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Ridge preservation with the socket-plug technique utilizing an alloplastic putty bone substitute or a particulate xenograft: a histological pilot study

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Abstract:	Following tooth extraction ridge preservation procedures are employed to regenerate bone in the extraction socket, limit consequent ridge resorption and provide a stable base for implant placement. The purpose of this study is to histologically evaluate and compare bone regeneration in extraction sockets grafted with either a putty alloplastic bone substitute or particulate anorganic bovine xenograft utilizing the socket-plug technique. Nineteen patients underwent twenty tooth extractions and ridge preservation following a standardized protocol. Ten sites were grafted with calcium phosphosilicate putty (CPS group) and the remaining ten with anorganic bovine bone substitute (BO group). Patients were recalled after 4-6 months to evaluate the bone regeneration and to proceed with implant placement. A bone core was obtained during the implant procedure from each site and was used for histological analysis. Histomorphometry revealed that residual graft values were significantly higher in the BO group (25.60%±5.89) compared to the CPS group (17.40%±9.39) ($P<0.05$). The amount of new bone regenerated was also statistically significant higher in the alloplast group (47.15% ± 8.5%) as compared to the xenograft group (22.2% ±3.5%) ($P<0.05$). Both bone substitutes demonstrated bone regeneration in the healed sockets. Results suggest that ridge preservation using a putty calcium phosphosilicate alloplastic bone substitute results in more timely graft substitution and increased bone regeneration when compared to an anorganic bovine bone xenograft.

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Alveolar ridge preservation with the socket-plug technique utilizing an alloplastic putty bone substitute or a particulate xenograft: a histological pilot study.

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ABSTRACT

Following tooth extraction ridge preservation procedures are employed to regenerate bone in the extraction socket, limit consequent ridge resorption and provide a stable base for implant placement.

The purpose of this study is to histologically evaluate and compare bone regeneration in extraction sockets grafted with either a putty alloplastic bone substitute or particulate anorganic bovine xenograft utilizing the socket-plug technique.

Nineteen patients underwent twenty tooth extractions and ridge preservation following a standardized protocol. Ten sites were grafted with calcium phosphosilicate putty (CPS group) and the remaining ten with anorganic bovine bone substitute (BO group). Patients were recalled after 4-6 months to evaluate the bone regeneration and to proceed with implant placement. A bone core was obtained during the implant procedure from each site and was used for histological analysis.

Histomorphometry revealed that residual graft values were significantly higher in the BO group (25.60%±5.89) compared to the CPS group (17.40%±9.39) ($P<0.05$). The amount of new bone regenerated was also statistically significant higher in the alloplast group (47.15% ± 8.5%) as compared to the xenograft group (22.2% ±3.5%) ($P<0.05$).

Results suggest that ridge preservation using a putty calcium phosphosilicate alloplastic bone substitute demonstrates more timely graft substitution and increased bone regeneration when compared to an anorganic bovine bone xenograft.

Keywords: ridge preservation, socket, collagen plug, putty, xenograft, bone regeneration

Introduction:

The success of osseointegrated implants rests in the quality and quantity of residual bone at the recipient site at the time of implant placement.[1] Loss of bone occurs due to ridge resorption. Increased resorption may occur due to the presence of endodontic pathology, periodontitis, trauma or aggressive maneuvers during extraction. The degree of ridge resorption greatly increases with the time elapsed since extraction with the greatest amount occurring in the immediate post-extraction period.[2, 3] Schropp et al in a 12 month prospective study showed that a 50% decrease in bone width occurred following extraction, with 2 thirds of the estimated loss occurring in the first three months[4].

In an attempt to preserve the alveolar bone and to avoid ridge augmentation prior to implant placement, numerous bio-compatible regenerative materials have been used to fill the post-extraction socket [5,6,7,8] The regeneration of bone in the post-extraction socket has been documented with the use of a variety of grafts and/or GBR membranes as opposed to healing of the extraction socket alone.[9, 10]

Autogenous bone grafts have always served as a gold standard for regeneration.[11] However, problems such as their procurement, quantity obtained, unpredictable resorption and need for a second surgical site makes their use in ridge preservation procedures questionable.

Allografts have been frequently used for various regenerative treatment purposes including augmentation of extraction sockets. However, issues have been reported regarding their immunogenicity and immunological reactivity[12, 13]. Allografts are generally considered to possess osteoconductive properties. Demineralized freeze-dried bone may exhibit osteoinductive properties, but this varies among each donor, each tissue bank and it may even vary between batches within the same bank[14, 15].

Xenografts have been used with good results in oral osseous surgeries. A bovine xenograft derived from hydroxyl-apatite that is de-proteinated has enjoyed frequent use in ridge preservation. This bone substitute has been documented to retain its natural micro-porous structure following processing so that it supports cell proliferation and migration and enhances blood vessel formation through the course meshed interconnecting pore system. It possesses a large internal surface, which enables an intensive contact with new bone tissue and a fine crystalline structure, which permits integration into the natural bone remodeling process. Several animal studies have shown this material to be promising in comparison with other bone

substitutes.[16, 17] According to Klinge and colleagues[18] bovine xenografts provide an ideal scaffold for new bone formation and supports osteoblastic cell attachment and proliferation when used in rabbits. However, histological studies have revealed the presence of remnants of amorphous graft particles even several months following its implantation in vivo.[19, 20]

Recently alloplastic bone substitutes that include synthetically derived biomaterials have been extensively used for regeneration in extraction socket. A 3rd generation bioactive glass alloplastic putty has been included in this study. This bone substitute is a pre-mixed composite of bioactive calcium phosphosilicate particulate and a synthetic absorbable binder in a putty form. The bioactive particulate is composed solely of elements that exist naturally in bone such as Ca, P, Na, Si, and O with the binder being a combination of polyethylene glycol and glycerin.[21] The surface reactions lead to the formation of a calcium phosphate layer which serves as a scaffold for new bone growth. This graft material has the ability to adhere to normal bone, help its remodeling as well as enable hemostasis.[22] It has been successfully used in various osseous defects with no reported adverse event and good patient acceptability.

