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Bone Augmentation in Infected Sites with Bovine-Derived Xenograft Mixed with Platelet-Rich Plasma Covered by Platelet-Poor Plasma

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Abstract

Purpose: The aim of this study was to assess the success of bone regeneration in infected and non-infected human dental defects, wtih respect to biological properties of bone remodeling.

Methods: Thirty-eight operated sites, consisting of twelve non-infected sites and twenty-six infected sites, from twenty-eight patients were included in this study. Bone regeneration was performed using particulate bovine-derived xenograft mixed with PRP derived from the patient's blood, covered by platelet-poor plasma (PPP) and/or a collagen membrane. At 6±1.8-months post augmentation, re-entry surgery was performed and bone samples were harvested at implant locations prior to implantation.

Results: Histomorphometric analysis of bone biopsies was used to evaluate new bone formation, soft tissue, and residual biomaterial in infected and non-infected sites. In all samples, the biomaterial particles were surrounded by newly generated bone. Among factors that were analyzed, gender, medical state, and smoking had no significant effect on bone regeneration. Variables including tooth location, platelet concentrate, and protective membrane addition were also analyzed for their effects on bone regeneration.

Conclusion: The results clearly demonstrate that both infected and non-infected sites were clinically successful in terms of bone regeneration geared for implantation, yet infected sites tend to exhibit delayed remodeling, resulting in higher levels of soft tissue and biomaterial remains.

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Introduction

The unveiling of osseointegration, recent progress in biomaterials and implant techniques, as well as the increased longevity, esthetic and functional demands, have contributed to an increased application of dental implants in restoration for partially and completely edentulous patients. The main reasons for tooth or implant loss are progressive periodontitis and peri-implantitis [1]. These dental inflammatory conditions are characterized by alveolar bone loss, which occurs either directly due to the colonization of bone by microorganisms, or indirectly, due to the local inflammatory response in the gingival soft tissues and periodontium [2]. The inflammatory environment initiates osteoclast activity and leads to excessive bone resorption [3-5]. This prevents positioning of dental implants and requires bone augmentation prior to the implant insertion [6,7]. The success of bone augmentation is assessed by the sufficient presence of alveolar bone and by the degree of remodeling and mineralization to provide an effective structure for implant placement.

Various techniques for augmentation are currently in use to treat bone atrophy [8]. One of the most common techniques for ridge augmentation is guided bone regeneration (GBR) with particulate bone graft substitutes, covered by a membrane (non-resorbable membrane or resorbable collagen membrane) to prevent ingrowth of soft tissue into the augmented site [9-12]. Bone healing involves interactions among numerous cell types and microenvironments. The monocyte–macrophage–osteoclast lineage, the mesenchymal stem cell–osteoblast lineage, along with early and transient inflammatory signals are essential for proper bone healing [13].

Whole blood-derived products, such as platelet-rich plasma (PRP) and platelet-poor plasma (PPP), have been in use for decades. PRP, and in some cases PPP, were demonstrated to facilitate angiogenesis, soft tissue repair, and bone regeneration in alveolar bone augmentation [14-19]. However, contradicting reports are present regarding the long-term beneficial use of PRP, thus additional studies are crucial.

The current study includes consecutive patients that underwent bone augmentation following tooth extraction or implant removal, due to endo-perio lesions or chronic peri-implantitis. Our aim was to assess the clinical and histological success of bone augmentation in infected sites relative to healthy, atrophied sites.

Materials and Methods

Patients

The study was conducted on successive patients that underwent bone augmentation following tooth extraction or implant removal, due to endo-perio lesions or chronic peri-implantitis. The control group includes patients that required bone augmentation in healthy, edentulous sites prior to implantation. The study was composed of 28 healthy individuals and 38 operated sites (12 non-infected sites and 26 infected sites).

