Investigative study

COLLAGENATED XENOGRAFT BIOMATERIAL INDUCES OSTEOBLAST DIFFERENTIATION MARKERS IN ADIPOSE-DERIVED STEM CELLS IN VITRO

L. Pastore[1], E. Zucchinelli[1] and L. Scapoli[2]

[1]Dental School, Albanian University, Tirana, Abania
[2]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Correspondence to:
Luca Scapoli, PhD
Department of Medical and Surgical Sciences,
University of Bologna,
Via Belmeloro 8,
40126 Bologna, Italy
e-mail: luca.scapoli@unibo.it

ABSTRACT

Bone regeneration is a complex biological process crucial for healing bone damage that involves a coordinated sequence of cellular and molecular events, including inflammation, stem cell recruitment, proliferation, differentiation, and matrix deposition. Various surgical techniques have been developed to help bone regeneration and restore tissue damaged by infections, tooth loss, neoplasms, or local trauma. The use of xenografts and alloplastic bone substitutes takes advantage of eliminating the restricted source and morbidity rate of the donor site of autologous and allogeneic grafts. In vitro, studies could help to evaluate the effectiveness of these products and can help to test the biocompatibility and biological characteristics of biomaterials. In this investigation, we studied if OsteoBiol, an animal-derived collagenated bone matrix, can promote osteoblast differentiation of adipocyte stem cells cultured in vitro. The expression levels of markers of bone differentiation were monitored at different time points by real-time Polymerase Chain Reaction. After 24 h of treatment, SPP1 was up-regulated, as were FOSL1, COL4A1, and MMP14. After 4 days of treatment, FOSL1 and COL4A1 remained increased, and COL1A1 was up-regulated. OsteoBiol promotes the expression of several important genes of osteoblast differentiation. Additional research could provide deeper insights into the underlying mechanisms and enhance the practical application of these findings in clinical settings.

KEYWORDS: *osteoblast differentiation, OsteoBiol, xenograft, adipocyte stem cells, implant dentistry, gene expression*

INTRODUCTION

Bone regeneration is a complex biological process crucial for healing bone fractures, repairing defects, and restoring bone tissue lost due to injury or disease. It involves a coordinated sequence of cellular and molecular events, including inflammation, cell recruitment, proliferation, differentiation, and matrix deposition (1).

Immediately following the trauma, the injury site is rich in blood cells from ruptured vessels and bone marrow cells, which could include both hemopoietic and adipose cells. Inflammatory cells release cytokines and growth factors that stimulate the recruitment of mesenchymal stem cells (MSCs) to the injury site (2, 3). MSCs differentiate into osteogenic cells, which synthesize and deposit new bone matrix, leading to callus formation and, eventually, bone

Received: 29 April 2022
Accepted: 27 May 2022

remodeling. Osteoblasts and osteocytes originate from the periosteum, bone marrow, and endosteum, indicating that these three tissues contribute simultaneously to bone repair (4).

Several strategies are employed to enhance bone regeneration, including autografts, allografts, bone morphogenetic proteins (BMPs), growth factors, and tissue engineering techniques (5, 6). Autografts, harvested from the patient's own bone, remain the gold standard due to their osteogenic potential and low risk of rejection (7). Allografts, derived from cadaveric donors, provide an alternative but carry risks of immunogenicity and disease transmission. BMPs and growth factors, such as BMP-2 and platelet-derived growth factor (PDGF), promote osteogenesis and angiogenesis, accelerating bone healing (2). Tissue engineering approaches involve the use of scaffolds, cells, and signaling molecules to create biomimetic environments that facilitate bone regeneration (5).

Using xenograft bone substitutes represents a valuable and safe technique that takes advantage of availability, avoiding the need for a donor site for autologous graft retrieving (7). The animal bone can be treated with different techniques to provide a scaffold for new bone formation, which after transplant is gradually resorbed over time, allowing for integration with host bone tissue (8, 9). OsteoBiol biomaterials consist of heterologous cancellous bone produced by a process that avoids the ceramization of the hydroxyapatite crystals and preserves collagen. OsteoBiol is utilized in a variety of dental and orthopedic surgeries for bone augmentation, ridge preservation, sinus lifting, and periodontal regeneration procedures. It functions as a filling material for bone defects and contributes to the stability and success rates of dental implants by promoting osseointegration (10).

Adipose-derived stem cells (ADSCs) represent a type of mesenchymal stem cell that can be harvested from adipose tissue and possess the potential to differentiate into various cell types, including adipocytes, osteoblasts, chondrocytes, and other mesodermal cells (11). As a result of their ability to be obtained through minimally invasive methods, ADSCs have been recognized as a valuable resource in the fields of tissue engineering and regenerative medicine (12, 13). In vitro, osteogenic differentiation can be simulated by supplementing the medium with ascorbic acid, b-glycerophosphate, dexamethasone, 1,25 vitamin D3, and BMP2 (14, 15). ADSCs cultured in the presence of these factors express genes that characterize osteoblast differentiation, including alkaline phosphatase, collagen type I, osteopontin, osteonectin, and Runx2 (16).

In this investigation, ADSCs were cultured in vitro with OsteoBiol, a hard biomaterial from animal bone matrix usually used in bone regeneration surgery, to verify if the biomaterial can promote stem cell differentiation toward osteogenic lineage.

MATERIALS AND METHODS

Adipocyte Stem Cells (ADSCs) isolation

Adipose tissue was extracted from the buccal fat pad (also called Bichat's fat pad) during the intervention to close oro-antral communication. It was digested for 1 h at 37°C in a solution containing 1 mg/ml collagenase type I and 1 mg/ml dispase, then dissolved in phosphate-buffered saline (PBS) supplemented with 100 U/ml penicillin, 100 µg/ml streptomycin, and 500 µg/ml clarithromycin. The solution was filtered using Falcon strainers with 70 µm pores (Sigma Aldrich, St Louis, Mo, U.S.A.) to separate mesenchymal stem cells. Stem cells were cultivated in α-MEM culture medium (Sigma Aldrich, St Louis, Mo, U.S.A.) supplemented with 20% Fetal Bovine Serum (FBS), 100 µM 2P-ascorbic acid, 2 mM L-glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin (Sigma Aldrich, St Louis, Mo, U.S.A.). The culture flasks were incubated at 37 °C and 5% CO_2, and the medium was changed twice per week.

ADSCs were characterized by immunofluorescence for the cytoskeletal component vimentin, positive mesenchymal stem cell markers CD90 and CD73, and the negative marker CD34 as described in Sollazzo et al. (17).

Cell treatment

ADSCs were seeded at a concentration of 1.0×10^5 cells/ml with a mechanically fragmented OsteoBiol sp-block (Tecnoss Dental SRL, Torino, Italy) at the concentration of 3 mg in 9 cm^2 (3 ml) wells in a DMEM culture medium supplemented with 10% serum and antibiotics. Another set of wells containing untreated cells was used as a control. The treatment was carried out at two time points: 24 h and 4 days.

The cells were maintained in a humidified atmosphere containing 5% CO_2 at 37°C. At the end of the treatment period, the cells were lysed and processed for total RNA extraction.

RNA isolation and gene expression quantification

Total RNA was isolated from the cells using RNeasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The pure RNA was quantified using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific).

cDNA synthesis was performed starting from 500 ng of total RNA using the PrimeScript RT Master Mix (Takara Bio Inc., Kusatsu, Japan). The reaction mixture was incubated at 37 °C for 15 min and inactivated by heating at 70°C for 10 s. cDNA was amplified by real-time quantitative PCR using an ABI PRISM 7500 (Applied Biosystems, Foster City, CA, USA). All PCR reactions were performed in a 20 µL volume. Each reaction contained 10 µl of 2x qPCRBIO SYGreen Mix Lo-ROX (PCR Biosystems, Ltd., London, UK), 400 nM of each primer, and cDNA.

Custom primers belonging to the "extracellular matrix, adhesion molecule" pathway, "osteoblast differentiation," and "inflammation" pathway were purchased from Sigma Aldrich. The selected genes grouped by functional pathways are as follows: osteoblast differentiation [SPP1 (Osteopontin), SPARC (Osteonectin), RUNX2 (Runt-related transcription factor 2), ALP (Alkaline phosphatase), BGLAP (Osteocalcin), FOSL1 (FOS-like antigen 1), SP7 (Osterix), ENG (Endoglin)], extracellular matrix, adhesion molecule [COL1A1 (Collagen type I alpha1), COL4A1 (Collagen type IV alpha 1), MMP14 (Matrix Metallopeptidase 12), MMP15 (Matrix Metallopeptidase 15)], inflammation [IL6 (Interleukin 6), IL6R (Interleukin 6 Receptor)] and RPL13 (Ribosomal protein L13) as reference gene.

All experiments were performed using non-template controls to exclude reagent contamination. PCR was performed using two analytical replicates.

The amplification profile was initiated by incubation for 10 min at 95 °C, followed by a two-step amplification for 15 s at 95 °C and 60 s at 60 °C for 40 cycles. In the final step, melt curve dissociation analysis was performed.

Statistical analysis

The relative gene expression was quantified with the delta/delta Ct calculation method (18), using the reference gene RPL13 to normalize gene expression levels. The gene expression levels change of treated cells were calculated as fold-changes relative to untreated cells; fold change was considered biologically relevant when the expression doubled, i.e. fold changes ≥ 2, or halved, i.e. fold changes ≤ 0.5.

RESULTS

ADCSs were phenotypically characterized using immunofluorescence. Fig. 1a shows cytoskeletal filaments stained with vimentin. The cell surfaces were positive for mesenchymal stem cell markers CD90 (Fig. 1b) and CD73 (Fig. 1c) and negative for markers of hematopoietic origin CD34 (Fig. 1d).

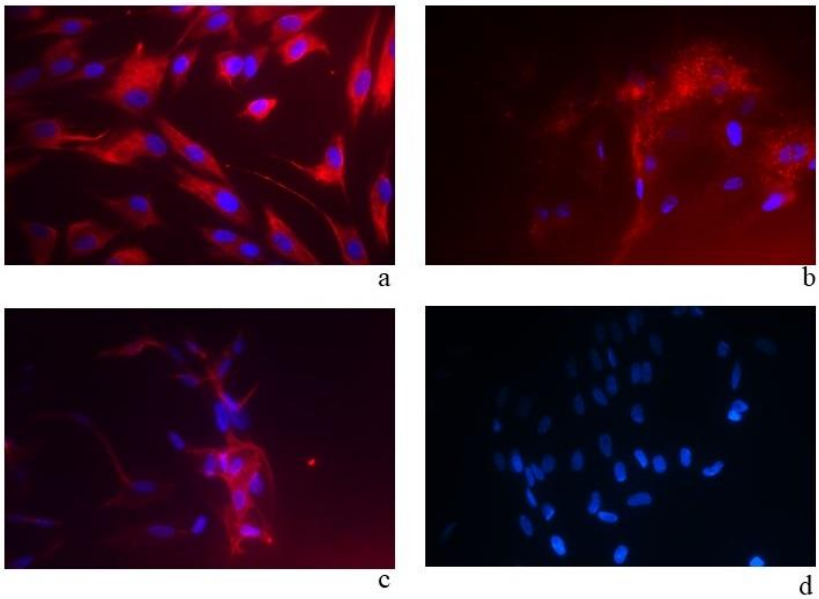

Fig. 1. *DPCSs by indirect immunofluorescence (Rhodamine). Immunofluorescence staining of vimentin (**a**), mesenchymal stem cell marker CD90 (**b**), CD73 (**c**), and hematopoietic markers CD34 (**d**). Nuclei were stained with DAPI. Original magnification x40.*

The expression level of genes involved in osteoblast differentiation was monitored in ADSCs grown with OsteoBiol xenograft biomaterial by quantitative real-time PCR and compared with untreated cells. The expression level variation of transcription factors, extracellular matrix, and inflammation pathways was measured after 24 h and 4 days of treatment as fold change levels. Several genes showed more than a two-fold increase in expression level. Indeed, after 24 h of treatment, SPP1, FOSL1, and COL4A1 and MMP14 were up-regulated. After 4 days of treatment, FOSL1 and MMP14 were further increased, and COLL1A1 was up-regulated.

DISCUSSION

ADSCs possess self-renewal capacity and can differentiate into multiple cell lineages, including adipocytes, osteoblasts, chondrocytes, and myocytes. Multipotent differentiation potential, together with their abundance in the easily accessible fat tissue, has been granted to ADSCs by the scientific community because they represent a promising tool in regenerative medicine and tissue engineering.

In this study, we utilized an in vitro ADSC culture to assess the osteoinduction capacity of OsteoBiol, a commonly used biomaterial in bone regeneration surgery. OsteoBiol is a collagenated bone matrix derived from animal cancellous bone, employed by surgeons as a filling material for bone defects or as a scaffold to facilitate bone growth. Our aim was to determine whether exposure to OsteoBiol can stimulate osteoblast differentiation of ADSCs. To test this, we monitored the expression levels of a selected panel of genes at 4 hours and 4 days post-treatment. It was observed that collagen type I and type IV, two structural extracellular matrix proteins, were over-expressed in ADSCs cultured on the OsteoBiol biomaterial.

The SPP1 gene was overexpressed early, only 4 hours after OsteoBiol administration. The SPP1 gene encodes for Osteopontin, which is recognized as a marker of bone differentiation due to its expression during the early stages of osteoclast and osteoblast progenitor differentiation (19). Osteopontin is a phosphorylated glycoprotein secreted by osteoblasts into the mineralizing extracellular matrix during bone development (20). The highest expression of this protein is seen in mature osteoblasts at sites of bone remodeling (21).

Osteopontin plays a crucial role in bone mineralization and the attachment of osteoclasts to the mineral matrix (22, 23). Osteoclast integrins binding to osteopontin activates signaling pathways that enhance osteoclast activity (24). Through this mechanism, OPN facilitates the resorption phase of bone remodeling, essential for removing old or damaged bone and regulating bone density. Osteopontin is also involved in various physiological and pathological processes, such as immune response and inflammation (25).

Collagen Type I is the primary structural protein in the extracellular matrix of bone. Type I collagen is not exclusively expressed by osteoblasts but is also produced by fibroblasts; however, collagen Type I remains a useful marker for osteoblast differentiation when expressed together with other bone markers (26). Collagen Type IV is a major basement membrane component that separates epithelial and endothelial cells from connective tissue (27). Several experimental evidences suggest that collagen type IV is not only produced by epithelial cells, but it is expressed in other tissues, where is involved in tissue genesis, differentiation, homeostasis, and remodeling (28). For example, collagen type IV appears to play a significant role in the differentiation of stem cells towards osteoblasts and adipoblasts. In these cells, the inhibition of miR-214-5p promotes the survival of osteoblasts and extracellular matrix production by targeting COL4A1 (29). Another investigation showed that miR-214-5p may weaken bone marrow stem cells' osteogenic differentiation by downregulating COL4A1. Additionally, miR-214-5p may promote adipogenic differentiation by downregulating the TGF-β/Smad2/COL4A1 signaling pathway (30).

Another line of evidence associates COL4A1 to different skeleton pathologies. A genomic region at 13q34, including COL4A1 and COL4A2 (collagen type IV alpha-1 and alpha-2 subunits), was significantly linked with forearm bone mineral density in a genome-wide linkage scan (31). A significant COL4A1 gene expression level was found in human osteoporosis fracture bone compared to bone from individuals with osteoarthritis or no bone pathology (32).