The aim of the present pilot study is to evaluate the quality of bone formation in extraction sockets following implantation with either a particulate bovine xenograft (Bio-oss, Osteohealth,

Shirley, NY) (BO) or a calcium phosphosilicate putty alloplastic bone substitute (NovaBone Dental Putty, NovaBone Products, Alachua, FL) (CPS Putty).

Materials and Methods:

The present study included 19 patients, presenting with 20 single-rooted teeth that were scheduled for extraction. Ten of these cases were treated in a private practice in Greece and the remaining ten in a private practice in India. Each of these patients had no systemic health issues with any underlying medical conditions that could affect the surgical or regenerative procedure. The exclusion criteria for this study were:

- Medical history that contraindicates oral surgical treatment
- Chronic therapy with NSAIDs and/or corticosteroids
- Pregnancy
- Severe periodontal disease
- Prior mucogingival or periodontal surgery at the experimental site
- Loss of more than 50% of the buccal plate at the time of extraction
- Heavy smoking (>10/day). Subjects smoking less than 10 cigarettes/day were included in the study and they were encouraged to abstain from smoking a week before as well as four weeks after the surgery.

Following a thorough oral evaluation, patients were informed about the diagnosis and treatment alternatives. Willing participants signed the consent form and were enrolled in the study. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. The patients were then stratified into two test groups following a simple random allocation approach at the site-level according to a computer-generated randomization list: Group BO and Group CPS. In each of the groups the tooth scheduled for extraction was removed using a flapless technique under local anesthesia (2% lidocaine with 1:100.000 epinephrine). Ridge preservation was performed according to the socket-plug technique as previously described by Kotsakis et al.[23]

Briefly, the extraction sockets of group BO were immediately grafted with particles of bovine xenograft and those of Group CPS were filled with Calcium Phosphosilicate putty. Following grafting a collagen plug (Collaplug, Zimmer Dental, Carlsbad, CA) was placed over the graft to occlude the socket and it was secured using a horizontal mattress technique with 4-0 vicryl suture material. Placement of removable interim prosthesis over the healing socket was avoided and the edentulous sites were provisionally restored with either a resin-fiber retained partial denture fixed on the neighboring teeth or left as it was according to the patients' esthetic demands.

Comment [A1]: Reviewer #2: Good article on the surface. A bit confusing as to how patients' were chosen to receive the Bio-oss vs. the CPS putty

Reviewer #1: Under the materials and methods I had some confusion. There were two groups of patients. One was in Greece and the other was in India. Do I understand correctly that the material used on each patient was determined from a randomly generated program?

More information were provided on the randomization process. Patients were allocated to each of the two test groups based on a computer-generated randomization list.

Antibiotics (Amoxycillin 500mg TID for 7 days) and non-steroid anti-inflammatory analgesics (Ibuprofen 400 mg QID for 3 days) were prescribed post-surgically. The patients were advised to follow a cold/soft diet for 24 hrs and use a chlorexhidine 0.2% oral gel for topical application two times daily for 2 weeks. Post-operative evaluation was done at 1, 3 and 6 weeks to check for complications including infection, wound dehiscence and resorption.

Periapical radiographs were taken at 5 to 6 months post-grafting to confirm radiographic bone healing of the extraction defects. At this stage implant placement was planned and samples for histological analysis were to be obtained simultaneously with the surgical procedure.

Mucoperiosteal flaps were raised to gain access to the underlying alveolar bone. Bone cores were obtained using a 2.7 mm inner diameter trephine bur. The cores obtained were stored in 10% buffered formalin and sent for histo-pathological examination.

Histological Technique:

Hard Tissue Research Laboratory, University of Minnesota, Minneapolis, Minnesota, USA performed non-decalcified histology and provided histomorphometric data on the cases that were performed in Greece. Upon receipt, specimens were dehydrated with a graded series of alcohols for 9 days. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC, Kulzer, Wehrheim, Germany). This was then followed by 20 days

Comment [A2]: Under Histological Technique I also had some confusion. Why were two different centers used for the histology?
One center (in the U.S.)used non-decalcified histology. The other center (in India) used a decalcified technique for the histology.

The convenience of sending samples was the reason why it was decided to use two histology centers. No bias in the study was evident from the results being very similar from both labs, even though no communication was allowed between scientists in the two labs.

...

Comment [A3]: Reviewer #2:, the variable histologic processing techniques made me wonder whether that would affect the conclusions.
Comparison of the results between the two labs did not reveal any significant difference in the results. Both techniques are scientifically valid, universally accepted and utilized by researchers frequently in the literature. Even in the case that there was a discrepancy in the results between labs, it would have been depicted in the standard deviations which in our case are very low in comparison to the means (47.15% ± 8.5% and 22.2% ±3.5% in CPS and BO groups respectively)

of infiltration with constant shaking at normal atmospheric pressure, the specimens were then embedded and polymerized by 450 nm light. Care was taken during specimen preparation that the temperature of the specimens never exceeded 40ºC, which were then cut and ground. Specimens were prepared in an apico-coronal direction, parallel to the long axis and were cut to a thickness of 150 µm on a cutting/grinding system (EXAKT Technologies, Oklahoma City, OK). The cores were polished to a thickness of 45-65 µm with a series of polishing sandpaper disks from 800 to 2,400 grit, using a microgrinding system, which was then followed by a final polish with 0.3 µm alumina polishing paste. The slides were stained with Stevenel's blue and Van Gieson's picro fuchsin and a cover slip placed for histologic analysis using bright field and polarized microscopy. Histomorphometric measurements were completed using a combination of spot insight program and Adobe PhotoShop (Adobe Systems, Inc.) At least two slides of each specimen were evaluated.