Sites of extraction and implant removal were disinfected prior to the augmentation procedure. After a healing period of six months, bone samples were collected from the implantation site. DSA performed all surgeries at the Schwartz-Arad Surgical Center between 2014 and 2016 under local or general anesthesia. Preoperative clinical examination, panoramic and CT scans of the operated area were performed. One hour before the surgical procedure, prophylactic antibiotics (Amoxicillin 1 g or Clindamycin 600 mg for penicillin-sensitive patients), and dexamethasone (8 mg) were administered. Rinsing with 0.5% chlorohexidine for 1-2 minutes was performed prior to surgery. Data collection and analysis were performed by independent researchers. Informed consent for the surgical procedure and study was obtained from the patients prior to procedure. The study was approved by research ethics committee of Tel Aviv University #0000993.

Tooth Extraction and Implant removal

Tooth extraction: Indications for tooth extraction were the appearance of chronic infection due to extensive untreatable periodontal or endodontic disease or presence of a pathological process (i.e. cysts).

Implant removal: Implant removal was determined necessary by chronic, untreatable peri-implantitis with extensive cervical bone loss.

After tooth or implant removal, the defects were disinfected with Iodine solution (Medi-market, Netanya, Israel) and hydrogen peroxide 3% (Medi-market, Netanya, Israel) and irrigated with cold sterile 0.9% saline (Medi-market, Netanya, Israel).

Augmentation procedure

Augmentation of the alveolar process was performed with the combination of a bone substitute (Bio-Oss ®, Geistlich Sons, Wolhusen, Switzerland) saturated in Metronidazole® (Medi-market, Netanya, Israel) and PRP and and covered with PPP, both obtained from patient's own blood (see below for details). Immediately after the augmentation procedure, panoramic imaging was obtained; all patients were prescribed oral antibiotics (amoxicillin 1.5 g for five days) or clindamycin (1.2 g for four days) and dexamethasone (4 mg for two days). Rinsing with 0.25% chlorohexidine was recommended twice a day for 10 days follow the procedure. Naproxen sodium was prescribed twice a day. Sutures were removed 3 weeks post-surgery and panoramic and CT scans of the operated sites were obtained after a waiting period of 5.86 ± 1.38 months prior to implantation. Non-infected sites were treated using the same augmentation procedure.

PRP and PPP preparation

The preparation of PRP and PPP was performed using the Harvest SmartPReP2® Multicellular Processing System (Harvest Terumo BCT, Inc. Lakewood, Colorado). The bone substitute was first saturated in the PRP activated by 20 mM CaCl2 plus 25 IU/ml human plasma thrombin (Omrix Biopharmaceutical Ltd., Israel). This mixture was used as a filling material in both tested and control sites. Occasionally, PPP (also activated by thrombin and CaCl2) was gently placed over the operated site with or without a collagen

membrane.

Sample harvesting and preparation

Directly preceding implantation, bone samples were collected from the augmentation sites. A surgical trephine drill (Ø =3mm) (Ofek Frides Ltd., Petah-Tikva, Israel) was used to harvest a small bone sample. Bone core biopsies were immediately stored in 10% buffered formaldehyde (Fisher Scientific, Atlanta, Georgia) and subsequently processed to obtain thin ground sections (Precise 1 Automated System, Assing, Rome, Italy). The specimens were dehydrated in an ascending series of alcohol rinses and embedded in glycol methacrylate resin (Technovit 7200 VLC, Heraeus Kulzer GmbH & Co, Wehrheim, Germany). Specimens were then sectioned along the longer axis using a high-precision diamond disc to approximately 150 microns and ground down to about 30 microns. From each specimen, two slides were obtained and stained with basic fuchsin and toluidine blue.

Histological and histomorphometric evaluation

Histomorphometry of newly formed bone, marrow spaces, and residual graft material were carried out on each specimen using a light microscope at low magnification (325) (Laborlux S, Ernst Leitz GmbH, Wetzlar, Germany) connected to a high-resolution video camera (3CCD, JVC KY-F55B, JVC, Yokohama, Japan) and interfaced to a monitor and personal computer (Intel Pentium III 1200 MMX, Intel Corporation, Santa Clara, Calif). This optical system was linked to a digitizing pad (MatrixVision GmbH, Oppenweiler, Germany) and a histometry software package with image-capturing capabilities (ImagePro Plus Version 4.5, Media Cybernetics Inc, Silver Spring, Md). The values for marrow space/soft tissue, residual graft material, and newly formed bone were recorded exactly 1 mm from the pre-existing bone, and the mean percentage values were calculated.