The Matrix metalloproteinase family of proteins (MMP) is involved in the digestion of extracellular matrix proteins during normal physiological processes such as embryonic development and tissue remodeling. Since MMP14 appears to play a multifaceted role in regulating various signaling pathways and cell fate decisions critical for bone formation and remodeling, this protein could be considered an additional marker of osteoblast differentiation (33). Research has shown that deleting the membrane-anchored MMP14 in mesenchymal progenitors redirects cells' fate from osteogenesis to adipo- and chondrogenesis (34). The same treatment did not have the same effect in committed osteoblasts (34). Interestingly, MMP14 seems to regulate the differentiation of mesenchymal stem cells into bone-producing osteoblasts in 3-dimensional collagen matrices (35). Moreover, MMP14 is essential for osteoblast survival during the osteoblast-to-osteocyte transition and is required for proper lacunae formation (36). Parathyroid hormone stimulates

osteocyte proliferation by activating the Wnt pathway and increasing MMP14 expression levels, which in turn appear to regulate soluble RANKL production, thus controlling bone resorption (37). Finally, MMP14 can regulate osteoclastogenesis. Suppressing MMP14 expression in osteoblasts had the effect of increasing the numbers and activity of osteoclasts (37, 38).

CONCLUSIONS

Xenografts are considered valid alternatives to autografts. Indeed, animal-derived biomaterials are available in large quantities, while advancements in processing techniques have significantly lowered the risk of immunogenic reactions and infection transmission. OsteoBiol is a collagenated exogenous bone-derived biomaterial successfully used in regenerative medicine. In this investigation, we showed that ADSCs cultured in vitro with OsteoBiol increased the expression levels of genes considered markers of osteodifferentiation. Indeed, these undifferentiated cells over-expressed SPP1, COL1A1, COL4A1, and MMP14 at different time points when cultured with OsteoBiol. However, additional research is necessary to clarify the specific mechanisms involved in the cell signaling pathways underlying the current results.

REFERENCES

1. Ai-Aql ZS, Alagl AS, Graves DT, Gerstenfeld LC, Einhorn TA. Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. *J Dent Res.* 2008;87(2):107-118. doi:https://doi.org/10.1177/154405910808700215
2. Lee BC, Yu KR. Impact of mesenchymal stem cell senescence on inflammaging. *BMB Rep*. 2020;53(2):65-73. doi:10.5483/BMBRep.2020.53.2.291
3. Marsell R, Einhorn TA. The biology of fracture healing. *Injury.* 2011;42(6):551-555. doi:https://doi.org/10.1016/j.injury.2011.03.031
4. Colnot C. Skeletal cell fate decisions within periosteum and bone marrow during bone regeneration. *J Bone Miner Res.* 2009;24(2):274-282. doi:https://doi.org/10.1359/jbmr.081003
5. Lin H, Sohn J, Shen H, Langhans MT, Tuan RS. Bone marrow mesenchymal stem cells: Aging and tissue engineering applications to enhance bone healing. *Biomaterials.* 2019;203(96-110. doi:https://doi.org/10.1016/j.biomaterials.2018.06.026
6. Donos N, Dereka X, Calciolari E. The use of bioactive factors to enhance bone regeneration: A narrative review. *J Clin Periodontol.* 2019;46 Suppl 21(124-161. doi:https://doi.org/10.1111/jcpe.13048
7. Shibuya N, Jupiter DC. Bone graft substitute: allograft and xenograft. *Clin Podiatr Med Surg.* 2015;32(1):21-34. doi:https://doi.org/10.1016/j.cpm.2014.09.011
8. Skoglund A, Hising P, Young C. A clinical and histologic examination in humans of the osseous response to implanted natural bone mineral. *Int J Oral Maxillofac Implants.* 1997;12(2):194-199.
9. Poulias E, Greenwell H, Hill M, et al. Ridge preservation comparing socket allograft alone to socket allograft plus facial overlay xenograft: a clinical and histologic study in humans. *J Periodontol.* 2013;84(11):1567-1575. doi:https://doi.org/10.1902/jop.2013.120585
10. Giuliani A, Iezzi G, Mazzoni S, Piattelli A, Perrotti V, Barone A. Regenerative properties of collagenated porcine bone grafts in human maxilla: demonstrative study of the kinetics by synchrotron radiation microtomography and light microscopy. *Clin Oral Investig*. 2018;22(1):505-513. doi:10.1007/s00784-017-2139-6
11. Shafaei H, Kalarestaghi H. Adipose-derived stem cells: An appropriate selection for osteogenic differentiation. *J Cell Physiol.* 2020;235(11):8371-8386. doi:https://doi.org/10.1002/jcp.29681
12. Ciuffi S, Zonefrati R, Brandi ML. Adipose stem cells for bone tissue repair. *Clin Cases Miner Bone Metab.* 2017;14(2):217-226. doi:https://doi.org/10.11138/ccmbm/2017.14.1.217
13. Fraser JK, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol.* 2006;24(4):150-154. doi:https://doi.org/10.1016/j.tibtech.2006.01.010
14. Gimble J, Guilak F. Adipose-derived adult stem cells: isolation, characterization, and differentiation potential. *Cytotherapy.* 2003;5(5):362-369. doi:https://doi.org/10.1080/14653240310003026
15. Lee SJ, Kang SW, Do HJ, et al. Enhancement of bone regeneration by gene delivery of BMP2/Runx2 bicistronic vector into adipose-derived stromal cells. *Biomaterials.* 2010;31(21):5652-5659. doi:https://doi.org/10.1016/j.biomaterials.2010.03.019
16. Halvorsen YD, Franklin D, Bond AL, et al. Extracellular matrix mineralization and osteoblast gene expression by human adipose tissue-derived stromal cells. *Tissue Eng.* 2001;7(6):729-741. doi:https://doi.org/10.1089/107632701753337681
17. Sollazzo V, Lucchese A, Palmieri A, et al. Calcium sulfate stimulates pulp stem cells towards osteoblasts differentiation. *International Journal of Immunopathology and Pharmacology.* 2011;24(2SUPPL.1):51S-57S. doi:https://doi.org/10.1177/03946320110240s210
18. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods.* 2001;25(4):402-408. doi:https://doi.org/10.1006/meth.2001.1262

19. Yamate T, Mocharla H, Taguchi Y, Igietseme JU, Manolagas SC, Abe E. Osteopontin expression by osteoclast and osteoblast progenitors in the murine bone marrow: demonstration of its requirement for osteoclastogenesis and its increase after ovariectomy. *Endocrinology.* 1997;138(7):3047-3055. doi:https://doi.org/10.1210/endo.138.7.5285
20. Beck GR, Jr., Zerler B, Moran E. Phosphate is a specific signal for induction of osteopontin gene expression. *Proc Natl Acad Sci U S A.* 2000;97(15):8352-8357. doi:https://doi.org/10.1073/pnas.140021997
21. Sodek J, Chen J, Nagata T, et al. Regulation of osteopontin expression in osteoblasts. *Ann N Y Acad Sci.* 1995;760(223-241. doi:https://doi.org/10.1111/j.1749-6632.1995.tb44633.x
22. Christensen B, Nielsen MS, Haselmann KF, Petersen TE, Sorensen ES. Post-translationally modified residues of native human osteopontin are located in clusters: identification of 36 phosphorylation and five O-glycosylation sites and their biological implications. *Biochem J.* 2005;390(Pt 1):285-292. doi:https://doi.org/10.1042/BJ20050341
23. Reinholt FP, Hultenby K, Oldberg A, Heinegard D. Osteopontin--a possible anchor of osteoclasts to bone. *Proc Natl Acad Sci U S A.* 1990;87(12):4473-4475. doi:https://doi.org/10.1073/pnas.87.12.4473
24. Ross FP, Chappel J, Alvarez JI, et al. Interactions between the bone matrix proteins osteopontin and bone sialoprotein and the osteoclast integrin alpha v beta 3 potentiate bone resorption. *J Biol Chem.* 1993;268(13):9901-9907.
25. Icer MA, Gezmen-Karadag M. The multiple functions and mechanisms of osteopontin. *Clin Biochem.* 2018;59(17-24. doi:https://doi.org/10.1016/j.clinbiochem.2018.07.003
26. Carpio L, Gladu J, Goltzman D, Rabbani SA. Induction of osteoblast differentiation indexes by PTHrP in MG-63 cells involves multiple signaling pathways. *Am J Physiol Endocrinol Metab.* 2001;281(3):E489-499. doi:https://doi.org/10.1152/ajpendo.2001.281.3.E489
27. Sage H. Collagens of basement membranes. *J Invest Dermatol.* 1982;79 Suppl 1(51s-59s. doi:https://doi.org/10.1111/1523-1747.ep12545773
28. Boudko SP, Danylevych N, Hudson BG, Pedchenko VK. Basement membrane collagen IV: Isolation of functional domains. *Methods Cell Biol.* 2018;143(171-185. doi:https://doi.org/10.1016/bs.mcb.2017.08.010
29. Li QS, Meng FY, Zhao YH, Jin CL, Tian J, Yi XJ. Inhibition of microRNA-214-5p promotes cell survival and extracellular matrix formation by targeting collagen type IV alpha 1 in osteoblastic MC3T3-E1 cells. *Bone Joint Res.* 2017;6(8):464-471. doi:https://doi.org/10.1302/2046-3758.68.BJR-2016-0208.R2
30. Qiu J, Huang G, Na N, Chen L. MicroRNA-214-5p/TGF-beta/Smad2 signaling alters adipogenic differentiation of bone marrow stem cells in postmenopausal osteoporosis. *Mol Med Rep.* 2018;17(5):6301-6310. doi:https://doi.org/10.3892/mmr.2018.8713
31. Niu T, Chen C, Cordell H, et al. A genome-wide scan for loci linked to forearm bone mineral density. *Hum Genet.* 1999;104(3):226-233. doi:https://doi.org/10.1007/s004390050940
32. Hopwood B, Tsykin A, Findlay DM, Fazzalari NL. Gene expression profile of the bone microenvironment in human fragility fracture bone. *Bone.* 2009;44(1):87-101. doi:https://doi.org/10.1016/j.bone.2008.08.120
33. Paiva KBS, Granjeiro JM. Matrix Metalloproteinases in Bone Resorption, Remodeling, and Repair. *Prog Mol Biol Transl Sci.* 2017;148(203-303. doi:https://doi.org/10.1016/bs.pmbts.2017.05.001
34. Tang Y, Rowe RG, Botvinick EL, et al. MT1-MMP-dependent control of skeletal stem cell commitment via a beta1-integrin/YAP/TAZ signaling axis. *Dev Cell.* 2013;25(4):402-416. doi:https://doi.org/10.1016/j.devcel.2013.04.011
35. Egeblad M, Rasch MG, Weaver VM. Dynamic interplay between the collagen scaffold and tumor evolution. *Curr Opin Cell Biol.* 2010;22(5):697-706. doi:https://doi.org/10.1016/j.ceb.2010.08.015
36. Papadogiannis F, Batsali A, Klontzas ME, et al. Osteogenic differentiation of bone marrow mesenchymal stem cells on chitosan/gelatin scaffolds: gene expression profile and mechanical analysis. *Biomed Mater.* 2020;15(6):064101. doi:https://doi.org/10.1088/1748-605X/aba325
37. Delgado-Calle J, Hancock B, Likine EF, et al. MMP14 is a novel target of PTH signaling in osteocytes that controls resorption by regulating soluble RANKL production. *FASEB J.* 2018;32(5):2878-2890. doi:https://doi.org/10.1096/fj.201700919RRR
38. Hikita A, Yana I, Wakeyama H, et al. Negative regulation of osteoclastogenesis by ectodomain shedding of receptor activator of NF-kappaB ligand. *J Biol Chem.* 2006;281(48):36846-36855. doi:https://doi.org/10.1074/jbc.M606656200

Evaluation Study

IMMEDIATE LOADING USING A ONE-PIECE IMPLANT WITH INTEGRATED MUA AND COMPUTER-AIDED PLANNING

A. Scarano[1†], F. Tricca[1], F. Ciuffolo[1], P. Scarano[1], C. Bugea[1†], S.A. Gehrke[2,3†] and S.R. Tari[1]

[1]Department of Innovative Technologies in Medicine and Dentistry, University of Chieti-Pescara, Chieti, Italy;
[2]Department of Research, Bioface/PgO/UCAM, Montevideo, Uruguay;
[3]Department of Biotechnology. Universidad Católica de Murcia (UCAM), Murcia, Spain

†These authors contributed equally to this work as co-first Authors

**Correspondence to:*
Antonio Scarano, DDS, MD
Department of Innovative Technology in Medicine and Dentistry,
University of Chieti-Pescara,
Via Dei Vestini 31,
66100 Chieti Italy
e-mail: ascarano@unich.it

ABSTRACT

Computer-aided dental implant planning increases the success and predictability of replacing missing teeth in fully and partially edentulous cases. Immediate loading techniques have raised the issue of dealing with it even in severe bone atrophy, in which the situations are characterized by numerous technical difficulties. It is known that each implant immediately loaded must be protected from excessive micro-movements, which can be deleterious in the healing phase and negatively influence the reparative processes of bone remodeling in the first weeks. The purpose of this paper is to evaluate a protocol for immediate loading with a one-piece implant with integrated MUA and computer-aided planning. The study involved 20 patients with 160 implants that were immediately solidified with a provisional prosthesis without reinforcement, made immediately after the surgery. Each patient received eight Uniko implants per arch. All implants subjected to immediate loading have resulted in a success rate of 100% over the 36 months that have occurred without fracture of the provisional**.** This technique, supported by computer-assisted design, has allowed the implementation of immediate loading in full edentulous patients.

KEYWORDS: *computer-aided dental implant, one-piece implant, integrated MUA, multi-unit abutment*

INTRODUCTION

The initial premise in implantology fervently maintained that the osseointegration process of a dental implant required three to six months to achieve complete bone healing in the absence of load and with a submerged technique (1-3). Over time, there has been increasing interest in transmucosal techniques and, subsequently, in the early or immediate loading of implants (4, 5). The push towards immediate loading originates from the consideration that during the healing phase of implants in edentulous jaws, providing the patient with removable temporary prostheses is not without disadvantages, such as the need for frequent relining and reduced stability with the risk of implant load on non-stabilized implants.

Received: 12 July 2022
Accepted: 18 August 2022

The quality and precision of the interface between the fixture and abutment are undoubtedly strategic elements in remodeling the crestal bone, the success, and the maintenance of the health of peri-implant hard and soft tissues (6). Schwartz et al. (7) described in great detail the events leading to bone formation around implants, highlighting that during the healing phases, the implant requires maximum stability relative to the bone. Being a dynamic entity, bone tissue modifies its characteristics in response to mechanical, bioelectric, and biohumoral stimuli (8, 9). It has been demonstrated that immediate loading does not impede osseointegration but can accelerate bone repair if implemented with appropriate techniques and rigorous clinical protocols (10).

The key is to counteract the loads that can produce micromovements at the interface between the implant and bone, which could interfere with the bone healing process and damage osteogenetic repair processes, preventing osseointegration and leading to the formation of fibrous tissue and encapsulation of the implant (11). According to Brunski et al. (11), implants can be loaded early or immediately if micromovements do not exceed the threshold of 100-150 μm, emphasizing that movements beyond this limit must be neutralized during the healing phase. Degidi et al. (12), in a clinical study involving and analyzing a significant number of implants, demonstrated the predictability and a high success rate of functional and non-functional immediate loading.