The Department of Oral Pathology, Oxford Dental College in India processed the cores that were obtained in India. All CPS Putty samples were subjected to microwave decalcification with 5% Nitric acid solution (95ml de-ionized water with 5ml Nitric acid). The tissue specimen was immersed in the above solution and placed in the microwave and heated up to 800w for 20 seconds and this cycle was repeated thrice with a one-hour interval between each cycle. This was followed by routine automatic tissue processing, embedding, sectioning and finally the sections

were stained with hematoxylin and eosin (H & E) stains. The above-mentioned modified technique was utilized for the CPS cores because based on the authors' experience hard tissue microtomy of CPS cores can cause artefactual voids due to the residual graft particles being separated particularly from the marrow portion of the cores. To prevent inconsistencies in the histomorphometrical analysis the Department of Oral Pathology's protocol includes this modified technique for handling bioglass cores. Microwave demineralization is a rapid method of partial demineralization to the point that the tissue is soft enough to cut with a routine soft tissue microtome. CPS cores being a bioactive glass do not undergo demineralization with nitric acid to the same extent as hydroxyapatite in bovine xenograft. As a result, there was no volumetric loss of CPS Putty at the end of processing and no consequent effect on the histomorphometric analysis. All BO specimens were routinely processed in an Automatic tissue processor, embedded in self-cure acrylic resin, mounted on a Hard tissue microtome (Leica SP 1600 Saw Microtome) and 50 micron sections were obtained, which were further ground by hand on an Arkansas stone, and stained routinely with H & E.

Statistical analysis:

A two-tailed, independent t-test was performed to compare histomorphometrical results regarding new bone formation and residual bone graft between the two groups. The level of statistical significance was set at the $p<.05$ level. Results from the histologic analysis of the

Comment [A4]: Reviewer #2:…In addition, the Bio-oss samples were processed differently than the CPS putty samples at this center in India. All of this is unclear to me as to why there were differences in where the samples were processed and why that was done. How this effects the conclusions is unclear as well. I would recommend a this section be expanded to discuss the differences in the histologic preparations and the possible effects on the conclusions. It would seem that the most rigorous analysis would involve all the samples being processed in an identical manner and method.

A justification for the modified procedure is provided in red font in the text. Based on our experience bioglass particles need special handling during sectioning, otherwise separation of the particles from the marrow will occur during processing and the results will be inaccurate. This modified technique is utilized to ensure that the cores are unaltered during histomorphometric measurements.

samples were presented descriptively.

Results:

Clinically and radiographically all sites healed without any complications or adverse reactions. No signs of infection or inflammatory response were observed during the healing period. Periapical radiographs taken at 5 to 6 months post-grafting (5.25+-0.2) showed radio-density similar to the adjacent bony structures in the CPS group (Figure 1) while cases in the BO group showed a greater level of radio-opacity (Figure 2). During surgical re-entry of the surgical sites, visual inspection revealed bone regeneration in the healed ridges with either of the test materials. The sockets that had been grafted with the xenograft presented visible residual particles on the area of the regenerated bone. This newly formed structure was regarded as bone and histological analysis was done to confirm clinical findings. All sockets received implants and results regarding implant primary implant stability and survival will be presented in a separate publication.

Histology & Histomorphometric Analysis

Histologic analysis of all samples consistently showed the presence of vital, healthy trabecular and woven bone and bone marrow with evidence of remodeling, indicated by resting and reversal lines with variable quantities of residual bone graft material. These sections were then

analyzed at 20x, 40x & 100X magnifications to ascertain the area occupied by bone tissue and residual bone graft. Figures 3A, B & C are histology sections of a representative CPS Putty case at 6 months. At all magnifications the sections show vital lamellar bone, highly vascular bone marrow and some residual graft particles. Figures 4A, B & C are histology sections of a representative BO case at 6 months. At all magnifications, the sections show viable bone with marrow tissue and residual graft substitute. Higher number of residual graft particles can be clearly observed in the sections with BO as compared to CPS Putty.

Table 1A displays vital bone in defects filled with CPS Putty that ranges from 36% - 57% (average 47.15% ± 8.5%). Residual bone graft (RBG) was found to range from 30% at 4months to a minimum of 3% at 6 months and an average of 17.4% ± 9.4%. The vital bone values in the BO group (Table 1B) ranged between 17% - 27% (average 22.2% ±3.5%). The difference in vital bone volume between the two groups was found to be statistically significant in favor of the CPS putty group $P<0.05$. Specimens in the BO group showed a range of RBG of a maximum of 38% at 4 months to a minimum of 18% at 6 months with an average of 25.7% ± 5.9%. (Figure 5) The amount of RBG was found to be significantly higher in the BO group ($P<0.05$). Table 2 presents a comparison of RBG between the study groups at two different observation intervals, at 4 & at 6 months. At 6 months there was a highly statistically significant reduction in residual graft volume in the CPS putty group when compared to BO ($P<0.001$).

Discussion: Extraction site reconstruction is frequently employed for alveolar ridge preservation when future placement of implants is the treatment of choice. Immediately following extraction of a tooth, a cascade of inflammatory events are initiated and a blood clot is formed which further directs the migration and proliferation of cells and the release of growth factors. By 4-6 weeks, most of the alveolus is filled with woven bone (osteoid tissue), while the soft tissue becomes keratinized. After a 4-6 months period, the mineralized tissue within the socket reorganizes into layers of lamellar bone.[24] Many biomaterials have been used in an attempt to enhance bone regeneration in the post-extraction socket. A clinical study by Becker et al. showed that, when bovine bone is used in ridge preservation it does not promote extraction socket healing. Bovine xenografts also do not contribute significantly to bone-to-implant interface. The same study also indicated that these grafts appeared inferior to the normal extraction socket healing, though they maintained ridge width possibly due to extended resorption time.[25]

The present study was conducted to comparatively assess the relative efficacy of BO to a newly developed alloplastic putty bone substitute using a flapless ridge preservation approach. CPS Putty is a third generation bioactive glass. Bioglass has been successfully implanted for over a decade in craniofacial surgeries, dental bone grafting, orthopedic and in spine indications[26]. BO though an excellent bone filler, it resorbs very slowly and has been shown to exhibit a high

239 percentage of residual graft particles for extended periods of time following its implantation.
240 CPS Putty not only provides an osteoconductive scaffold but also functions by a process of
241 osteostimulation[27]. It stimulates osteoblast recruitment, proliferation and differentiation at the
242 defect site and increases rate of bone formation not just at the edges but throughout the defect. It
243 has been engineered to exhibit faster rate of particle resorption and bone regeneration. In a recent
244 study, Gonshor et al., concluded that a high percentage of vital bone (48.2%) was noted in series
245 of 22 sockets that were restored with CPS putty.[28]. In comparison results of a clinical study
246 where BO was left to heal in extraction sockets for 9 months showed that the amount of osseous
247 tissue in the superficial area of the healed socket was 17.1%. The average bone tissue fraction
248 increased to 48.3% in the mid section area, but it displayed 4 times more woven bone than
249 lamellar. Only in the most apical site of the healed socket, bone tissue reached 63.9%, after 9
250 months of healing.[29]
251
252
253 In our study, a collagen wound dressing material that was used instead of a membrane helped in
254 achieving excellent hemostasis and induced blood clot formation along with stabilization of the
255 blood coagulum.[30, 31] This collagen barrier is an integral biomaterial when utilizing the socket-
256 plug technique and has been found to stimulate platelet aggregation and enhances fibrin linkage.