Statistics

Continuous variables were expressed as mean ± standard deviation (SD) and analyzed with Student's t test or the Mann Whitney test when appropriate. Categorical variables were analyzed using the chi-square test. Analyses were performed with SPSS V.25 for Windows.

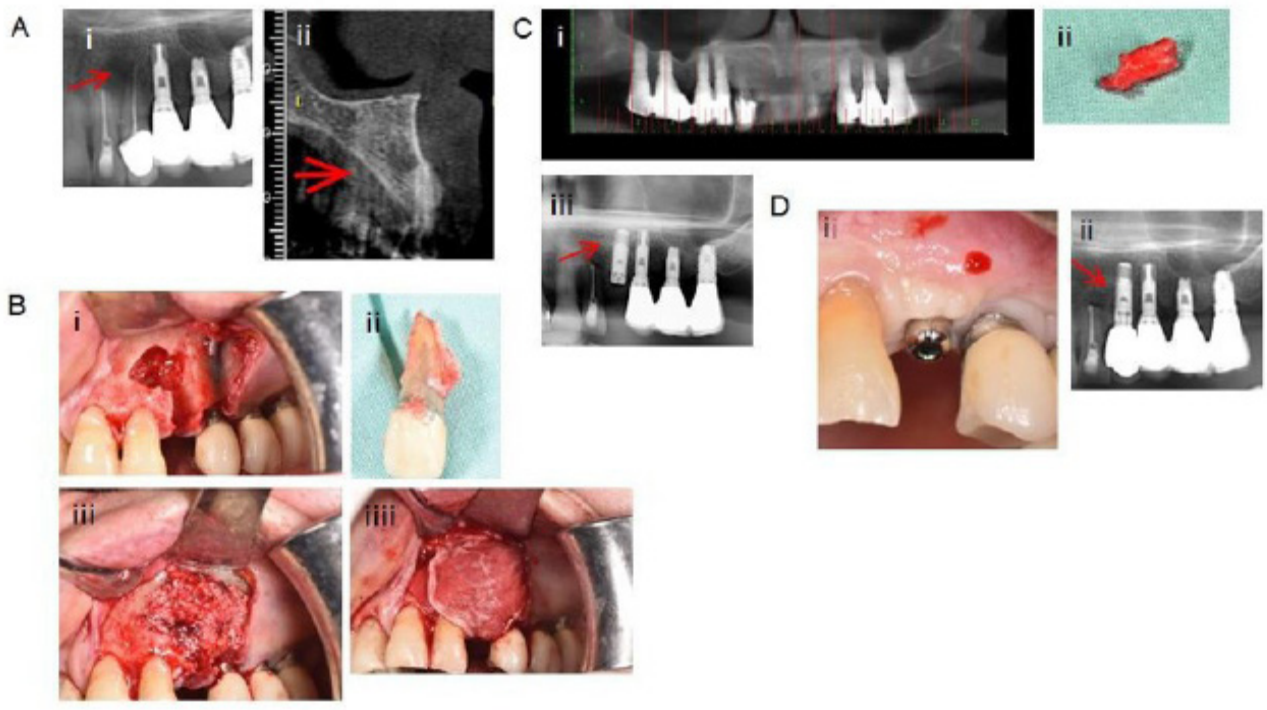

Figure 1: Work flow of augmentation procedure. A) The diagnostic stage: panoramic view (i) and CT section (ii) showing the bone defect. Arrows indicate areas with resorbed bone. B) First stage of procedure: the extracted tooth and socket after debridement (i, ii). Ridge preservation procedure: the bone defect was filled with Bio-Oss® mixed with Metronidazole and PRP (iii) covered with PPP (iiii). C) Second stage of procedure: CT of the filled socket 5 months after ridge preservation (i), bone sample of the augmented bone (ii), and X-ray of the implant after position at the site from which the bone sample was taken (iii). D) Implant exposure after 6 months, showing placement of the prosthetic (i) and X-ray of implant 1.5 years post rehabilitation (ii). Arrows indicate the implant site.