For many years, it was thought that the success of an immediately loaded implant rehabilitation depended on the large number of implants involved to distribute occlusal loads, limit the distance between pillars, and avoid the fracture of the temporary prosthesis. Subsequently, the criteria of careful pre-surgical diagnosis, a correct treatment plan, and the application of techniques capable of eliminating or reducing the possibility of micro-movements and the consequent risks to the surrounding bone prevailed. Protecting the bone-implant interface from micromovements is a strategic element of the success and survival of implants. In recent years, various techniques have been described to improve the predictability of immediate loading: bars as support for overdentures (13), the use of previous prostheses to achieve implant stability, or the use of acrylic temporaries by combining transition implants and standard ones (14-17).

Longoni et al. (18), described a method to reduce prosthetic misfit with an implant-supported prosthesis using a technique that involved intraoral bonding with composite material and laser welding of the framework in the laboratory. In the early 80s, Mondani et al. (19) and Ar et al. (20) described a method to reduce the misfit or lack of adaptation of complete prostheses on implants, proposing an intraoral welding technique that avoided laborious laboratory procedures.

Szmukler-Moncler et al. (21), described an intraoral welding technique to join implants using a preconstructed round titanium wire, followed by an immediate acrylic provisional application immediately post-surgery directly in the oral cavity. The present work aims to evaluate a protocol of immediate loading using a one-piece implant with integrated MUA and Computer-aided planning.

MATERIALS AND METHODS

Twenty patients with at least one completely edentulous arch (average age of 61.4 years) requiring prosthetic rehabilitation were selected. Exclusion criteria included severe systemic diseases, patients irradiated less than a year ago or undergoing chemotherapy, patients with severe periodontal disease, and heavy smokers. After a careful preliminary oral examination, the general health status and necessary information regarding the immediate loading technique procedure were assessed. In each case, the patient prepared and signed an informed consent form. The study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki.

A total of 160 Uniko implants (Isomed System, Due Carrare, Padova, Italy) of varying diameters were placed depending on clinical conditions (Fig. 1). Each patient received eight Uniko implants. All 160 implants were splinted through resin prostheses without reinforcement and immediately loaded. None of the selected patients required additional techniques to increase bone volumes concurrently with implant insertion. Patients were prescribed appropriate pre- and post-surgical pharmacological therapy: amoxicillin (1 g twice daily for 5 days) and analgesics for 1 week (Ibuprofen 600 mg), as needed. Before surgery, all patients performed rinses with 0.2% chlorhexidine digluconate for 2 minutes. Local anesthesia was administered with Articaine® (Ubistesin 4% - Espe Dental AG Seefeld, Germany) combined with epinephrine 1:100,000.

Fig. 1. *The morphology of a one-piece implant with integrated Multi Unit Abutment (MUA).*

The superimposition of STL and DICOM files allowed the virtual planning of one-piece implants in the ideal prosthetic implant position using the dedicated software Isoguide (Isomed System, Due Carrare, Padova, Italy) (Fig. 2-4).

The stackable guides were then realized and composed of a fixed base template and additional removable components (Fig. 5). Initially secured with anchor pins to the bone, the fixed template was no longer removed. The removable components, which were screwed to the base template, were used to perform implant surgery and immediate prosthetic loading.

A CBCT scan was performed to evaluate the bone height and thickness, and standard triangulation language (STL) files obtained from the digital scan were aligned with the digital imaging and communication in medicine (DICOM) data retrieved from the CBCT scan.

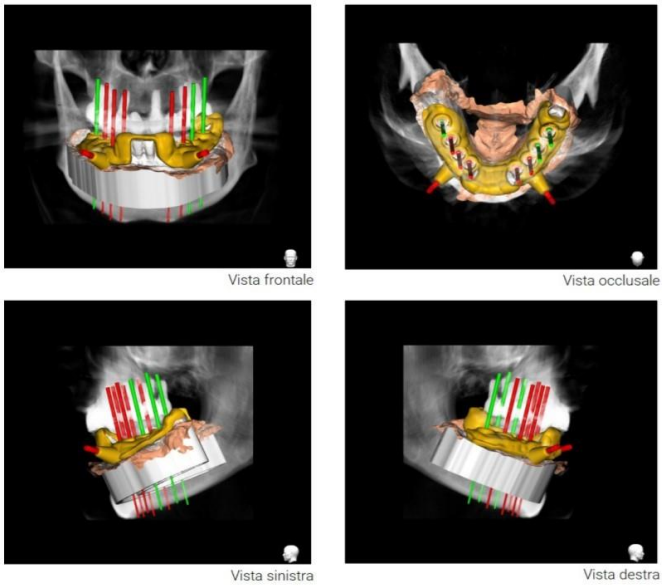

Fig. 2. *Steps of guided computer planning.*

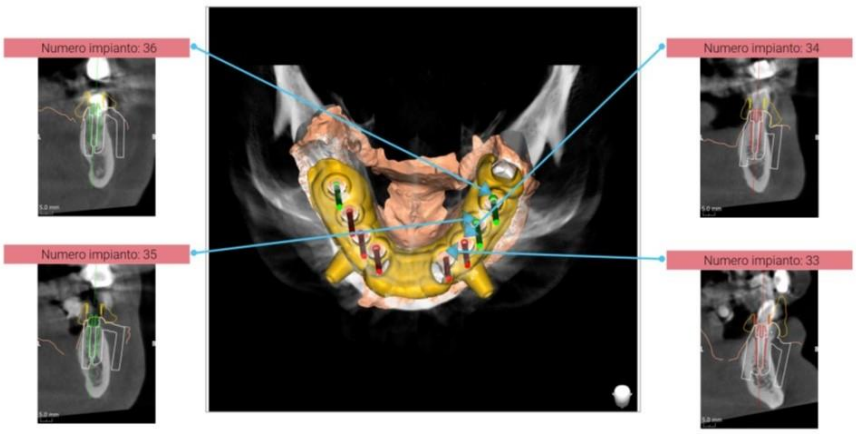

Fig. 3. *Steps of guided computer planning with 3D visualization of implant position.*

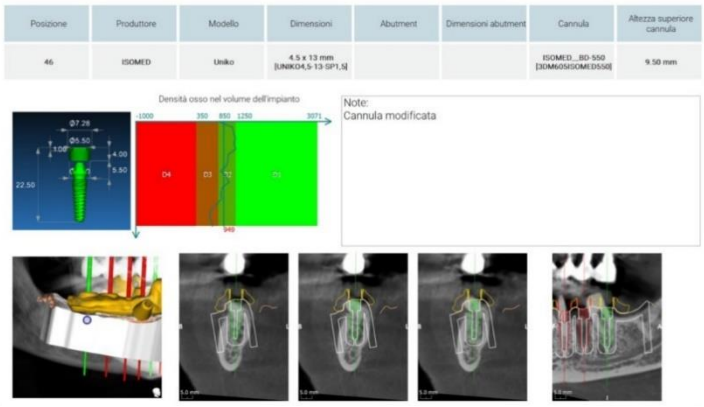

Fig. 4. *Implant structure and visualization of bone quality.*

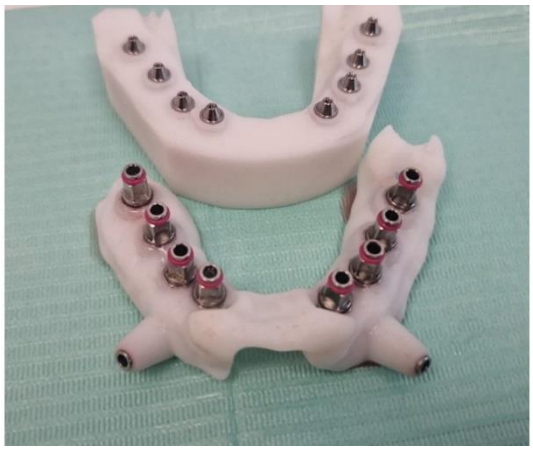

Fig. 5. *Structure containing implants and position of the prosthesis.*

A Transmucosal Implant (Isomed System, Due Carrare, Padova, Italy) was placed as a natural extension through the gingival thickness using a surgical guide. The software is also able to assess the quality of bone tissue. The provisional restoration was delivered 6 hours after surgery or the next day, depending on the complexity of the cases, the duration of the surgeries, and the patient's psycho-physical condition. The completed fixed provisional prosthesis was placed in the patient's mouth and fixed with retention screws appropriate for each MUA. The screw access holes were then sealed by placing a Teflon followed by a light-curable temporary composite (Fermit®, Ivoclar Vivadent), finishing the closure, and polishing the provisional restoration to a mirror finish to reduce bacterial plaque formation and ensure satisfactory aesthetics.

Before discharging the patient, radiographic examinations with intraoral radiographs were performed using a parallel technique to evaluate the adaptation of the titanium structure to the transmucosal collars (Fig. 6). After delivering the immediate prosthesis, the patient was followed up after 7 days and subsequently every 30 days.

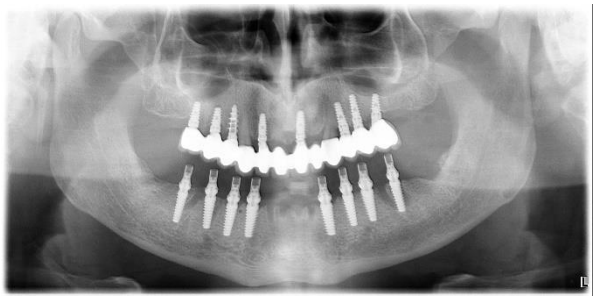

Fig. 6. *Post-operative x-ray demonstrating perfect prosthesis congruence on UNIKO implants.*

No intraoperative complications, such as soft tissue lacerations, profuse bleeding, template fractures, or implant misplacement with consequent dehiscences or fenestrations, occurred during the procedure. All implants achieved a range insertion torque range of 35-50 Ncm, so immediate prosthetic loading could be performed safely. The presence of a one-piece implant with integrated MUA and computer-aided planning and the provisional prosthesis has shown a significant impact on the health of peri-implant tissues in immediate loading, as it reduces mechanical stress on each implant and allows for excellent healing and quality of peri-implant tissues.

All 160 implants in the study achieved a 100% success rate over 6 months. During the observation period, there were no fractures of the provisional prosthesis or loosening of the screw of the abutments, and radiographic checks were performed to evaluate the peri-implant bone levels.

DISCUSSION

A one-piece implant with integrated MUA and computer-aided planning can increase the passivity of the prosthesis, which is crucial in the immediate loading rehabilitation of fully edentulous patients. Another advantage of integrated MUA is eliminating the micro gap between the implant and abutment, which is responsible for crestal bone resorption (22, 23). It is now established that micromovements exceeding 100-150 microns (11) lead to fibrous tissue formation, preventing implant osseointegration (21).

Various protocols have been described in recent years, but they have not proven effective in routinely achieving a passive structure while reducing chairside costs and time (18). Acrylic resin bridges with significant distances between the abutments tend to “warp” as they are subject to flexion and often fracture under occlusal forces; this is particularly true for the edentulous mandible, which presents a biomechanical elastic complex particularly sensitive to functional loads. This is due to the “U” shape of the mandible, the posterior insertion of the masticatory muscles, and the complex elastic structures that make up the bone (24). During the mandibular opening, the lateral pterygoid muscles exert a lateral protrusion, contract simultaneously, and exert downward traction on the condyles. Consequently, there is elastic flexion of the mandible, with the distance at the mandibular ramus level of both sides reducing on the frontal plane. Additionally, there is flexion at the mandibular symphysis, reducing the width of the posterior segment of the mandible (25).

In the past, it has been observed that the fragility of acrylic resin prosthetic restorations was able to redistribute occlusal loads physiologically only by introducing a greater number of implants to reduce mobility during the first weeks, where initial primary stability is lost before achieving secondary stability (25-27). Conversely, Degidi et al. (28) demonstrated the importance of rigid splinting in the mandible, indicating it as the most favorable condition for immediate loading, even with a reduced number of implants.

Creating a titanium splinting structure directly in the mouth highlights the advantages of immediate loading. It allows for verifying its real passive adaptation in the patient’s mouth. Moreover, it avoids delegating the structure’s fabrication to the laboratory, which would require subsequent in-mouth trials, increasing the cost and extending the wait time for verifying the structure’s adaptation to the implants and fabricating the provisional prosthesis. Degidi et al. (28), demonstrated the utility of intraoral welding using synchro-welding to achieve rigid splinting of implants subjected to immediate loading. The solution described in this work helps counteract jaw flexions so that they do not impact the provisional prostheses, causing fractures and destabilizing the ongoing osteogenic process.

This technique consists of a one-piece implant with integrated MUA, which distributes the occlusal loads over multiple implants. With reduced costs, this protocol enables the fabrication of immediate-load prostheses in the short term, gaining greater patient acceptance. Further investigations on a larger sample of clinical cases will validate the procedure described here as a routine and predictable solution for immediate loading through stabilizing the provisional prosthesis.

CONCLUSIONS

In the cases examined, no provisional fractures occurred. The one-piece implant with integrated MUA supported (Uniko) by careful computer-assisted planning has demonstrated clinical efficacy and reliability. It also enabled the implementation of sufficiently predictable immediate loading protocols, even in challenging cases.