It has also been demonstrated to be chemotactic for fibroblasts in vitro which might promote cell migration and primary wound coverage.[32] Histological results of this study point out that the collagen plug is an adequate barrier for ridge preservation when most of the buccal plate is maintained following extraction since no epithelial infiltrate was noted in the regenerated sockets.

Conclusion:

Both BO and CPS Putty showed regeneration of bone within the socket, thus it can be considered that both present clinically viable alternatives for alveolar ridge preservation. While at 4 months the RBG between the two study groups was comparable, CPS Putty showed a significantly less percentage of RBG and a greater amount of bone regeneration at the 6-month interval than BO. Consequently, CPS putty may present a clinical advantage in terms of the quality of the regenerated bone over BO when reduced treatment time between ridge preservation and implant placement is required. Large scale randomized clinical studies are required to evaluate the clinical efficacy of CPS Putty bone substitute and reaffirm our findings.

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Legends:

Figure 1: Representative radiograph of a socket regenerated with CPS Putty at 5 months. Note that the radiodensity in the socket area is very similar to the adjacent ungrafted area.

Figure 2: Representative radiograph of a socket regenerated with BO at 6 months. Note that the socket area exhibits higher radiodensity indicative of residual graft particles.

Figure 3: Representative images of CPS Putty core at 6 months: A) medium (20x), B) high (40x) and C) very high (100x) magnifications. The red-stained tissue is mineralized, newly regenerated bone with visible cell nuclei. Some residual graft particles can be seen in all the microphotographs.

Figure 4: Representative images of BO core at 6 months: A) medium (20x), B) high (40x) and C) very high (100x) magnifications. Large remnants of residual graft particles can be noted. Red area denotes newly formed bone with visible cell nuclei.

Figure 5: Graphical representation of the percentage of vital bone and residual bone graft in both groups

Table 1: Vital Bone and Residual Graft values for the A) CPS Group B) BO Group

Table 2: Comparative evaluation of the RBG percentages between the two study groups at two time intervals.

Table 1A

Tooth #	Time (Months)	Vital Bone	RBG
14	6	55%	3%
35	4	38%	24%
11	4	55%	18%
21	5	41%	26%
24	6	41%	13%
25	5	55%	8%
21	4	40%	28%
11	4	36%	30%
44	5	54%	16%
24	6	57%	8%

Table 1B

Tooth #	Time (Months)	Vital Bone	RBG
45	4	17%	38%
23	6	22%	26%
13	6	19%	24%
11	6	24%	20%
35	5	26%	26%
33	6	26%	22%
44	4	18%	32%
15	6	21%	28%
24	6	27%	18%
25	6	22%	23%

Table 2

RBG	CPS Putty	BO
4 months	23.67±5.57*	35.00±4.24
6 months	8.00±4.08**	23.14±3.44
All samples	17.40±9.39*	25.60±5.89

*Indicates a statistically significant (P<.05) reduction in RBG values in favor of the CPS Putty group

**Indicates a highly statistically significant (P<.001) reduction in RBG values in favor of the CPS Putty group

Figure
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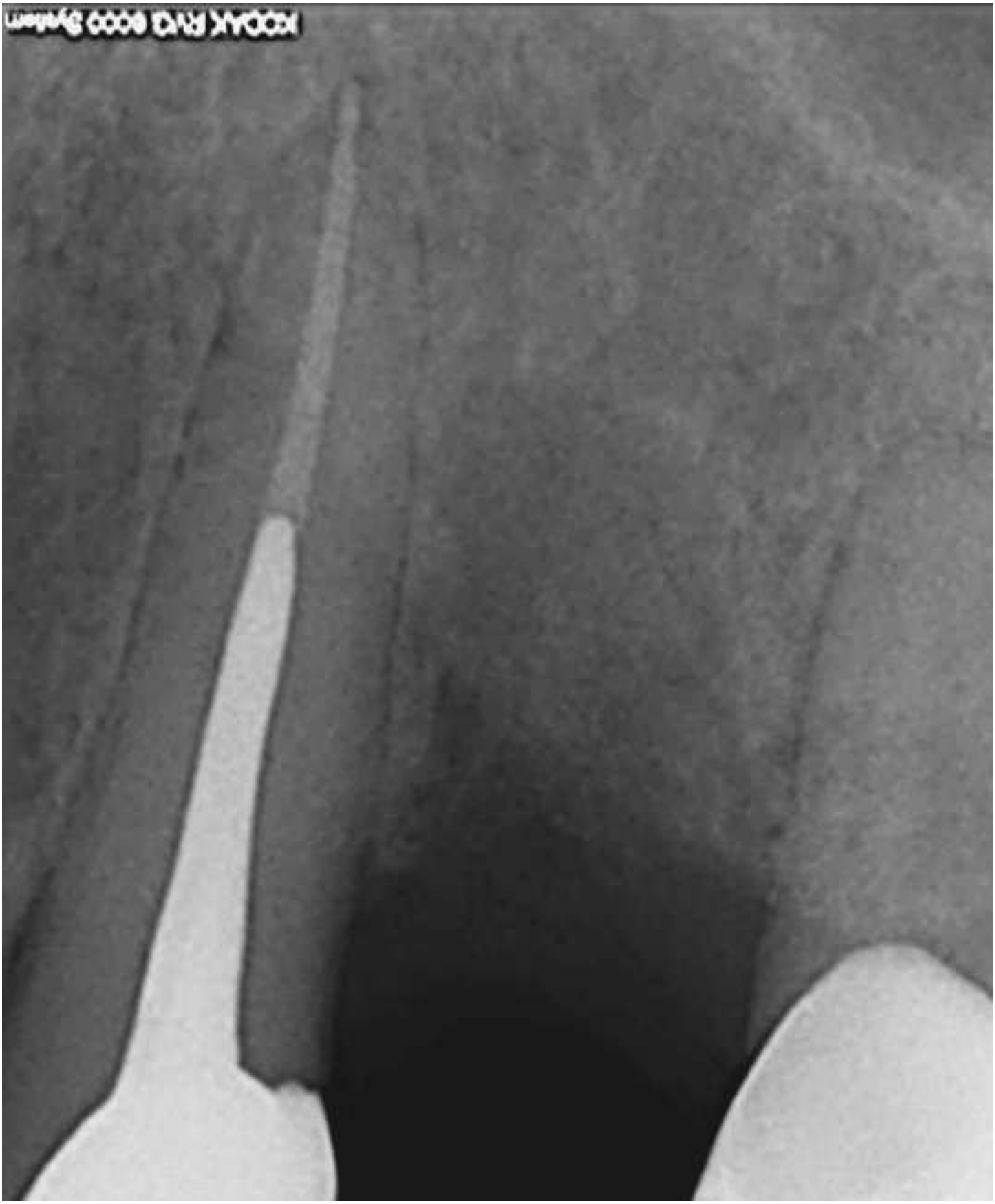