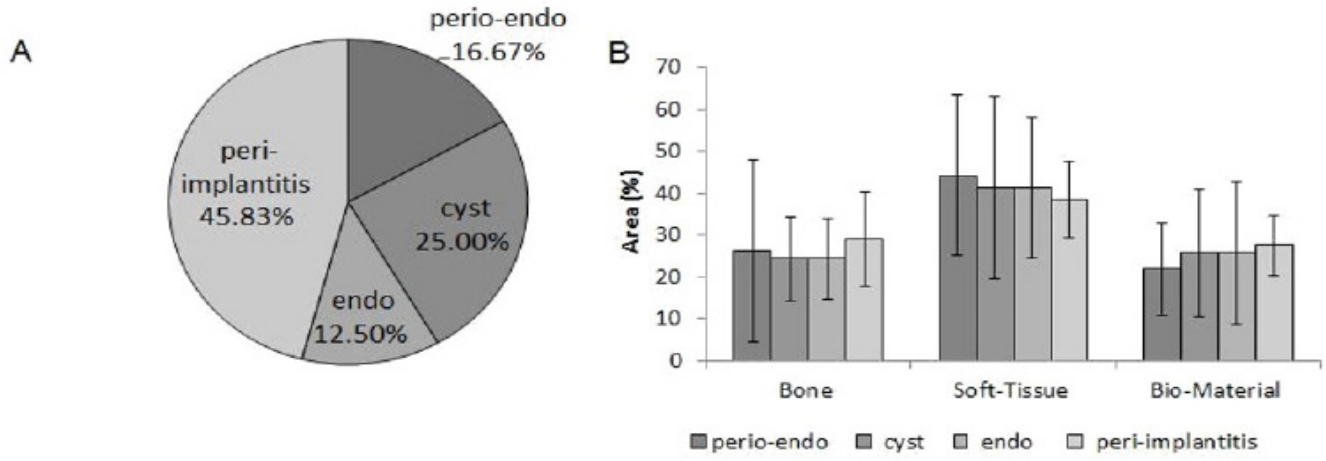

Figure 2: Summary of clinical features of patients. A) Distribution of samples according to the clinical reason for tooth extraction / implant removal (%). B. Area (%) of new bone, bio-material, and soft tissue for each clinical condition as described in A.