Conflicts of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Brånemark PI, Hansson BO, Adell R, et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scandinavian Journal of Plastic and Reconstructive Surgery Supplementum*. 1977;16:1-132.
2. Adell R, Lekholm U, Rockler B, Brånemark PI . A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *International Journal of Oral Surgery*. 1981;10(6):387-416. doi:https://doi.org/10.1016/s0300-9785(81)80077-4
3. Albrektsson T, Dahl E, Enbom L, et al. Osseointegrated Oral Implants. *Journal of Periodontology*. 1988;59(5):287-296. doi:https://doi.org/10.1902/jop.1988.59.5.287
4. Buser D, Belser UC, Lang NP. The original one-stage dental implant system and its clinical application. *Periodontology 2000*. 1998;17(1):106-118. doi:https://doi.org/10.1111/j.1600-0757.1998.tb00128.x
5. Szmukler-Moncler S, Piattelli A, Favero GA, Dubruille JH. Considerations preliminary to the application of early and immediate loading protocols in dental implantology. *Clinical Oral Implants Research*. 2000;11(1):12-25. doi:https://doi.org/10.1034/j.1600-0501.2000.011001012.x
6. Assenza B, Scarano A, Petrone G, et al. Crestal Bone Remodeling in Loaded and Unloaded Implants and the Microgap: A Histologic Study. *Implant Dentistry*. 2003;12(3):235-241. doi:https://doi.org/10.1097/01.id.0000074081.17978.7e
7. Schwartz Z, Boyan BD. Underlying mechanisms at the bone-biomaterial interface. *Journal of Cellular Biochemistry*. 1994;56(3):340-347. doi:https://doi.org/10.1002/jcb.240560310
8. Berglundh T, Lindhe J, Jonsson K, Ericsson I. The topography of the vascular systems in the periodontal and peri-implant tissues in the dog. *Journal of Clinical Periodontology*. 1994;21(3):189-193. doi:https://doi.org/10.1111/j.1600-051x.1994.tb00302.x
9. Davies JE. Understanding Peri-Implant Endosseous Healing. *Journal of Dental Education*. 2003;67(8):932-949. doi:https://doi.org/10.1002/j.0022-0337.2003.67.8.tb03681.x
10. A. Piattelli, Corigliano M, Scarano A, G. Costigliola, Paolantonio M. Immediate Loading of Titanium Plasma-Sprayed Implants: An Histologic Analysis in Monkeys. *J Periodontol* . 1998;69(3). doi:https://doi.org/10.1902/jop.1998.69.3.321
11. Brunski JB. Biomechanical factors affecting the bone-dental implant interface. *Clinical Materials*. 1992;10(3):153-201. doi:https://doi.org/10.1016/0267-6605(92)90049-y
12. Degidi M, Adriano Piattelli. Comparative analysis study of 702 dental implants subjected to immediate functional loading and immediate nonfunctional loading to traditional healing periods with a follow-up of up to 24 months. *Int J Oral Maxillofac Implants*. 2005;20(1):99-107.
13. Chiapasco M, Gatti C, Rossi E, Haeflige W, Markwaldel. TH. Implant-retained mandibular overdentures with immediate loading. *Clinical Oral Implants Research*. 1997;8(1):48-57. doi:https://doi.org/10.1111/j.1600-0501.1997.tb00007.x
14. Balshi TJ, Wolfinger GJ. Conversion prosthesis: a transitional fixed implant-supported prosthesis for an edentulous arch--a technical note. *Int J Oral Maxillofac Implants*. 1996;11(1):106-111.
15. Jaffin RA, Kumar A, Berman CL. Immediate Loading of Implants in Partially and Fully Edentulous Jaws: A Series of 27 Case Reports. *Journal of Periodontology*. 2000;71(5):833-838. doi:https://doi.org/10.1902/jop.2000.71.5.833
16. Rodrígues AHC, Morgano SM, Guimarães MM, Ankly R. Laboratory-processed acrylic resin provisional restoration with cast metal substructure for immediately loaded implants. *The Journal of Prosthetic Dentistry*. 2003;90(6):600-604. doi:https://doi.org/10.1016/j.prosdent.2003.08.006
17. Froum S, Emtiaz S, Bloom Mj, Scolnick J, Tarnow Dp. The use of transitional implants for immediate fixed temporary prostheses in cases of implant restorations. *Pract Periodontics Aesthet Dent*. 1998;10(6):737-746; quiz 748.
18. Longoni S, Sartori M, Davide R. A simplified method to reduce prosthetic misfit for a screw-retained, implant-supported complete denture using a luting technique and laser welding. *The Journal of Prosthetic Dentistry*. 2004;91(6):595-598. doi:https://doi.org/10.1016/j.prosdent.2004.02.016
19. Mondani PL, Mondani PM. [The Pierluigi Mondani intraoral electric solder. Principles of development and explanation of the solder using syncrystallization]. *Rivista di odontostomatologia e implantoprotesi*. 2018;4(4).
20. Ar H, Borelli P. Intra-oral welding of implants for an immediate load with overdentures. *J Oral Implantol*. 1993;19(1):34-38.
21. Szmukler-Moncler S, Salama H, Reingewirtz Y, Dubruille JH. Timing of loading and effect of micromotion on bone-dental implant interface: review of experimental literature. *Journal of biomedical materials research*. 2014;43(2). doi:https://doi.org/10.1002/(sici)1097-4636(199822)43:2%3C192::aid-jbm14%3E3.0.co;2-k
22. Mihali S, Wang HL, Karancsi O, Bratu EA. Internal hexagon versus conical implant–abutment connections: evaluation of 3-year postloading outcomes. *Journal of Oral Implantology*. 2020;47(6). doi:https://doi.org/10.1563/aaid-joi-d-19-00160
23. Scarano A, Valbonetti L, Degidi M, et al. Implant-Abutment Contact Surfaces and Microgap Measurements of Different Implant Connections Under 3-Dimensional X-Ray Microtomography. *Implant Dentistry*. 2016;25(5):656-662. doi:https://doi.org/10.1097/id.0000000000000465

24. Zarone F, Apicella A, Nicolais L, Aversa R, Sorrentino R. Mandibular flexure and stress build-up in mandibular full-arch fixed prostheses supported by osseointegrated implants. *Clinical Oral Implants Research*. 2003;14(1):103-114. doi:https://doi.org/10.1034/j.1600-0501.2003.140114.x
25. Hobkirk JA, Schwab J. Mandibular deformation in subjects with osseointegrated implants. *Int J Oral Maxillofac Implants*. 1991;6(3):319-328.
26. Becker W, Becker BE, Huffstetler S. Early Functional Loading at 5 Days for Brånemark Implants Placed into Edentulous Mandibles: A Prospective, Open-Ended, Longitudinal Study. *Journal of Periodontology*. 2003;74(5):695-702. doi:https://doi.org/10.1902/jop.2003.74.5.695
27. Balshi TJ;Wolfinger GJ. Conversion prosthesis: a transitional fixed implant-supported prosthesis for an edentulous arch--a technical note. *The International journal of oral & maxillofacial implants*. 2021;11(1).
28. Degidi M, Gehrke P, Spanel A, Piattelli A. Syncrystallization: A Technique for Temporization of Immediately Loaded Implants with Metal-Reinforced Acrylic Resin Restorations. *Clinical Implant Dentistry and Related Research*. 2006;8(3):123-134. doi:https://doi.org/10.1111/j.1708-8208.2006.00011.x

Case Report

ONE SHOT SINUS LIFT, IMPLANT INSERTION, AND ALVEOLAR GUIDED BONE REGENERATION: A CASE REPORT

L. Tomaselli

Correspondence to:
Luigi Tomaselli, DDS, MS
Private practice
Via Azzurra, 26
40138 Bologna, Italy
e-mail: gigitomaselli@gmail.com

ABSTRACT

Rehabilitation of the edentulous maxilla in the molar region is a challenging problem. In several cases, there is a scarce quantity of residual sinus floor bone, and the alveolar ridge high is reduced, carrying an increased inter-arches distance. In these cases, applying a single maxillary sinus lift technique for implant insertion is inappropriate since it requires constructing high crowns for prosthetic rehabilitation. High crowns are inappropriate not only from an aesthetic point of view but also functionally uncorrected since they determine the wrong crown/ratio proportion. In these cases, a sinus lift, implant insertion, and alveolar-guided bone regeneration can be performed in one operation. Here a case report is described and literature reviewed.

KEYWORDS: *sinus, alveolus, ridge, bone, fixture*

INTRODUCTION

A maxillary sinus lift (1-14), also known as a sinus augmentation or sinus elevation, is a surgical procedure performed to increase the amount of bone in the posterior maxilla. This procedure is undertaken when there is insufficient bone height in the back of the upper jaw, often due to the natural expansion of the maxillary sinus. During a maxillary sinus lift, a dental surgeon accesses the sinus cavity through a later window in the upper jawbone and lifts the sinus membrane, creating a space between the sinus membrane and bone. This space is then filled with bone graft material, which can be obtained from the patient (autograft), a donor (allograft), or a synthetic source (alloplast). The bone graft serves as a scaffold for new bone formation, promoting the growth of additional bone inside the sinus. Dental implants can be inserted after a period of 6-8 months of bone healing (two-stage procedure) or in the same operation of sinus lift (one-stage procedure). Maxillary sinus lifts are crucial for individuals who require dental implants in the upper jaw but lack sufficient bone volume. This procedure has become a routine and successful method for addressing bone deficiencies in the posterior maxilla, enabling more patients to benefit from dental implant-supported restorations.

Guided Bone Regeneration (GBR) is a dental surgical technique designed to enhance the growth of new bone in areas where bone loss has occurred, typically in preparation for dental implant placement or other restorative procedures (15-20). The goal of GBR is to create a stable environment that encourages the natural regeneration of bone tissue. During a GBR procedure, a barrier membrane is placed over the deficient bone area to protect it from soft tissue invasion and to create a secluded space for bone regeneration. This membrane acts as a barrier, preventing the infiltration of non-bone-forming tissues and allowing bone cells to populate and regenerate in the protected space. The barrier membrane may be made of biocompatible materials such as resorbable or non-resorbable membranes, and it serves as a scaffold for bone growth. Additionally, bone graft materials, often sourced from the patient (autograft), a donor (allograft), or synthetically

Received: 02 July 2022
Accepted: 31 July 2022

produced (alloplast), may be placed beneath the membrane to provide additional support and stimulate the formation of new bone. Over time, the body's natural healing processes integrate the bone graft material and promote the development of new bone, effectively restoring lost bone volume. GBR is commonly employed in cases where there is insufficient bone for successful dental implant placement or where bone loss has occurred due to periodontal disease, trauma, or other factors.

The success of GBR depends on factors such as the patient's overall health, the quality of the bone graft material, and the proper placement of the barrier membrane. This technique has proven effective and reliable in implant dentistry, restoring adequate bone structure and facilitating the long-term success of dental implants and other restorative procedures.

In several cases, there is a scarce quantity of residual sinus floor bone, and the alveolar ridge high is reduced, carrying an increased inter-arches distance. In these cases, applying a single maxillary sinus lift technique for implant insertion is inappropriate since it requires the construction of high crowns for prosthetic rehabilitation. High crowns are inappropriate not only from an aesthetic point of view but also functionally uncorrected since they determine the wrong crown/ratio proportion. In these cases, a sinus lift, implant insertion, and alveolar-guided bone regeneration can be performed in one operation.

CASE REPORT

A 61-year-old female patient presented requesting implant-prosthetic rehabilitation of the maxilla. The patient presented a severe bone atrophy in the maxilla. In agreement with the patient, it was decided to replace upper removable prostheses with implant-prosthetic rehabilitation. The patient underwent an orthopantomography and cone-beam computed tomography scan (Fig. 1, 2).

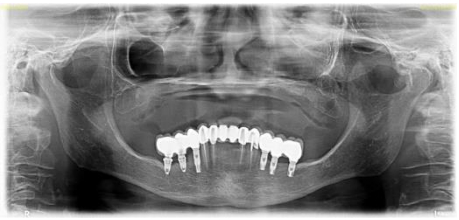

Fig. 1. *Pre-operative orthopantomography.*

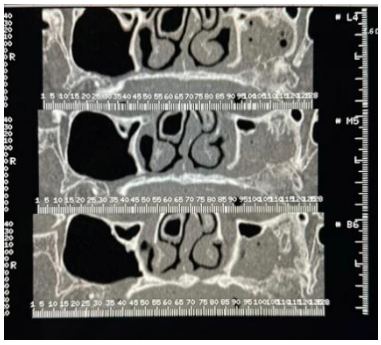

Fig. 2. *Pre-operative cone-beam computed tomography scan.*

The left maxillary sinus appeared opaque. Before surgery, the patient was informed about the operative risk and complications, and written consent was obtained from the patient for publication of this case report and accompanying images. After local anesthesia with articaine, the vestibular and palatine mucosa was incised and detached until the maxilla was completely skeletonized (Fig. 3).

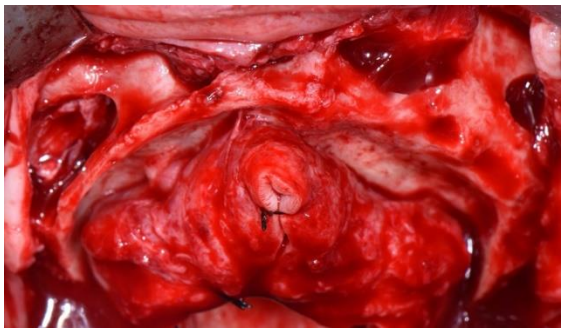

Fig. 3. *Vestibular and palatine mucosa was incised and detached until the maxilla was skeletonized entirely.*

A bilateral maxillary sinus lift was performed, and six implants were placed in the maxillary residual bone. Guided bone regeneration was performed with the placement of heterologous bone (Geistlich Bio-Oss® Thiene VI, Italy) and reinforced membranes (Geistlich Bio-Gide®, Thiene VI, Italy) fixed to the maxilla with mini-screws (Fig. 4). Three implants were inserted into the palate to stabilize the denture while waiting for bone regeneration and implant osteointegration (Fig. 5). Finally, the mucosa was sutured and a control orthopantomography was performed. The 3 implants emerge from the palatine mucosa (Fig. 6, 7).

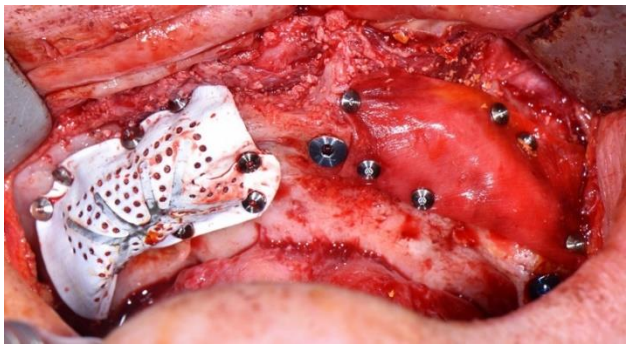

Fig. 4. *A reinforced membrane is visible on the right maxilla, while a resorbable membrane is on the left side. They cover bone grafts and are stabilized with pins.*

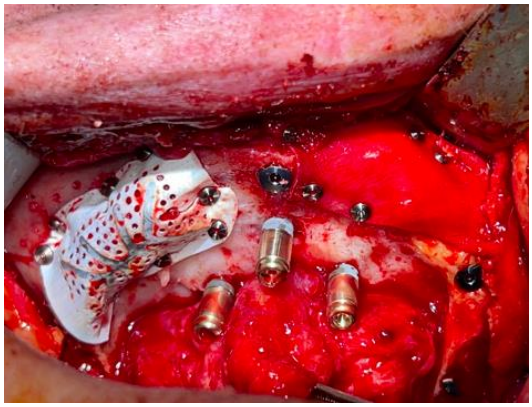

Fig. 5. *Three implants were inserted into the palate to stabilize the removable denture while waiting for bone regeneration and implant osteointegration.*

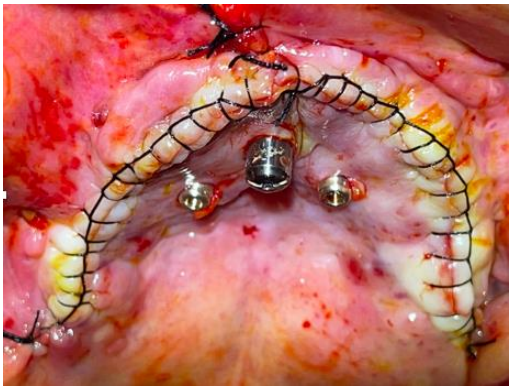

Fig. 6. *Mucosa is sutured, and 3 implants emerge from the palatal mucosa.*

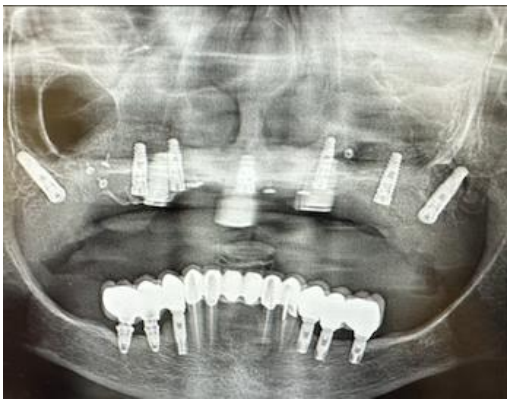

Fig. 7. *A control orthopantomography showing the inserted implants and pins stabilizing membranes.*

Six months after surgery, the maxillary mucosa was again incised and dissected to remove the 3 temporary fixtures inserted in the palate, uncover submerged implants and place the healing screws (Fig. 8-10). In the following month, the mucosa appeared completely healed, and the implants could be loaded for prosthetic implant rehabilitation (Fig. 11-14). Follow-up at 2 years showed successful implant placement. (Fig. 15).