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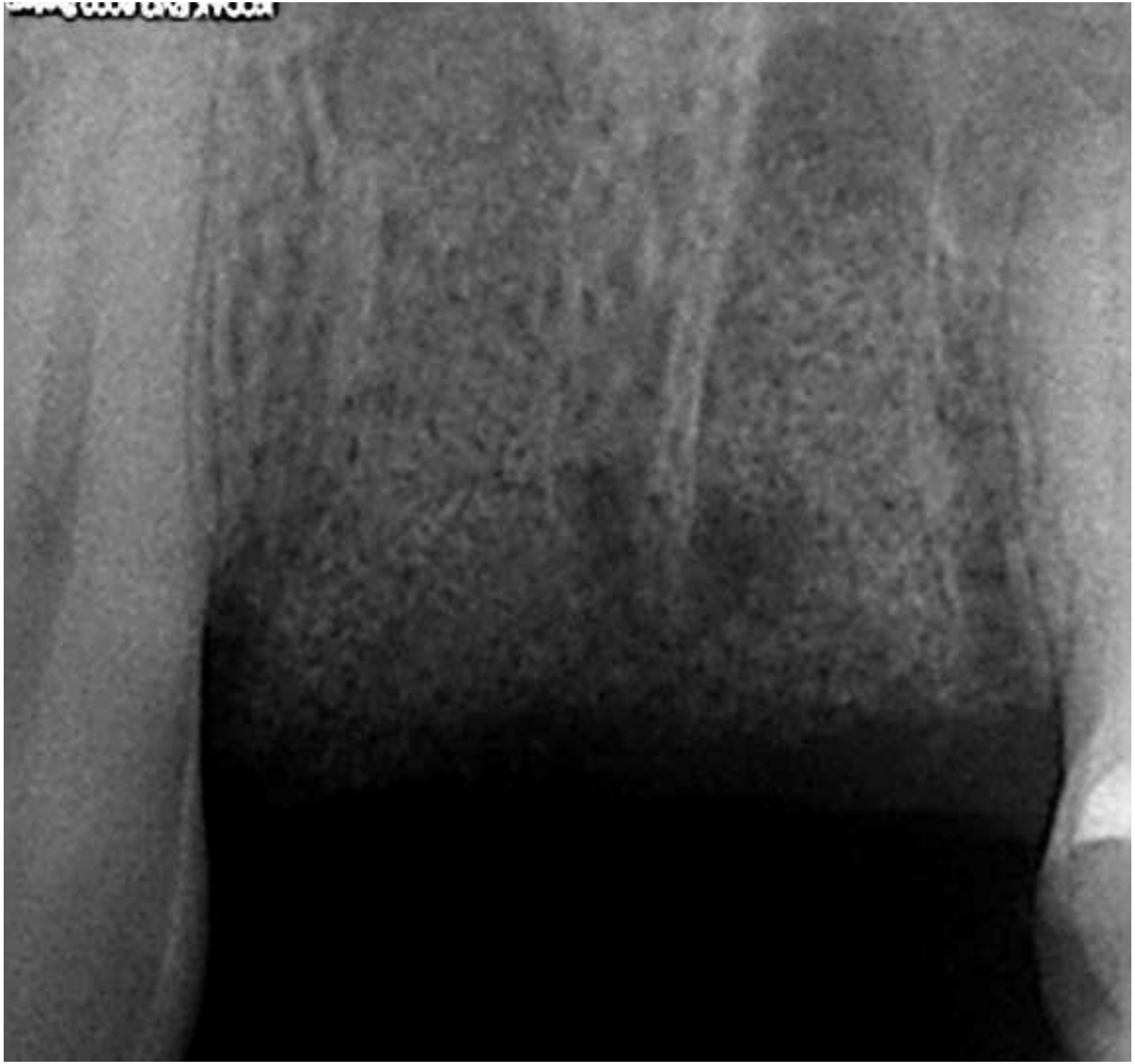