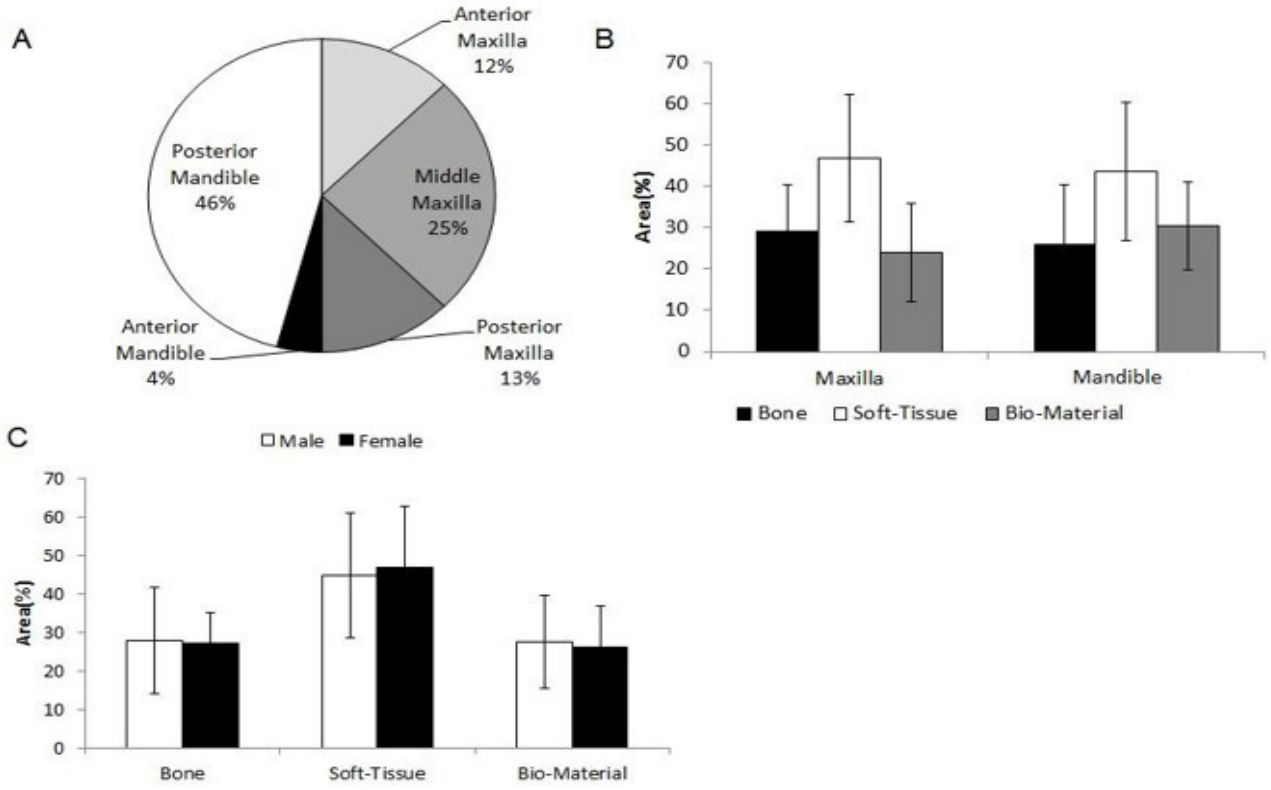

Figure 3: Location of surgical site and gender have no effect on the levels of bone formation, biomaterial remaining, or soft tissue present. A) Surgical site distribution. B) New bone, biomaterial, and soft tissue levels according to surgery location. C) New bone, biomaterial, and soft tissue levels in infected sites in male vs female subjects.

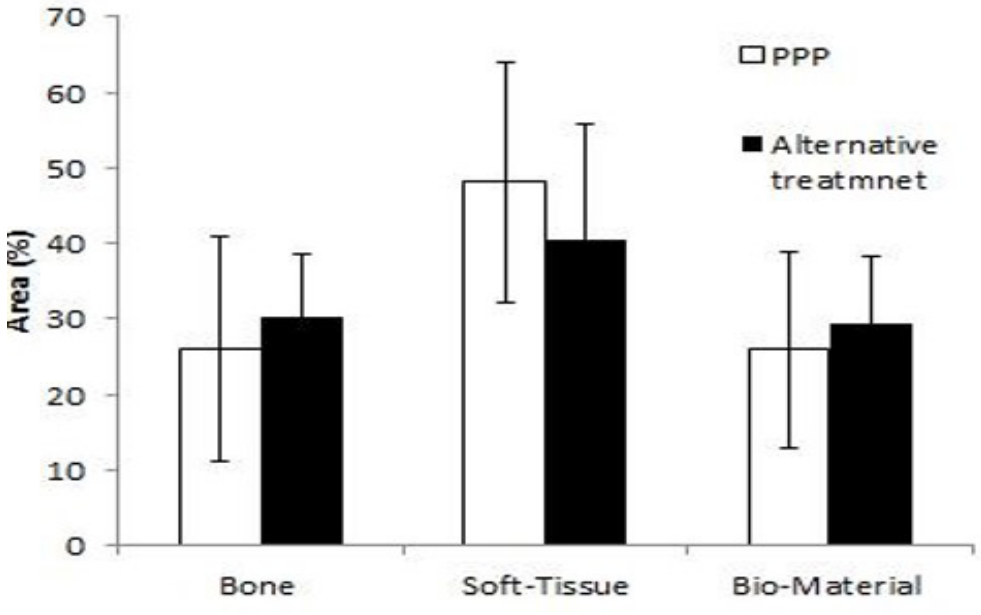

Figure 4: PPP does not significantly affect bone formation, biomaterial remaining, or soft tissue present compared to other treatments. New bone, bio-material, and soft tissue levels in infected sites treated with platelets poor plasma (PPP) or alternative treatments (resorbable membrane; resorbable membrane+ PPP).