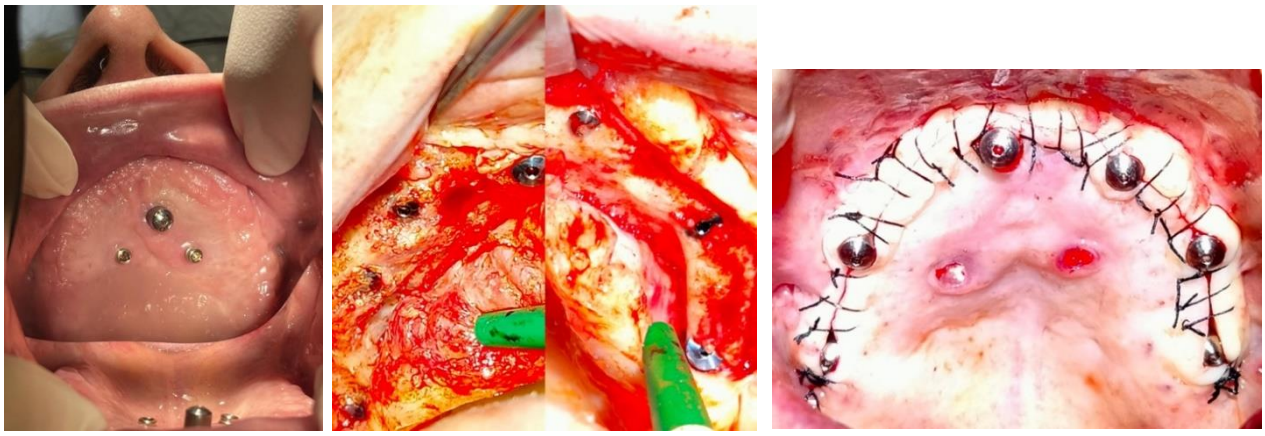

Fig. 8-10. *Six months after surgery, the maxillary mucosa was again incised and dissected to uncover the implants and place the healing screws.*

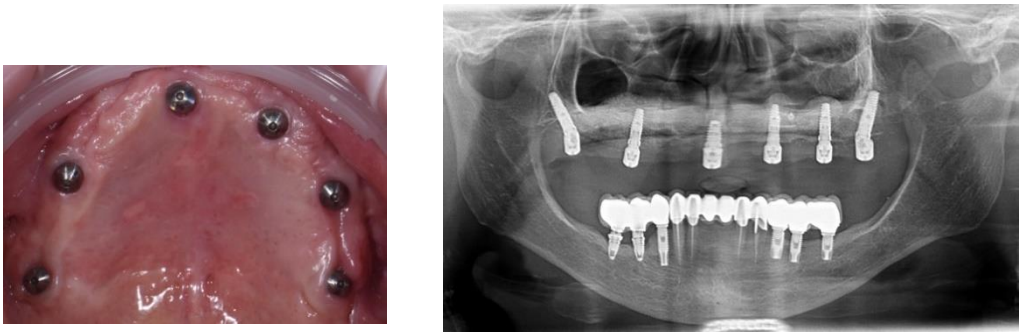

Fig. 11, 12. *One month later, the mucosa appeared completely healed, and the implants were loaded for prosthetic implant rehabilitation.*

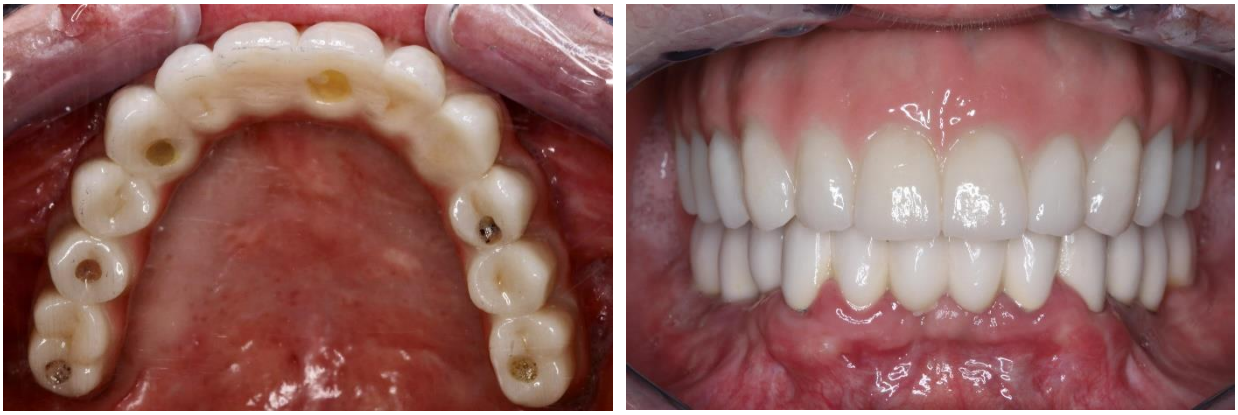

Fig. 13, 14. *Final prosthesis.*

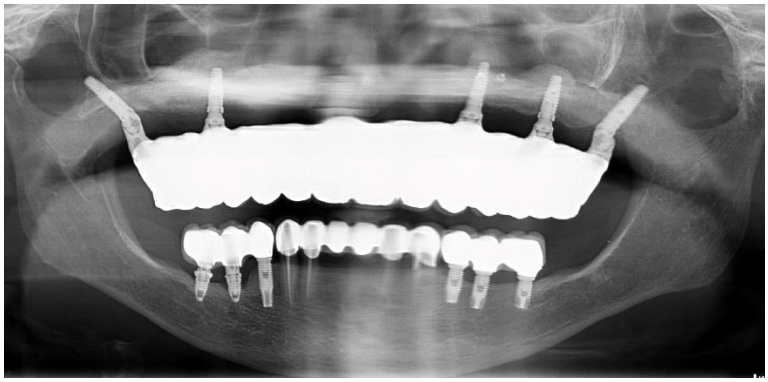

Fig. 15. *X-ray at 2-year follow-up.*

DISCUSSION

For the last twenty years, sinus lift and GBR has been applied to rehabilitate the posterior upper jaw. Several systematic reviews focus on the indication, contraindication, and outcome of these surgical techniques (1-20).

In 2010, Esposito et al. (1-3) investigated whether and when augmentation of the maxillary sinus is necessary and which are the most effective augmentation techniques for rehabilitating patients with implant-supported prostheses. The authors concluded that 5 mm short implants can be successfully loaded in maxillary bone with a residual height of 4 to 6 mm, but their long-term prognosis is unknown. Elevating the sinus lining with 1 to 5 mm of residual bone height without adding a bone graft may be sufficient to regenerate new bone and allow rehabilitation with implant-supported prostheses. Bone substitutes might be successfully used as replacements for autogenous bone. If the residual alveolar bone height is 3 to 6 mm, a crestal approach to lifting the sinus lining to place 8 mm implants may lead to fewer complications than a lateral window approach to place implants at least 10 mm long.

There is no evidence that PRP treatment improves the clinical outcome of sinus lift procedures with autogenous bone or bone substitutes. In 2014, Pinchasov et al. (4) reviewed the scientific literature with respect to bone formation in the sinus after the membrane elevation procedure without using any bone substitutes. It shows that 100% of the reviewed articles presented increased bone formation and high implant survival rates resulting from the graft-free technique. In 2014, Ali et al. (5) found that a thorough knowledge of conventional augmentation procedures such as bone augmentation techniques, guided bone regeneration, alveolar distraction, maxillary sinus elevation techniques with or without grafting, and contemporary techniques of implant placement provide effective long-term solutions in the management of the atrophic maxilla. In 2015, Fugazzotto et al. (6) and Kao et al. (7) showed that maxillary sinus lift is a predictable procedure to provide adequate bone height for implant placement.

However, complications are encountered during or after the execution of the sinus lift procedure. In 2016, Kelly et al. (8) focused on the effectiveness of recombinant human bone morphogenetic protein-2 (rhBMP-2) as a viable alternative to bone graft substitute in localized alveolar ridge augmentation and maxillary sinus floor augmentation. They show that for localized alveolar ridge augmentation, rhBMP-2 substantially increases bone height. However, rhBMP-2

does not perform as well as the autograft or allograft in maxillary sinus floor augmentation. In 2019, Ragucci et al. (9) reported that membrane perforations represent the most common complication. Consequently, their review aimed to elucidate the relevance of this phenomenon on implant survival and complications. The authors found that the overall survival rate of the implants into the sinus cavity was 95.6%, without statistical differences according to the penetration level. The clinical and radiological complications were 3.4% and 14.8%, respectively. The most frequent clinical complication was epistaxis, and the radiological complication was the thickening of the Schneiderian membrane without reaching a statistically significant difference according to the level of implant penetration inside the sinus.

In 2020, Iwanaga et al. (10) review the reported anatomy and variations of the maxillary sinus septa, greater palatine artery/nerve, and posterior superior alveolar artery and discuss what has to be assessed preoperatively to avoid iatrogenic injury. They stated that to determine the risk of injury of surgically significant anatomical structures in the maxillary sinus and hard palate, the operator should have preoperative three-dimensional images in their mind based on anatomical knowledge and palpation. The same year, Bernardi et al. (11) examined the properties of the platelet concentrates harvested bone and dentin-derived materials, reporting favorable results.

In 2021, Bhalla et al. (12) reviewed the traditional lateral sinus lift maxillary approach to achieve vertical augmentation and the trans-crestal osteotome intraoral approach. The same year, Díaz-Olivares et al. (13) proposed a treatment protocol for repairing intraoperative perforation of the Schneiderian membrane during maxillary sinus floor augmentation procedures with a lateral window technique. After that, the authors assessed subsequent implant survival rates placed below repaired membranes compared with intact membranes, determining whether membrane perforation constitutes a risk factor for implant survival. They concluded that Schneiderian membrane perforation during maxillary sinus floor augmentation procedures with a lateral approach is not a risk factor for dental implant survival. The knowledge of the exact size of the membrane perforation is essential for deciding on the right treatment plan.

Regarding alveolar ridge augmentation, Cordaro et al. (15) evaluated a surgical approach for 3D reconstruction of the posterior maxilla with autogenous mandibular bone in 16 patients. Bone blocks were harvested from the mandible and used as lateral or vertical block grafts (onlay); they were also partially milled and used for sinus elevation (inlay). In 4 cases, an organic bovine bone was added at the periphery of the blocks. Four months after grafting, implants were placed in a second operation and loaded after 12 weeks. Lateral and vertical augmentations were measured immediately after grafting and re-entry for implant placement. The mean lateral augmentation performed was 5.5mm, reduced to 4.3mm ($p<0.01$) after 4 months' healing. Mean vertical augmentation was 3.2mm, reduced to 2.1mm ($p<0.01$) after healing. The amounts of lateral and vertical graft resorption were similar (1.2mm vs. 1.1mm) but were different when compared with the original graft (22% vs. 34%). Forty-nine implants were placed 4 months after grafting. Implant parameters were evaluated after 32-48 months of follow-up and demonstrated 100% survival rates. The authors concluded that the use of mandibular bone grafts for 3D augmentation of the posterior maxilla has shown promising results and minor complications.

In 2016, Mestas et al. (16) systematically reviewed the survival rates of titanium dental implants placed using split crest procedures for alveolar ridge expansion. They found that using split crest techniques appears to provide predictable alveolar ridge augmentation and high survival rates in the short and long term for implants placed in the maxilla or mandible. The same year, Baj et al. (17) reviewed not only bone graft and guided bone regeneration for rehabilitation of alveolar ridge but also sinus floor elevation and bone osteogenesis distraction, a process of bone generation between two bone segments in response to tensile stress. In 2019, three studies were reported (18-20). Starch-Jensen et al. (18) tested the hypothesis of no difference in implant treatment outcome after maxillary alveolar ridge expansion with split-crest technique compared with lateral ridge augmentation with autogenous bone block graft. They found that the split-crest technique is helpful for horizontal augmentation of maxillary alveolar deficiencies with a high survival rate of prostheses and implants.

Khoury et al. (19) use a tunneling approach to evaluate the long-term outcome of the split bone block technique for vertical bone augmentation in the posterior maxilla in combination with sinus floor elevation. Patients were treated for extensive vertical and horizontal alveolar bone defects without simultaneous implant placement and followed up for at least 10 years postoperatively. Autogenous bone blocks were harvested from the mandibular retromolar area. The harvested bone blocks were split longitudinally. Implants were inserted and exposed after every 3 months, and prosthetic restoration was performed. They found that the combination of thin autogenous bone blocks and bone particles allows an acceleration of transplant revascularization and, thus, of graft regeneration, shortening the patient treatment time and long-term three-dimensional volumetric bone stability. Finally, Cha et al. (20) investigated whether or not alveolar ridge preservation reduces vertical changes in the posterior maxilla compared to spontaneous healing following tooth extraction.

For this research, forty subjects requiring extraction of maxillary posterior teeth with root apices protruding into the maxillary sinus floor were consecutively enrolled. Patients were randomly assigned to one of two surgical interventions: an alveolar ridge preservation procedure using collagenated bovine bone mineral and a resorbable collagen membrane (test) or no grafting (control). Cone-beam computed topographies were taken immediately and 6 months after surgery, before dental implant placement. The authors found that alveolar ridge preservation in the posterior maxilla maintained the vertical bone height more efficiently and resulted in less need for sinus augmentation procedures at 6 months compared to spontaneous healing.

Our case report demonstrated that performing a one-shot sinus lift, implant insertion, and alveolar-guided bone regeneration is possible in cases with a reduced quantity of residual sinus floor bone and increased inter-arches distance. Major attention should be paid to several complications associated with maxillary bone augmentation and implant dentistry. These complications can be broadly categorized into intraoperative, early postoperative, and late postoperative complications. Intraoperative complications include perforation of the sinus membrane, damage to neurovascular structures, and inadequate bone graft stability. Early postoperative complications encompass infection, hematoma formation, and graft failure. Late postoperative complications involve implant failure, peri-implantitis, and soft tissue complications.

Complications in maxillary bone augmentation and implant dentistry can arise due to various factors, including surgical technique, patient-related factors, and anatomical considerations. Preoperative evaluation, careful treatment planning, and meticulous surgical execution are crucial to minimize complications. Additionally, prompt recognition and appropriate management of complications are vital to achieve successful outcomes.

Maxillary bone augmentation and implant dentistry offer practical solutions for patients with missing teeth. However, it is important to be aware of the potential complications associated with these procedures. Understanding the etiology, prevention strategies, and management techniques of these complications is essential for dental professionals to provide optimal patient care. By staying updated with the latest research and advancements, clinicians can minimize complications and improve the long-term success rate of maxillary bone augmentation and implant dentistry.

CONCLUSIONS

Our case report demonstrated that in cases with a reduced quantity of residual sinus floor bone and increased inter-arches distance can be treated by performing a one-shot sinus lift, implant insertion, and alveolar-guided bone regeneration. However, different groups should report more studies to establish this procedure's indications and complications.