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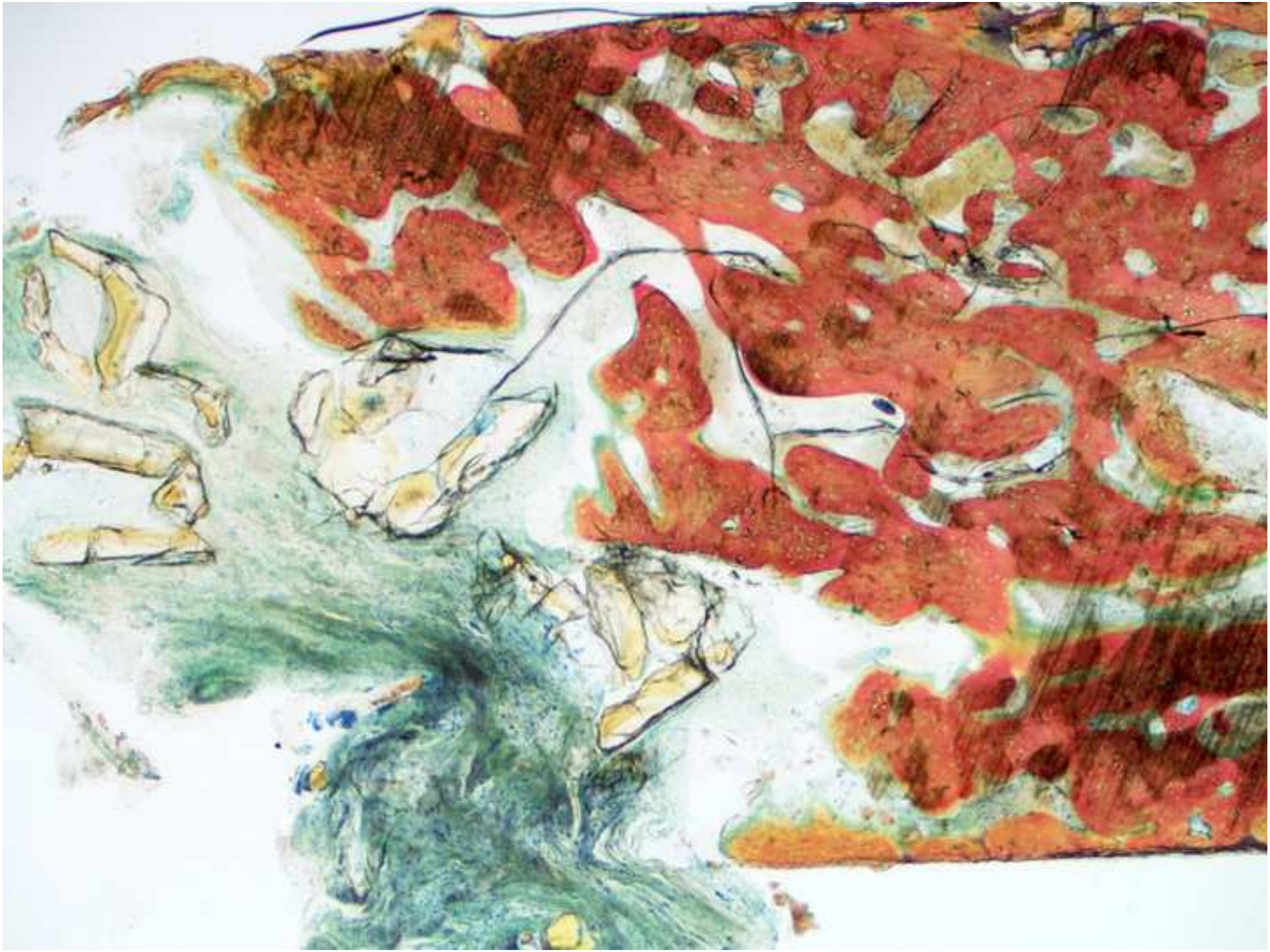

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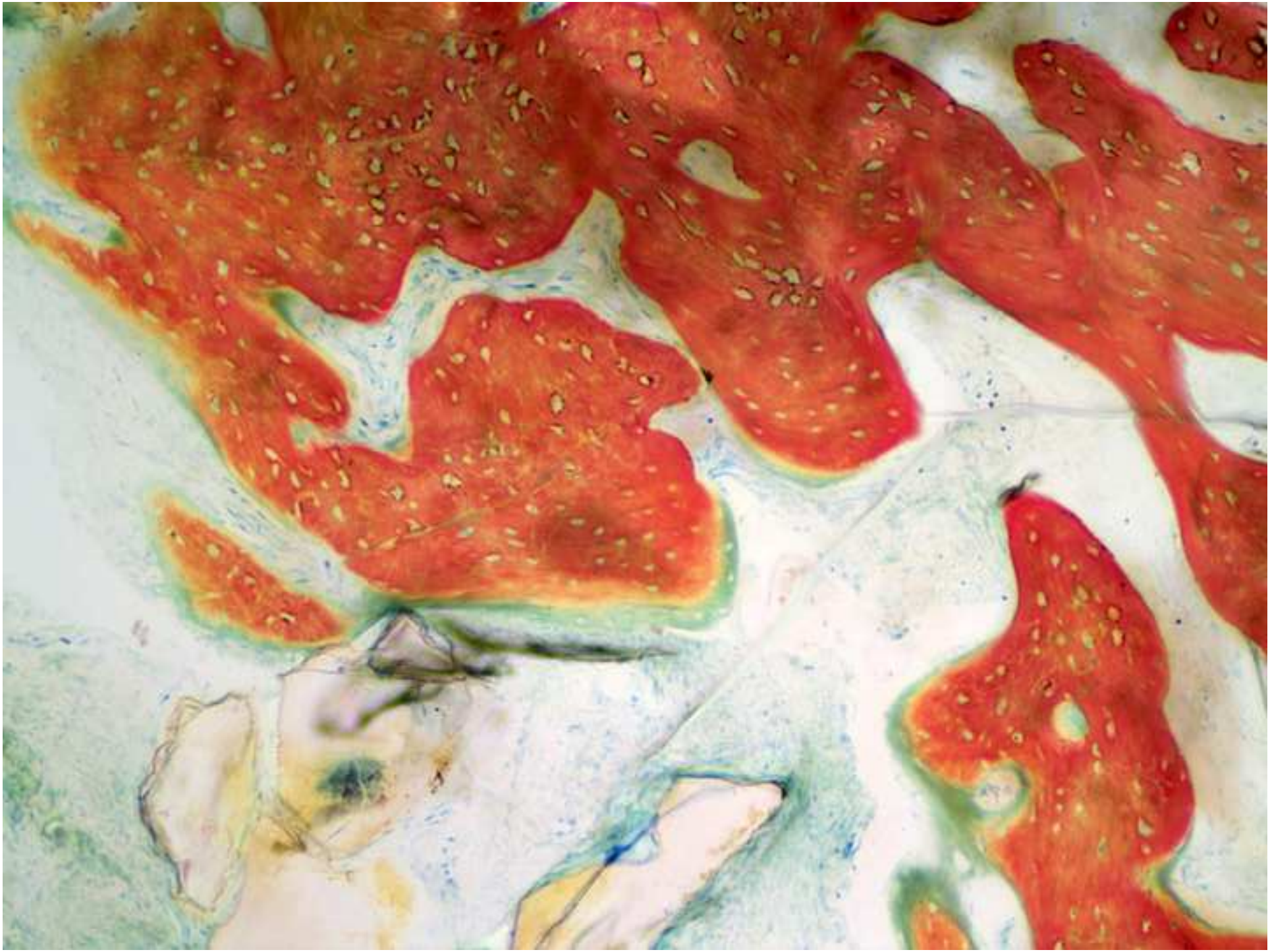