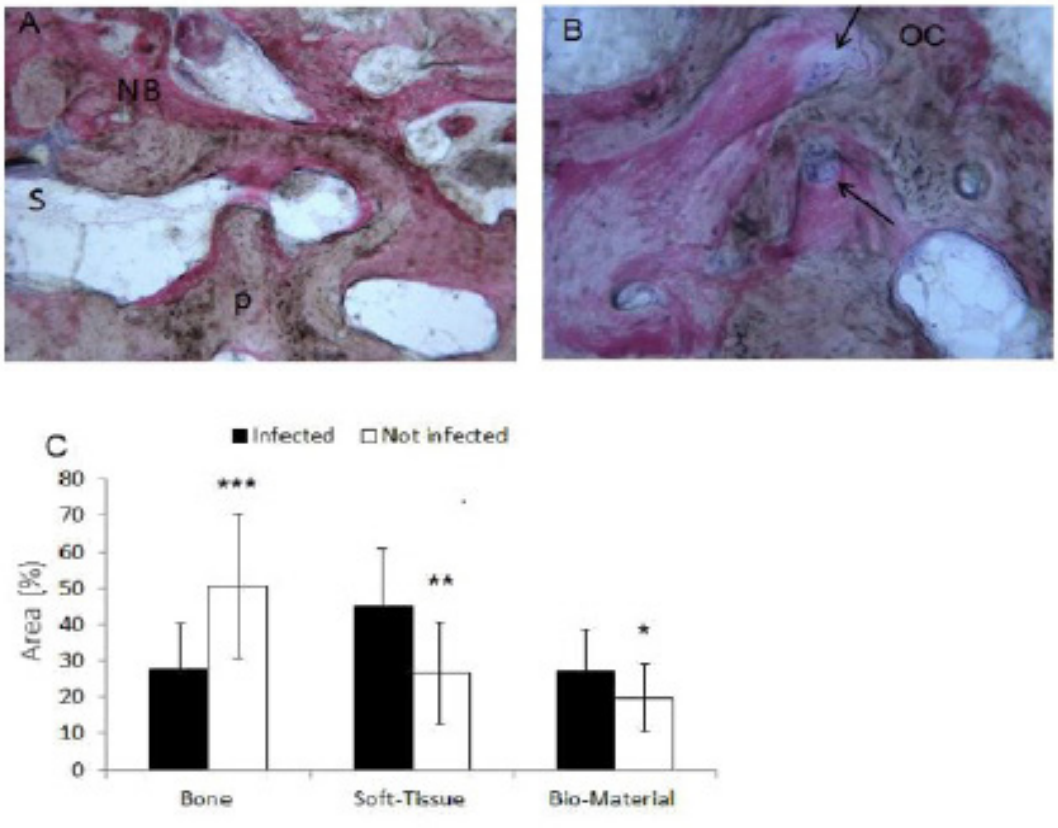

*Figure 5: Non-infected sites show improved bone remodeling comapred to infected sites. Histochemical slide imaging of bone sample taken from center of the socket at time of implant placement, stained with toluidine blue. (A) At ×40 magnification. (B) At ×100 magnification. p (biomaterial particle); NB (new bone); s (soft tissue); OC (osteoclast). (C) Quantification of New bone formation, area of soft tissue and biomaterial remnants in infected and non-infected sites. *** p=0.00015; **p=0.002; *p=0.036.*

Results

Bone samples from 38 sites obtained from 28 patients were quantitatively analyzed for the presence of soft tissue and residual biomaterial, and bone formation. Sites that displayed infection markers such bleeding on probe, gingivitis, or deep periodontal pockets were included in the study group. The control group was composed of patients that required alveolar bone augmentation in non-infected sites.

Figures 1 depicts a typical treatment timeline starting at diagnosis (Figure 1A i, ii) followed by first-stage surgery-including the extraction of the infected tooth due to an untreatable endo-perio lesion, curating the granulation tissue, suceeded by the augmentation procedure (Figure 1B i-iiii). At the second stage (six months after the augmentation), a bone core sample was obtained at the location of the implant, and the implant was simultaneously placed (Figure 1C i-iii). A radiograph of the implant one year after rehabilitation reveals complete recovery of the bone surrounding the implant (Figure 1D i, ii).