REFERENCES

1. Esposito M, Grusovin MG, Kwan S, Worthington HV, Coulthard P. Interventions for replacing missing teeth: bone augmentation techniques for dental implant treatment. *Cochrane Database Syst Rev*. 2008. doi:https://doi.org/10.1002/14651858.cd003607.pub3
2. Esposito M, Grusovin MG, Rees J, et al. The effectiveness of sinus lift procedures for dental implant rehabilitation is a Cochrane systematic review. *European Journal of Oral Implantology*. 2010;3(1):7-26.
3. Esposito M, Felice P, Worthington HV. Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. *Cochrane Database of Systematic Reviews*. 2014;13(5). doi:https://doi.org/10.1002/14651858.cd008397.pub2
4. Pinchasov G, Juodzbalys G. Graft-Free Sinus Augmentation Procedure: a Literature Review. *Journal of Oral and Maxillofacial Research*. 2014;5(1). doi:https://doi.org/10.5037/jomr.2014.5101
5. Ali SA, Karthigeyan S, Deivanai M, Kumar A. Implant Rehabilitation For Atrophic Maxilla: A Review. *The Journal of Indian Prosthodontic Society*. 2014;14(3):196-207. doi:https://doi.org/10.1007/s13191-014-0360-4
6. Fugazzotto P, Melnick PR, Al-Sabbagh M. Complications When Augmenting the Posterior Maxilla. *Dental Clinics of North America*. 2015;59(1):97-130. doi:https://doi.org/10.1016/j.cden.2014.09.005
7. Kao SY, Lui MT, Cheng DH, Chen TW. Lateral trap-door window approach with maxillary sinus membrane lifting for dental implant placement in atrophied edentulous alveolar ridge. *Journal of the Chinese Medical Association*. 2015;78(2):85-88. doi:https://doi.org/10.1016/j.jcma.2014.05.016
8. Kelly MP, Vaughn OLA, Anderson PA. Systematic Review and Meta-Analysis of Recombinant Human Bone Morphogenetic Protein-2 in Localized Alveolar Ridge and Maxillary Sinus Augmentation. *Journal of Oral and Maxillofacial Surgery*. 2016;74(5):928-939. doi:https://doi.org/10.1016/j.joms.2015.11.027
9. Ragucci GM, Elnayef B, Suárez-López del Amo F, Wang HL, Hernández-Alfaro F, Gargallo-Albiol J. Influence of exposing dental implants into the sinus cavity on survival and complications rate: a systematic review. *International*

Journal of Implant Dentistry. 2019;5(1). doi:https://doi.org/10.1186/s40729-019-0157-7

10. Iwanaga J, Tanaka T, Ibaragi S, et al. Revisiting major anatomical risk factors of maxillary sinus lift and soft tissue graft harvesting for dental implant surgeons. *Surgical and Radiologic Anatomy*. 2020;42(9):1025-1031. doi:https://doi.org/10.1007/s00276-020-02468-w
11. Bernardi S, Macchiarelli G, Bianchi S. Autologous Materials in Regenerative Dentistry: Harvested Bone, Platelet Concentrates and Dentin Derivates. *Molecules*. 2020;25(22):5330. doi:https://doi.org/10.3390/molecules25225330
12. Bhalla N, Dym H. Update on Maxillary Sinus Augmentation. *Dental Clinics of North America*. 2021;65(1):197-210. doi:https://doi.org/10.1016/j.cden.2020.09.013
13. Díaz-Olivares LA, Cortés-Bretón Brinkmann J, Martínez-Rodríguez N, et al. Management of Schneiderian membrane perforations during maxillary sinus floor augmentation with lateral approach in relation to subsequent implant survival rates: a systematic review and meta-analysis. *International Journal of Implant Dentistry*. 2021;7(1). doi:https://doi.org/10.1186/s40729-021-00346-7
14. Cordaro L, Amadé DS, Cordaro M. Clinical results of alveolar ridge augmentation with mandibular block bone grafts in partially edentulous patients prior to implant placement. *Clin Oral Implants Res*. 2002;13(1):103-111. doi:10.1034/j.1600-0501.2002.130113.x
15. Cordaro L, Torsello F, Accorsi Ribeiro C, Liberatore M, Mirisola di Torresanto V. Inlay–onlay grafting for three-dimensional reconstruction of the posterior atrophic maxilla with mandibular bone. *International Journal of Oral and Maxillofacial Surgery*. 2010;39(4):350-357. doi:https://doi.org/10.1016/j.ijom.2010.02.016
16. Mestas G, Alarcón M, Chambrone L. Long-Term Survival Rates of Titanium Implants Placed in Expanded Alveolar Ridges Using Split Crest Procedures: A Systematic Review. *The International Journal of Oral & Maxillofacial Implants*. 2016;31(3):591-599. doi:https://doi.org/10.11607/jomi.4453
17. Baj A, Trapella G, Lauritano D, Candotto V, Mancini G, Giannì A. An overview on bone reconstruction of atrophic maxilla: success parameters and critical issues. *J Biol Regul Homeost Agents*. 2016;30(2 Suppl 1):209-215.
18. Starch-Jensen T, Becktor JP. Maxillary Alveolar Ridge Expansion with Split-Crest Technique Compared with Lateral Ridge Augmentation with Autogenous Bone Block Graft: a Systematic Review. *Journal of Oral and Maxillofacial Research*. 2019;10(4). doi:https://doi.org/10.5037/jomr.2019.10402
19. Khoury F, Hanser T. Three-Dimensional Vertical Alveolar Ridge Augmentation in the Posterior Maxilla: A 10-year Clinical Study. *The International Journal of Oral & Maxillofacial Implants*. 2019;34(2):471-480. doi:https://doi.org/10.11607/jomi.6869
20. Cha J, Song YW, Park S, Jung RE, Jung U, Thoma DS. Alveolar ridge preservation in the posterior maxilla reduces vertical dimensional change: A randomized controlled clinical trial. *Clinical Oral Implants Research*. 2019;30(6). doi:https://doi.org/10.1111/clr.13436

Case Series

HETEROLOGOUS BONE LAMINA AND UMBRELLA SCREW TECHNIQUE FOR SINGLE-TOOTH PREMOLAR ALVEOLAR DEFECTS PREVENTION AFTER THE EXTRACTION: A CASE SERIES

F. Lorusso[1], L. Calò[1], S. A. Gehrke[2,3], A. Scarano[1*], G. Di Palma[4] and S.R. Tari[1]

[1]Department of Innovative Technologies in Medicine & Dentistry, University of Chieti-Pescara, Italy;
[2]Department of Research, Bioface/PgO/UCAM, Montevideo, Uruguay;
[3]Department of Biotechnology, Universidad Católica de Murcia (UCAM), Murcia, Spain;
[4]University of Bari, Bari, Italy

[*]*Correspondence to:*
Antonio Scarano, DDS, MD
Department of Innovative Technologies in Medicine & Dentistry,
University of Chieti-Pescara,
Via Dei Vestini 31,
66100 Chieti, Italy
e-mail: ascarano@unich.it

ABSTRACT

The post-extraction alveolar defect could represent a clinical challenge for dental implant rehabilitation in the aesthetic area. The aim of the present study was to investigate the effectiveness of heterologous bone lamina supported by an umbrella screw for the prevention of bone defect collapse after tooth extraction in the maxillary aesthetic region. A total of 2 male patients were treated in the present case series. The heterologous bone lamina supported by a screw was applied at the level of the premolar region to maintain the bone peaks. After 6 months, a full flap thickness flap was elevated, and the fixation screw was removed. A dental implant has been positioned to support a single crown fixed rehabilitation. An excellent maintenance of the buccal and interproximal bone peaks was obtained. No signs of early exposure and inflammation were reported during the healing period and dental implant positioning. Within the limits of the present study, the heterologous bone lamina showed an optimal mechanical stability and space-maintaining capability.

KEYWORDS: *regeneration, dental, implant, therapy, bone, lamina*

INTRODUCTION

Treating single-tooth extraction in the aesthetic region of the jaws could represent a clinical challenge for successful dental implant rehabilitation (1). As a consequence of the avulsion, compartmental bone resorption is contemplated, considering both horizontal and vertical vectors that can determine an alteration of the bone volume balance (2, 3). This condition could produce two critical points concerning the possibility of dental implant rehabilitation: the positioning of an implant fixture adequate in length and diameter and maintaining the aesthetic impact of the crown emerging profile in case of bone peak loss (4). Conversely, the correct prosthetic profile also determines prosthesis maintenance and plaque biofilm control (5). Several techniques and biomaterials have been proposed for this scope, including bone graft positioning, titanium mesh, and membrane bone regeneration procedure (6, 7). Autologous graft

Received: 23 June 2022
Accepted: 19 July 2022

represents the gold standard for bone augmentation procedures due to the space-maintaining capacity and intrinsic osteogenic capability (7).

On the other hand, the xenograft procedure takes advantage of the space-maintaining and scaffolding capability of the biomaterial, which can create a favorable environment for blood clot stability (8, 9). Autologous bone graft use is often limited by donor site accessibility and its healing period management (7). In the alternative literature, the socket shield technique has also been proposed to preserve the buccal bone plate (10). The heterologous bone lamina is a xenograft characterized by a dual-layer structure composed of a double cortical and cancellous side (11). This biomaterial is characterized by a high wettability with the blood and body fluids that confer remarkable graft plasticity and adaptability to the recipient site (11). The clinical rationale of heterologous lamina is associated with the creation of a regenerative compartment through the stabilization of the blood clot. This technique has also been used to produce bone graft augmentation without using graft materials in several clinical occurrences including sinus augmentation (11). The aim of the present study was to evaluate the clinical efficacy of the heterologous lamina for preventing single-tooth alveolar defect collapse after extraction in the aesthetic region.

CASE SERIES

The present study has been conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Two patients were visited for the extraction of the upper premolar and delayed dental implant positioning. The treatment planning considered a delayed approach for dental implant surgery and bone volume preservation after the tooth extraction. The subjects underwent a clinical and occlusal examination at the initial visit, and panoramic radiographs were evaluated. A radiographic scan was performed before the procedure to conduct the preliminary assessment of the surgical site. Before the procedure, the chlorhexidine digluconate solution rinse 0.2% was administered for 1 minute. The local anesthesia was conducted by Articaine® (Ubistesin 4%-Espe Dental AG Seefeld, Germany) with epinephrine 1:100.000. A full-thickness mucoperiosteal flap was elevated, and the premolar was extracted, preserving the bone level peaks. At the base of the palatal cortical wall, a specially designed bone fixation screw has been applied (Ustomed, Tuttlingen, Germany) to support the heterologous bone lamina (Osteobiol, Tecnoss Dental S.R.L., Turin, Italy) during the healing period of 6 months. A second phase of surgical access has been realized at 6 months for bone fixation screw removal and dental implant positioning. The surgical site has been prepared atraumatically in accordance with the manufacturer protocol using a surgical motor (300 Plus Intrasurg, Kavo, Germany). The healing abutment positioning and provisional phases were performed at six months, with the prosthetic finalization of a single crown rehabilitation.

Case 1

A male patient with an age of 45 years old was visited for upper premolar 2.5 affected by periodontal probing and teeth mobility with a mean PPD of 5.6±1.4. No significant pathologies and risk factor conditions were reported at the anamnesis (Fig. 1-2).

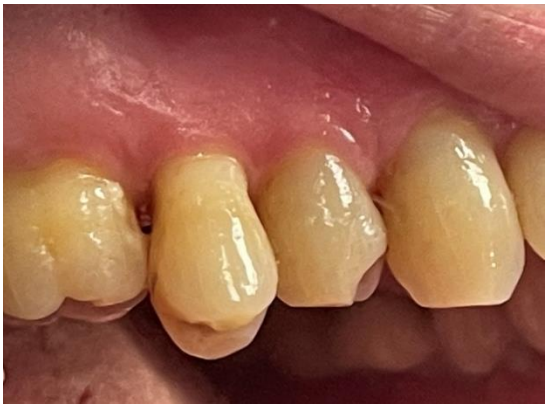

Fig. 1. *Occlusal view of the surgical site.*

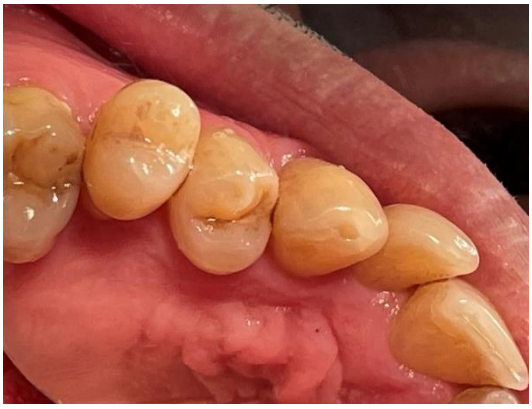

Fig. 2. *Lateral view of the surgical site.*

The bone fixation screw was positioned in accordance with the manufacturer protocol (Fig. 3-7) (Ustomed, Tuttlingen, Germany).

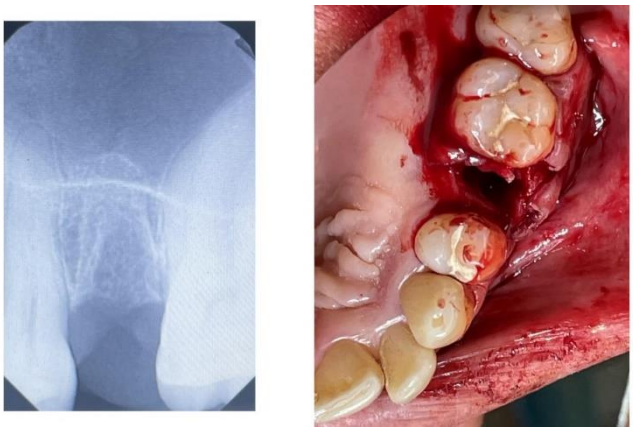

Fig. 3. *Detail of the post-extraction site.* ***Left****: A periapical radiograph was taken after the procedure.* ***Right****: Occlusal view of the surgical site.*

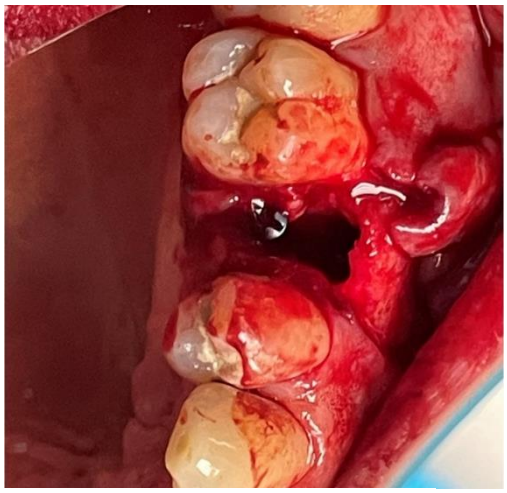

Fig. 4. *Fixation screw positioned in the palatal region of the residual defect.*

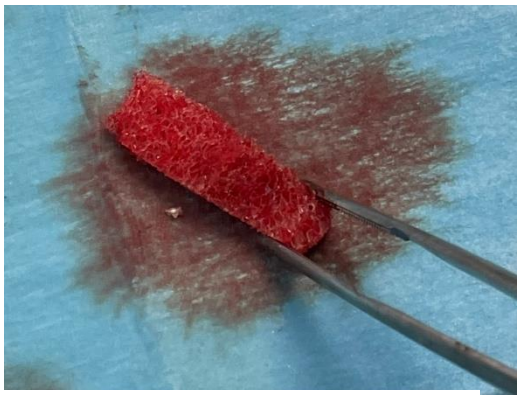

Fig. 5. *Heterologous lamina segment morphologically adapted.*

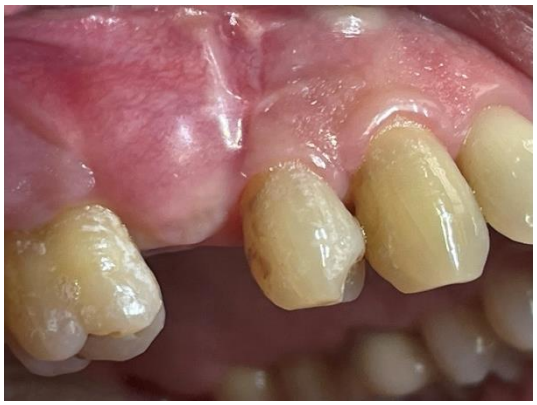

Fig. 6. *Lateral view of the site after the healing period.*

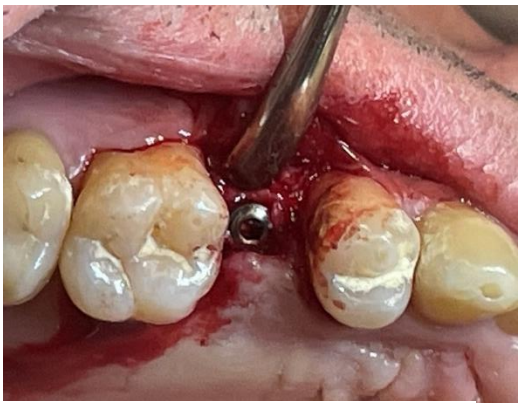

Fig. 7. *Occlusal view of the site after the dental implant positioning.*

The post-operative period was uneventful, and no significant complications were reported after the 14-day healing phase and 6 months from the first phase of surgery. The implant surgery was performed by elevating the total thickness of the mucoperiosteal flap to expose the bone ridge. The buccal bone wall, as did the mesial and distal peak profiles, appeared well preserved. A 3.5 diameter and 12mm length implant fixture (Isomed Implant, Due Carrare, Italia) was positioned in accordance with the manufacturer protocol.