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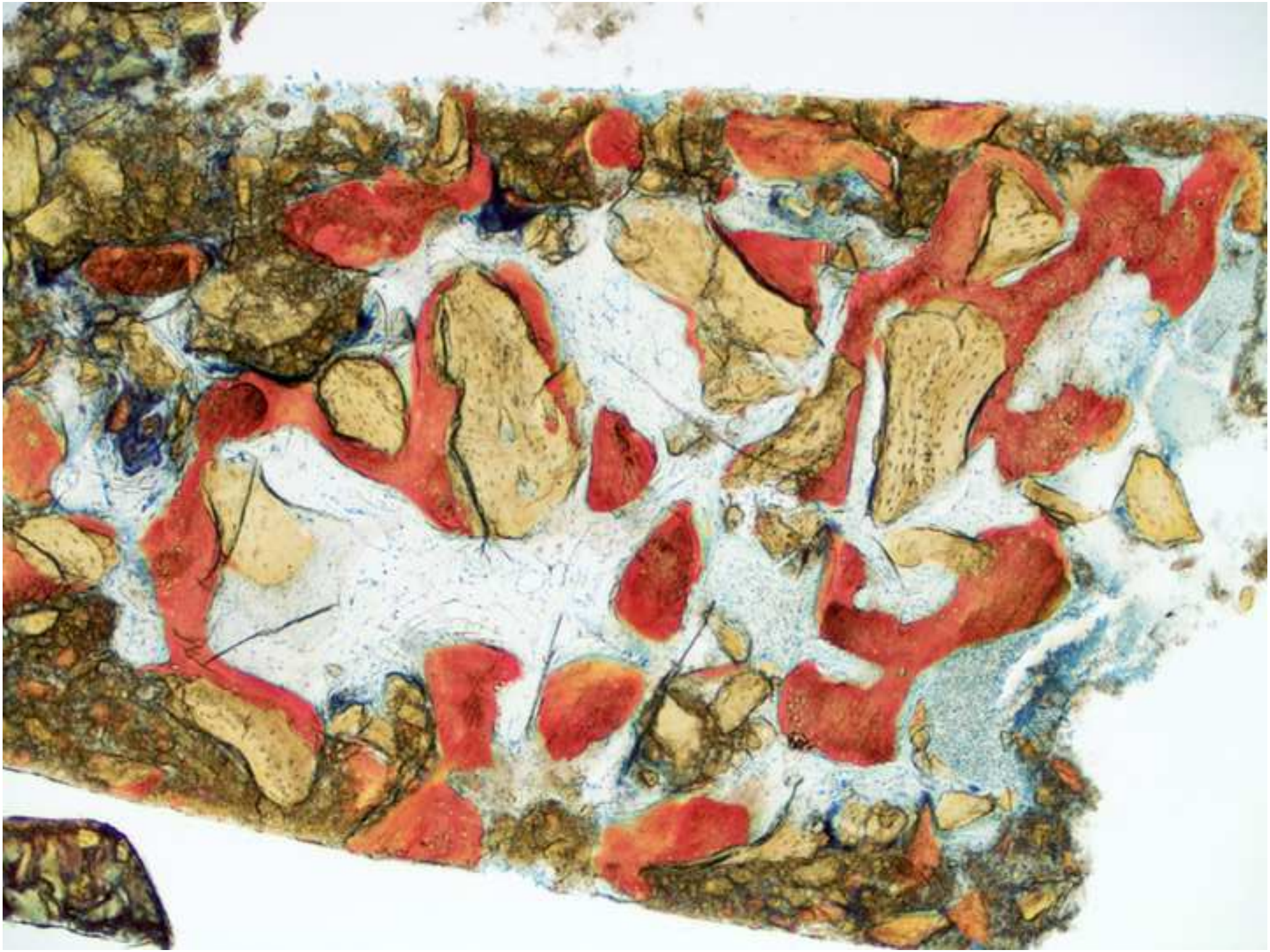

