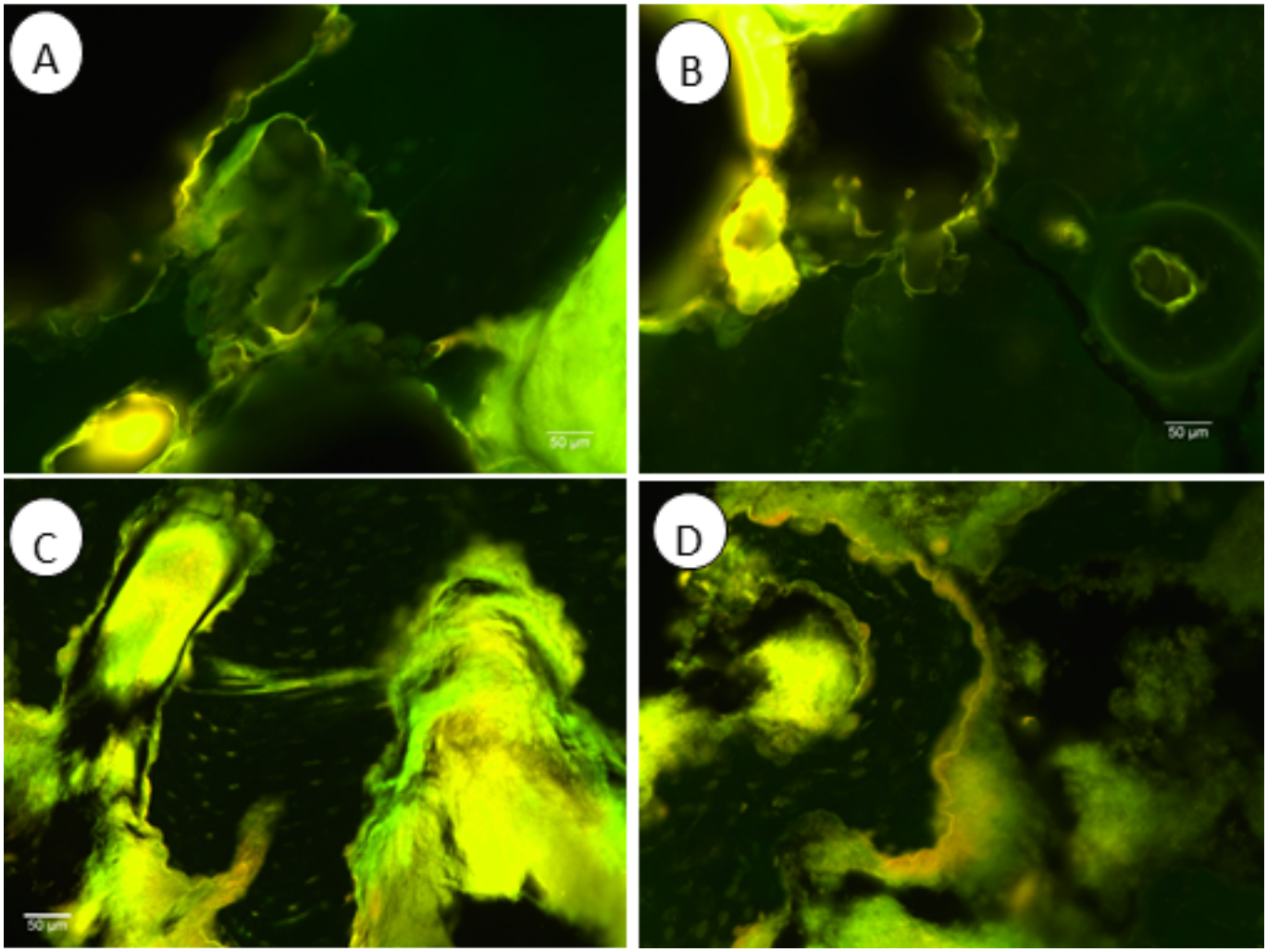

Figure 4. Morphological evaluation revealing the bone eroded surfaces. (**A and B**) Cortical fragments. (**C and D**) Cancellous bone fragments.

GDR: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Ethics approval: Ethical approval was waived by the local Ethics Committee of the Federal University of Santa Catarina (Register number CAAE: 54374221.3.0000.0121, Approval number 5.268.529), in view of the nature of the study and all the procedures performed were part of the routine care of the patients, and in accordance with the Declaration of Helsinki.

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