Case 2

A male patient (36 years old) was visited for an upper premolar 2.4 bone defect resulting from a tooth fracture and previous bone regenerative procedure failure relapses. No significant diseases and risk factors were reported during the initial visit. A buccal bone collapse was present, and the mesial and distal bone peaks were partially preserved. The chlorhexidine digluconate solution rinses 0.2% was administered for 1 minute, and a total thickness mucoperiosteal flap was elevated. A specially designed bone fixation screw has been applied on the top of the bone ridge (Ustomed, Tuttlingen, Germany) to support the heterologous bone lamina (Osteobiol, Tecnoss Dental S.R.L., Turin, Italy) during the healing period of 6 months (Fig. 8).

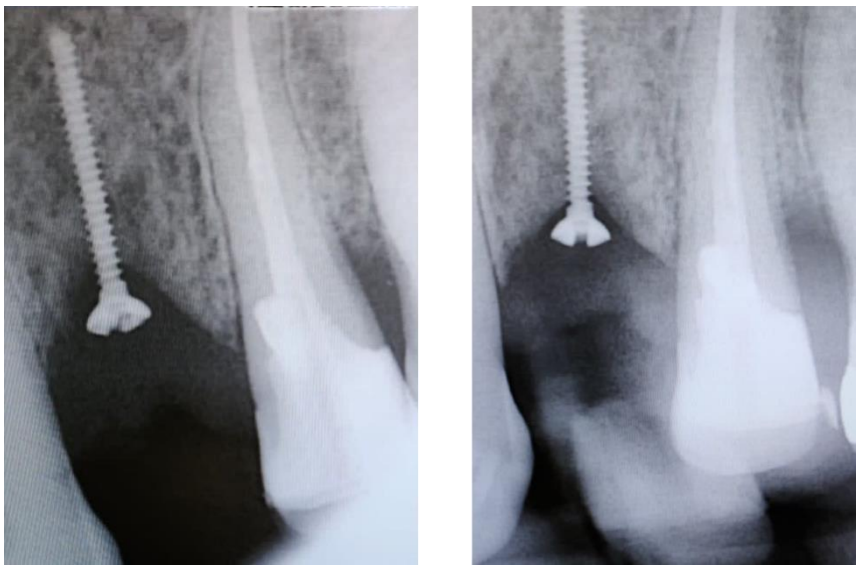

Fig. 8. *Radiogram scans taken at the baseline (left) and after 6 months from the surgery.*

The implant site has been prepared in accordance with the manufacturer protocol (Isomed Implant, Due Carrare, Italia) using a surgical motor (300 Plus Intrasurg, Kavo, Germany). The prosthetic finalization has been obtained through a single crown rehabilitation.

DISCUSSION

Dental implant rehabilitation in the aesthetic region of the jaws represents a challenge in operative dentistry, considering the difficulties determined by the restoration of the emerging design of the prosthesis and the long-term maintenance (12). The tooth loss could significantly impair the bone ridge profile, determining wall defect (13). In addition, the position of the teeth could also play a role in post-extraction bone deficiency. The present investigation aimed to report the use of heterologous bone lamina to prevent the bone defect collapse associated with tooth extraction in the aesthetic region. Both clinical cases reported excellent maintenance of the bone peaks, creating a regenerative compartment without using a bone graft. No marginal exposures and dehiscences were observed after the 6 months healing period. On the other hand, the heterologous bone lamina stabilized with screws reported excellent integration and adaptability. Also, the defect regenerates sites due to the biomaterial's mechanical properties and clinical stability. Yang et al. proposed a classification of dehiscences based on the mesial-distal views (14).

Some reported a 5-8% incidence in the literature observed in cadaver and clinical studies (14-16). Guided bone regeneration procedures are considered highly predictable techniques for this purpose, considering the biomaterials biocompatibility, space maintenance, integration, and adaptability to the defect site (17, 18). Titanium mesh has been

reported as a useful technique for horizontal and vertical bone ridge augmentation (19). The Ti-mesh is a non-resorbable device characterized by excellent mechanical properties and space-maintaining capability. Still, the disadvantage of low flexibility represents a critical factor for its use (20, 21). The exposure tendency of T-mesh membranes is still debated in the literature, and several authors correlate this event to the management of the prevention of sharp angles and consequent mucosal irritation accompanied by bacterial contamination of the site that could produce a potential marginal volume graft resorption of 15-25% (22). The bone lamina is a resorbable and highly biocompatible biomaterial used in several clinical conditions, including treating residual bone defects after jaw cyst enucleation (23). Scarano et al. (23) reported a volume reduction of the residual bone defect of 92.1% after 12 months from the treatment with no addition of bone graft. The same authors reported excellent maintenance of the structure architecture and the anatomical profile of the bone ridge.

CONCLUSIONS

Within the limitations of the present study, the heterologous bone lamina seems to be effective to prevent the single tooth bone defect collapse with no exposures after the healing period. Further randomized investigations with histologic analysis are necessary to confirm the findings observed by the present case series and to characterize the regenerated bone microscopically.

REFERENCES

1. Jovanovic S. Bone rehabilitation to achieve optimal aesthetics. *Practical periodontics and aesthetic dentistry: PPAD*. 2014;9(1).
2. An X, Jeong SM, Choi BH. Natural bone healing in compromised sockets after tooth extraction. *Journal of Oral Implantology*. 2020;47(3). doi:https://doi.org/10.1563/aaid-joi-d-19-00210
3. Arya V, Malhotra VL, Rao JD, Kirti S, Malhotra S, Sharma RS. Reduction in the post-extraction waiting period for dental implant patients using plasma rich in growth factors: anin vivostudy using cone-beam computed tomography. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*. 2019;45(5):285. doi:https://doi.org/10.5125/jkaoms.2019.45.5.285
4. Ackermann KL, Barth T, Cacaci C, Kistler S, Schlee M, Stiller M. Clinical and patient-reported outcome of implant restorations with internal conical connection in daily dental practices: prospective observational multicenter trial with up to 7-year follow-up. *International Journal of Implant Dentistry*. 2020;6(1). doi:https://doi.org/10.1186/s40729-020-00211-z
5. Grossner-Schreiber B, Griepentrog M, Haustein I, et al. Plaque formation on surface modified dental implants. An in vitro study. *Clinical Oral Implants Research*. 2001;12(6):543-551. doi:https://doi.org/10.1034/j.1600-0501.2001.120601.x
6. Ahmed M, Abu Shama A, Hamdy RM, Ezz M. Bioresorbable versus titanium space-maintaining mesh in maxillary sinus floor elevation: a split-mouth study. *International Journal of Oral and Maxillofacial Surgery*. 2017;46(9):1178-1187. doi:https://doi.org/10.1016/j.ijom.2017.04.001
7. Akamaru T, Kawahara N, Tsuchiya H, Kobayashi T, Murakami H, Tomita K. Healing of Autologous Bone in a Titanium Mesh Cage Used in Anterior Column Reconstruction After Total Spondylectomy. *Spine*. 2002;27(13):E329-E333. doi:https://doi.org/10.1097/00007632-200207010-00024
8. Amaral Valladão CA, Freitas Monteiro M, Joly JC. Guided bone regeneration in staged vertical and horizontal bone augmentation using platelet-rich fibrin associated with bone grafts: a retrospective clinical study. *International Journal of Implant Dentistry*. 2020;6(1). doi:https://doi.org/10.1186/s40729-020-00266-y
9. Scarano A, Degidi M, Iezzi G, et al. Maxillary Sinus Augmentation With Different Biomaterials: A Comparative Histologic and Histomorphometric Study in Man. *Implant Dentistry*. 2006;15(2):197-207. doi:https://doi.org/10.1097/01.id.0000220120.54308.f3
10. Chen K, Li Z, Liu X, et al. Immediate Implant Placement with Buccal Bone Augmentation in the Anterior Maxilla with Thin Buccal Plate: A One-Year Follow-Up Case Series. *Journal of prosthodontics (Print)*. 2021;30(6):473-480. doi:https://doi.org/10.1111/jopr.13350
11. Scarano A, de Oliveira P, Traini T, Lorusso F. Sinus Membrane Elevation with Heterologous Cortical Lamina: A Randomized Study of a New Surgical Technique for Maxillary Sinus Floor Augmentation without Bone Graft. *Materials*. 2018;11(8):1457. doi:https://doi.org/10.3390/ma11081457
12. De Angelis N, Signore A, Alsayed A, et al. Immediate Implants in the Aesthetic Zone: Is Socket Shield Technique a Predictable Treatment Option? A Narrative Review. *Journal of Clinical Medicine*. 2021;10(21):4963. doi:https://doi.org/10.3390/jcm10214963
13. Bramanti E, Norcia A, Cicciù M, et al. Postextraction Dental Implant in the Aesthetic Zone, Socket Shield

Technique Versus Conventional Protocol. *Journal of Craniofacial Surgery*. 2018;29(4):1037-1041. doi:https://doi.org/10.1097/scs.0000000000004419

14. Yang Y, Yang H, Pan H, Xu J, Hu T. Evaluation and New Classification of Alveolar Bone Dehiscences Using Cone-beam Computed Tomography in vivo. *International Journal of Morphology*. 2015;33(1):361-368. doi:https://doi.org/10.4067/S0717-95022015000100057
15. Rupprecht RD, Horning GM, Nicoll BK, Cohen ME. Prevalence of Dehiscences and Fenestrations in Modern American Skulls. *Journal of Periodontology*. 2001;72(6):722-729. doi:https://doi.org/10.1902/jop.2001.72.6.722
16. Evangelista K, Vasconcelos K de F, Bumann A, Hirsch E, Nitka M, Silva MAG. Dehiscence and fenestration in patients with Class I and Class II Division 1 malocclusion assessed with cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2010;138(2):133.e1-133.e7. doi:https://doi.org/10.1016/j.ajodo.2010.02.021
17. Caballe-Serrano J, Munar-Frau A, Ortiz-Puigpelat O, Soto-Penaloza D, Penarrocha M, Hernandez-Alfaro F. On the search of the ideal barrier membrane for guided bone regeneration. *Journal of Clinical and Experimental Dentistry*. 2018;10(5). doi:https://doi.org/10.4317/jced.54767
18. Benic GI, Eisner BM, Jung RE, Basler T, Schneider D, Hämmerle CHF. Hard tissue changes after guided bone regeneration of peri-implant defects comparing block versus particulate bone substitutes: 6-month results of a randomized controlled clinical trial. *Clinical Oral Implants Research*. 2019;30(10). doi:https://doi.org/10.1111/clr.13515
19. Assenza B, Piattelli M, Scarano A, Iezzi G, Petrone G, Piattelli A. Localized Ridge Augmentation Using Titanium Micromesh. *Journal of Oral Implantology*. 2001;27(6):287-292. doi:https://doi.org/10.1563/1548-1336(2001)027%3C0287:lrautm%3E2.3.co;2
20. Hartmann A, Seiler M. Minimizing risk of customized titanium mesh exposures – a retrospective analysis. *BMC Oral Health*. 2020;20(1). doi:https://doi.org/10.1186/s12903-020-1023-y
21. Zhou L, su yucheng, Wang J, Wang J, Wang X, Liu Q. Effect of Exposure Rates with Customized versus Conventional Titanium Mesh on Guided Bone Regeneration: A Systematic Review and Meta-Analysis. *Journal of Oral Implantology*. 2021;48(4). doi:https://doi.org/10.1563/aaid-joi-d-20-00200
22. Maiorana C, Santoro F, Rabagliati M, Salina S. Evaluation of the use of iliac cancellous bone and anorganic bovine bone in the reconstruction of the atrophic maxilla with titanium mesh: a clinical and histologic investigation. *Int J Oral Maxillofac Implants*. 2001;16(3):427-432.
23. Scarano A, Ciccarese S, Amuso D, Mortellaro C, Lorusso F. Cortical bone lamina approach for mandibular large cystic defect: a case report. *Journal of biological regulators and homeostatic agents*. 2019;33(6 Suppl. 2).

Case Report

ORAL MUCOSA PIGMENTATION RELATED TO IMATINIB MESYLATE: A CASE REPORT

A. Romano

Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania "Luigi Vanvitelli", Naples, Italy

Correspondence to:
Antonio Romano, DDS
Multidisciplinary Department of Medical-Surgical and Dental Specialties,
University of Campania "Luigi Vanvitelli",
Naples, Italy
e-mail: antonio.romano4@unicampania.it

ABSTRACT

Imatinib Mesylate (IM), a tyrosine kinase inhibitor, is a first-line medication for treating chronic myeloid leukemia and gastrointestinal stromal tumors. Clinical studies revealed excellent hematological responses without significant side effects. Dermatologic side effects are ordinary, with rash and superficial edema the most recurring. Moreover, IM treatment is often associated with hypopigmentation. Intraoral side effects are very infrequent. However, IM may lead to mucosal pigmentation. This paper reports a patient with chronic myeloid leukemia treated with IM for seven years, referred with diffuse solitary bluish-brown pigmentations in the hard palate.

KEYWORDS: *pigmentation, oral cavity, leukemia, skin*

INTRODUCTION

Oral pigmentations linked to excessive melanin production are characteristic clinical findings, and their etiology varies, denoting a broad spectrum from physiologic pigmentations to manifestations of systemic diseases (1). Some physiologic pigmentation is connected to ethnicity and is mainly found in dark-skinned populations (2). They are often bilateral and found in buccal and gingival mucosa. (3). Systemic diseases such as Addison's disease, Peutz-Jehgers syndrome, and other rare diseases, such as Nelson syndrome, polyostotic fibrous dysplasia, and hyperthyroidism, are associated with oral melanotic pigmentation (4). Deposit of melanin in the connective tissue may even be found after long-standing inflammation in conditions such as pemphigus, oral lichen planus, and pemphigoid (5).