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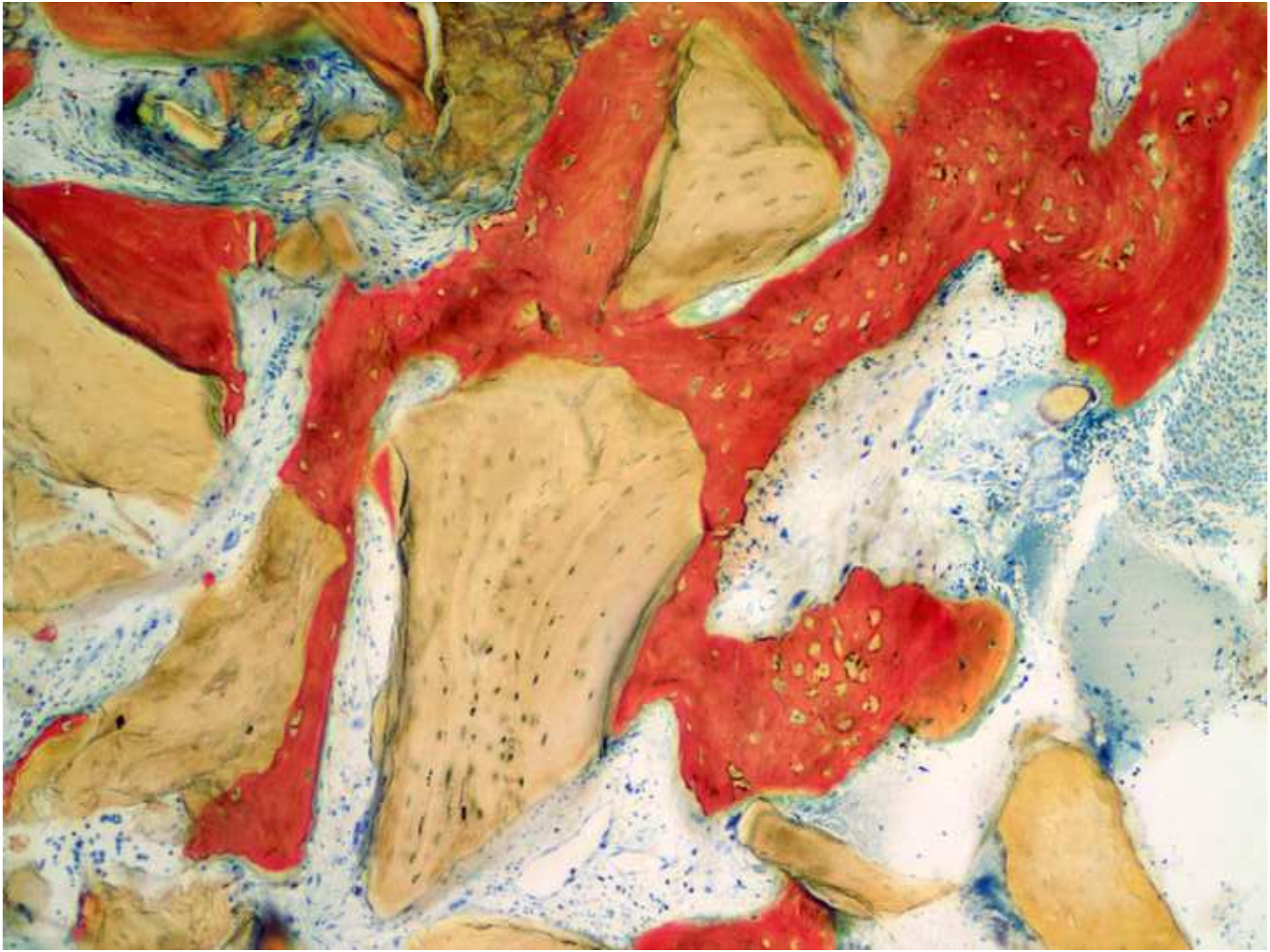

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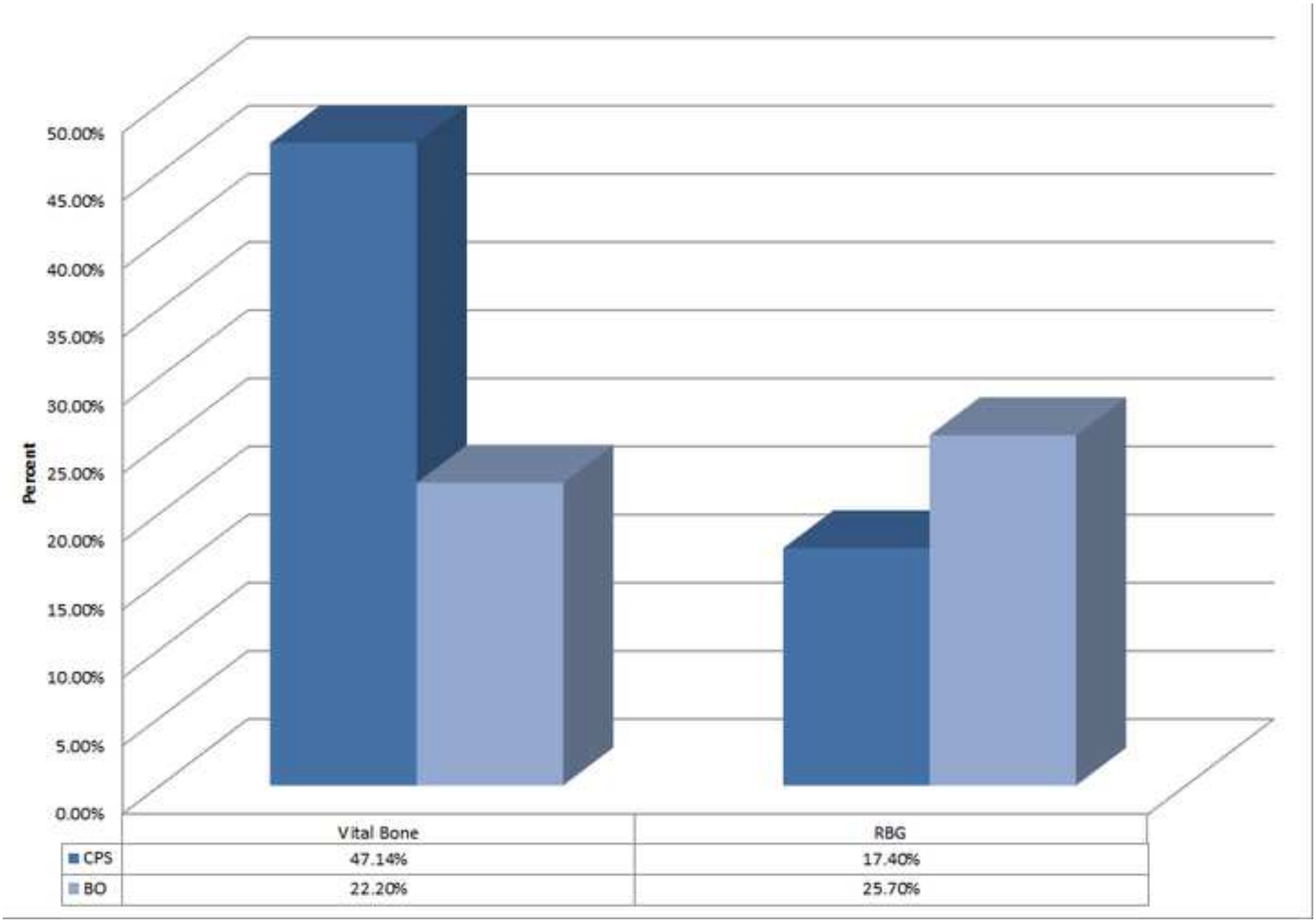

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