A prevalent reason for tooth extraction in this cohort was untreatable periodontitis (16.67%), and for implant removal was peri-implantitis (45.83%, Figure 2A). However, there were no differences in the levels of newly formed bone, biomaterial, or soft tissue found among the various cases (Figure 2B).

Ridge augmentation was required mainly in the posterior mandible (Figure 3A). Yet, no marked differences in bone augmentation and regeneration were observed between the maxilla and mandible (Figure 3B). Out of the patients, 40.12% were male and 59.88% were female, with ages ranging from 33 to 85 years (mean 59.38 ± 11.57 years). Comparison between bone regeneration in infected sites showed no difference between genders (Figure 3C).

There is an ongoing debate regarding the contribution of PPP in promoting bone regeneration: studies have shown that PPP could improve wound healing and reduce pain [20, 21]. In this study, we evaluated the effect of PPP addition compared to alternative treatments (Figure 4). The results show no significant differences in bone regeneration among sites covered by PPP alone versus sites covered by a resorbable membrane with or without PPP.

Crucially, the histological analysis also shows that the Bio-Oss particles appear to fuse with newly formed bone (stained in red), revealing intimate contact between bone and grafted particles (Figure 5 A,B).

The environmental signals around healthy, atrophied sites allow improved bone-remodeling compared to infected sites. As shown in Figure 5C, new bone around biomaterial particles was 45% lower in chronic infected sites compared to non-infected sites ($p=0.0001$). In contrast, both the soft tissue levels and biomaterial remnants were significantly higher in infected sites relative to non-infected sites by 69% ($p=0.002$) and 37% ($p=0.036$) respectively.

Discussion

Tooth extraction is one of the most frequent procedures in oral and maxillofacial surgery. Ridge preservation procedures performed at the time of extraction aim to maximize bone formation and minimize the soft tissue expansion within the socket. We hypothesized that augmentation in infected sites with biomaterial will not differ significantly from the same augmentation procedure in non-infected sites: therefore, we evaluated the potential amount of bone formation following volume preservation using bone substitutes in infected and non-infected sites as well as the influence of different factors on the outcome of bone regeneration. Out of the 28 patients included in the study, the majority of extractions and implant removals were performed in the posterior mandibular (46%). It is well established that the posterior mandible has several disadvantages in the placement of dental implants. The posterior mandible is limited by the mental foramen anteriorly and the caudal inferior alveolar nerve, and usually suffers extensive bone deficiency [22]. Despite the high incidence of tooth extraction at the posterior mandible, the rates of bone regeneration were similar in the mandible and maxilla.

Failing implants are usually removed due to progressive peri-implantitis and subsequent bone loss [4]. According to the 2012 European academy of osseointegration (EAO) the prevalence of peri-implantitis is 10% in regards to implants and 20% in patients within 5 to 10 years after implant placement [23].

Indeed, most of the studied cases suffered from peri-implantitis and bone loss (45.83%). Socket preservation is used to minimize the dimensional changes in soft and hard tissues after tooth extraction [24-26]. Currently, a variety of bone substitutes are available, many of them lacking optimal functionality. Bone substitutes used for socket preservation must have excellent osteo-conductive properties and appropriate strength, and ideally the material will participate in bone remodeling, gradually replacing the bone graft substitute over time. Chronic inflammation leads to the secretion of pro-inflammatory cytokines, which are primarily responsible for the activation of osteoclasts and the subsequent bone destruction. In

the current study extracted sites were preserved by using bovine-derived bone substitute (Bio-Oss) saturated with platelet concentrate. Histological analysis of the samples indicated an intimate contact between new bone and biomaterial particles generating an alveolar ridge adequate for implantation. The bone quality in infected sites was lower than in not-infected sites as demonstrated by significantly low levels of new bone in adittion to high levels of soft tissue and biomaterial remains. These parameters reveal a potential for improved bone remodeling in non-infected sites relative to infected sites and emphasize that local inflammatory effects of the infected environment and should be taken under consideration when performing ridge preservation.

Conflict of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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