Likewise, tobacco and several drugs, i.e., antimalarials, tetracyclines, chemotherapeutic drugs (doxorubicin, bleomycin, 5-fluorouracil, cyclophosphamide), phenothiazines, quinidine, amiodarone, and clofazimine, may cause oral pigmentation (6). Imatinib mesylate (IM - STI-571, Gleevec®; Novartis Pharma, Basel, Switzerland) is a tyrosine kinase inhibitor that targets Bcr-Abl-protein, c-Kit, and platelet-derived growth factor receptors (7). The drug was initially conceived for the therapy of chronic myeloid leukemia (CML) but is also considered the first-line treatment for patients with metastatic gastrointestinal stromal tumors (GIST) (8). IM treatment correlates with side effects, such as diarrhea, nausea, periorbital edema, and myelosuppression (7). Dermatologic side effects are not uncommon, with rash and superficial edema as the most common; additional side effects are pruritic maculopapular exanthema, erythroderma, small vessel vasculitis, graft-versus-host-disease, and lichenoid eruptions (9). In difference, intraoral side effects appear rare,

Received: 14 June 2022
Accepted: 12 July 2022

with occasional dental hyperpigmentation and lichenoid reactions (10, 11). The present paper aimed to depict a patient with similar solitary melanotic maculae in the palatal mucosa.

CASE REPORT

A 46-year-old woman was referred in March 2021 to the Unit of Oral Pathology and Medicine at the University of Campania "Luigi Vanvitelli" to evaluate a pigmented lesion in the hard palate. She was a nonsmoker, and the lesion was discovered at a routine examination by the patient's regular dentist. The patient had chronic myeloid leukemia (CML) and, since 2015, was treated with IM 400 mg daily. The patient used no other medication. The palatal mucosa showed a bluish-brown U-shaped pigmentation symmetrically distributed on both sides of the hard palate (Fig. 1). The lesion was asymptomatic, and there were no other pigmentations or lesions in the oral mucosa. The patient refused a biopsy. A follow-up in June 2021 confirmed that the pigmented lesion persisted and was clinically unchanged.

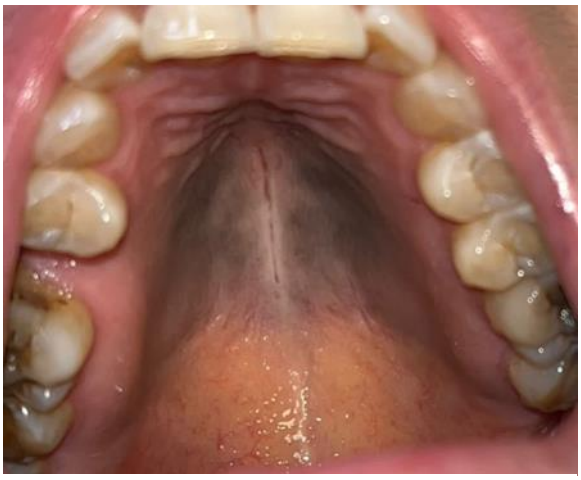

Fig. 1. *Clinical presentation of the palatal mucosa.*

DISCUSSION

Solitary pigmented lesions in the hard palate associated with IM treatment have been previously described in the literature (12-14). The histopathologic examination in the literature indicated melanin pigment in the lamina propria, consistent with melanotic maculae—noninflamed palatal mucosa covered by normal epithelium (13). Multiple pigment-laden cells with roundish or spindled shapes were found in the lamina propria. A few pigmented cells were also seen in the submucosal tissue (14).

The oral melanotic macula is a recurring lesion in the population, with the palate being the most typical site (15). The lesions are generated by grown melanin production by melanocytes, and the deposited melanin is located within the basal cell layer of the epithelium, the lamina propria, or both (16). Some additional etiologic factors must be evaluated before handling the probable relationship between the observed melanotic macules and IM therapy (5). The patient had no systemic conditions usually associated with melanosis development or used other drugs associated with excessive melanin pigmentation; furthermore, she was a nonsmoker. From a clinical point of view, a differential diagnosis was pigmentation associated with bleeding and following degeneration of hemoglobin, and palatal hyperpigmentation has also been reported in association with hemochromatosis (17). Regardless, there was no history of trauma, and the patient had no laboratory findings indicating hemochromatosis.

IM has been associated with hyperpigmentation of fingernails and skin and hypopigmentation of skin, although such cases are rare (18). It is not understood how IM can cause both losses of pigment and darkening of the skin in various patients (13, 19, 20). IM is a specific protein kinase inhibitor approved by the Food and Drug Administration in 2001 for treating CML (21). It blocks the activity of the mutated BCR-ABL tyrosine kinase of CML; IM also blocks the binding of ligands to c-kit receptors on melanocytes, lowering the activity of melanocytes and leading to hypopigmentation (22). Nonetheless, IM may even lead to hyperpigmentation of the skin or mucosa. It likely does this through a drug metabolite chelated to iron and melanin, in a similar mechanism to minocycline and anti-malarial drugs (23). The diagnosis of IM-related pigmentation hangs on a thorough medical history and distinctive clinical features (24). Fortunately, the hyperpigmented lesions are benign, and no treatment is required (25).

REFERENCES

1. Mumcu G, Cimilli H, Sur H, Hayran O, Atalay T. Prevalence and distribution of oral lesions: a cross-sectional study in Turkey. *Oral Diseases*. 2005;11(2):81-87. doi:https://doi.org/10.1111/j.1601-0825.2004.01062.x
2. Hassona Y, Sawair F, Al-karadsheh O, Scully C. Prevalence and clinical features of pigmented oral lesions. *International Journal of Dermatology*. 2015;55(9):1005-1013. doi:https://doi.org/10.1111/ijd.13133
3. Dhanuthai K, Theungtin N, Theungtin N, et al. Pigmented Oral Lesions: A Multicenter Study. *European Journal of Dentistry*. 2021;16(02):315-319. doi:https://doi.org/10.1055/s-0041-1735790
4. Gondak RO, da Silva-Jorge R, Jorge J, Lopes MA, Vargas PA. Oral pigmented lesions: Clinicopathologic features and review of the literature. *Medicina Oral, Patología Oral y Cirugía Bucal*. 2012;17(6):e919-e924.

doi:https://doi.org/10.4317/medoral.17679

5. Meleti M, Vescovi P, Mooi WJ, van der Waal I. Pigmented lesions of the oral mucosa and perioral tissues: a flow-chart for the diagnosis and some recommendations for the management. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2008;105(5):606-616. doi:https://doi.org/10.1016/j.tripleo.2007.07.047
6. Rosebush MS, Briody AN, Cordell KG. Black and Brown: Non-neoplastic Pigmentation of the Oral Mucosa. *Head and Neck Pathology*. 2019;13(1):47-55. doi:https://doi.org/10.1007/s12105-018-0980-9
7. Corbin AS, O'Hare T, Gu Z, et al. KIT signaling governs differential sensitivity of mature and primitive CML progenitors to tyrosine kinase inhibitors. *Cancer Research*. 2013;73(18):5775-5786. doi:https://doi.org/10.1158/0008-5472.CAN-13-1318
8. Waller CF. Imatinib Mesylate. *Recent Results in Cancer Research*. 2018;212:1-27. doi:https://doi.org/10.1007/978-3-319-91439-8_1
9. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *The Lancet Oncology*. 2005;6(7):491-500. doi:https://doi.org/10.1016/s1470-2045(05)70243-6
10. Wahiduzzaman M, Pubalan M. Oral and cutaneous lichenoid reaction with nail changes secondary to imatinib: report of a case and literature review. *Dermatology Online Journal*. 2008;14(12):14.
11. Singh N, Bakhshi S. Imatinib-induced dental hyperpigmentation in childhood chronic myeloid leukemia. *Journal of Pediatric Hematology/Oncology*. 2007;29(3):208-209. doi:https://doi.org/10.1097/MPH.0b013e318033a76c
12. Donnell CC, Walton RL, Carrozzo M. The blue palate-A case series of imatinib-related oral pigmentation and literature review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2021;131(1):49-61. doi:https://doi.org/10.1016/j.oooo.2020.10.015
13. Mattsson U, Halbritter S, Mörner Serikoff E, Christerson L, Warfvinge G. Oral pigmentation in the hard palate associated with imatinib mesylate therapy: a report of three cases. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2011;111(5):e12-16. doi:https://doi.org/10.1016/j.tripleo.2010.11.006
14. Romeo U, Palaia G, Fantozzi PJ, Tenore G, Bosco D. A Rare Case of Melanosis of the Hard Palate Mucosa in a Patient with Chronic Myeloid Leukemia. *Case Reports in Dentistry*. 2015;2015:817094. doi:https://doi.org/10.1155/2015/817094
15. Shen ZY, Liu W, Bao ZX, Zhou ZT, Wang LZ. Oral melanotic macule and primary oral malignant melanoma: Epidemiology, location involved, and clinical implications. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2011;112(1):e21-e25. doi:https://doi.org/10.1016/j.tripleo.2011.02.040
16. Lambert MW, Maddukuri S, Karanfilian KM, Elias ML, Lambert WC. The physiology of melanin deposition in health and disease. *Clinics in Dermatology*. 2019;37(5):402-417. doi:https://doi.org/10.1016/j.clindermatol.2019.07.013
17. Fistarol SK, Itin PH. Disorders of pigmentation. *Journal of the German Society of Dermatology*. 2010;8(3):187-201; quiz 201-202. doi:https://doi.org/10.1111/j.1610-0387.2009.07137.x
18. Mcpherson T, Sherman V, Turner R. Imatinib-associated hyperpigmentation, a side effect that should be recognized. *Journal of the European Academy of Dermatology and Venereology*. 2009;23(1):82-83. doi:https://doi.org/10.1111/j.1468-3083.2008.02706.x
19. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. *Cancer*. 2003;98(11):2483-7. doi: 10.1002/cncr.11812.
20. Lucchese A, Willers J, Mittelman A, Kanduc D, Dummer R. Proteomic scan for tyrosinase peptide antigenic pattern in vitiligo and melanoma: role of sequence similarity and HLA-DR1 affinity. *J Immunol*. 2005;175(10):7009-20. doi: 10.4049/jimmunol.175.10.7009.
21. Blay JY, Reichardt P. Advanced gastrointestinal stromal tumor in Europe: a review of updated treatment recommendations. *Expert Review of Anticancer Therapy*. 2009;9(6):831-838. doi:https://doi.org/10.1586/era.09.34
22. Fanta S, Sonnenberg M, Skorta I, et al. Pharmacological inhibition of c-Abl compromises genetic stability and DNA repair in Bcr-Abl-negative cells. *Oncogene*. 2008;27(31):4380-4384. doi:https://doi.org/10.1038/onc.2008.68
23. McPartlin S, Leach M. Loss of skin pigment caused by imatinib therapy. *British Journal of Haematology*. 2005;129(4):448. doi:https://doi.org/10.1111/j.1365-2141.2005.05431.x
24. Bombeccari GP, Garagiola U, Pallotti F, et al. Hyperpigmentation of the hard palate mucosa in a patient with chronic myeloid leukaemia taking imatinib. *Maxillofacial Plastic and Reconstructive Surgery*. 2017;39(1):37. doi:https://doi.org/10.1186/s40902-017-0136-y
25. Li CC, Malik SM, Blaeser BF, et al. Mucosal Pigmentation Caused by Imatinib: Report of Three Cases. *Head and Neck Pathology*. 2011;6(2):290-295. doi:https://doi.org/10.1007/s12105-011-0325-4

Review

OROANTRAL COMMUNICATION, ITS CAUSES, COMPLICATIONS, TREATMENTS AND RADIOGRAPHIC FEATURES: A PICTORIAL REVIEW

F. Tricca[1], F. Postiglione[1], C. Bugea[1], I. Alla[1], S.A. Gehrke[2,3] and A. Scarano[1]

[1]Department of Innovative Technologies in Medicine and Dentistry, University of Chieti-Pescara, 66100 Chieti, Italy;
[2]Department of Research, Bioface/PgO/UCAM, Montevideo, Uruguay;
[3]Department of Biotechnology. Universidad Católica de Murcia (UCAM), Murcia, Spain

**Correspondence to:*
Prof. Antonio Scarano, DDS, MD
Department of Innovative Technology in Medicine and Dentistry,
University of Chieti-Pescara,
Via Dei Vestini 31,
66100 Chieti Italy
e-mail: ascarano@unich.it

ABSTRACT

The term oroantral communication is used indiscriminately in literature as a synonym for 'oro-antral perforation', 'antro-oral communication' (OAC), 'oroantral fistula' (OAF), 'antro-alveolar fistula'. Although these terms are synonyms, OAF develops when the OAC does not close spontaneously, remains manifest, and becomes epithelialized. The development of this epithelized tissue represents a pathological pathway for bacteria and is generally thought to be generated soon, at least 48/72 h from the creation of the communication. The aim of this review was to provide a pictorial review of incidence and treatment for oroantral communications and fistulas and to avoid the risk of recurrence. By conducting an electronic search on the MEDLINE bibliographic database (Pubmed), 63 articles with a period from 1994 to 2021 were selected using the following algorithm: "sinus lift" OR "sinus augmentation" OR "sinus graft" OR "maxillary sinus floor elevation" OR "sinus floor augmentation" AND"oro-antral communication" OR "antro-oral communication" OR " oroantral communication" OR "oro-antral fistula" OR "oroantral fistula" OR "oro-sinusal communication" OR "antro-alveolar fistula" OR "fistula" OR "oro-sinusal fistula" OR "sinus-oral fistula" OR "sinus communication" OR "OAF". The electronic search yielded 63 articles. No language restrictions were applied, and only cohort studies were considered, excluding case series, case reports, RCTs, and CCTs. Titles and abstracts were examined using the previously defined inclusion and exclusion criteria. After thorough analysis, 21 articles were excluded, and 3 studies were included in the qualitative and quantitative data synthesis. The incidence of AOC, regardless of the technique used, appears to be a relatively rare complication. The surgical protocols used, the surgeon's experience, implant management, and intra-operative complications could play an active role in post-operative complications. Further studies are needed to establish a comparison between the techniques.

KEYWORDS: *oroantral communication, sinus augmentation, sinus lift, sinus graft, maxillary sinus, floor elevation*

INTRODUCTION

An oroantral communication (OAC) is defined as a pathological pathway that is created between the maxillary sinus and the oral cavity as a complication of dental extraction surgery, trauma, sinus surgery, implant failures (i.e., peri-

Received: 21 May 2022
Accepted: 18 June 2022

implantitis, infection of the graft material, migration of the implant into the sinus), osteomyelitis or removal of neoplasms involving the posterior areas of the upper jaw (1).

The term oroantral communication is used indiscriminately in literature as a synonym for 'oro-antral perforation', 'antro-oral communication', 'oroantral fistula' (OAF), 'antro-alveolar fistula'. Although these terms are synonyms, OAF develops when the OAC does not close spontaneously, remains manifest, and becomes epithelialized.

The development of this epithelized tissue represents a pathological pathway for bacteria and is generally thought to be generated soon, at least 48/72 h from the creation of the communication (2, 3). Symptoms are variable and can occur even after a long time. Most commonly, epistaxis passage of fluid between the oral and nasal cavities, pain, postnasal drip, altered vocal resonance, and difficulty in sucking or puffing out the cheeks are reported (4). In addition, if left untreated, such preferential pathways can lead to numerous complications, such as secondary sinus infection with sinusitis (acute or chronic) along with pseudopolyp formation or herniation of the sinus mucosa through communication.

Diagnosis represents a critical issue, especially in doubtful cases. Parvini et al. (5) illustrated a pragmatic and useful decision-making process, i.e., the Valsalva maneuver, compressing the patient's nostrils and blowing out air, could be useful (6). The increase in endosinusal pressure leads to the formation of bubbles at the level of the communication, unmasking the condition. However, a negative test does not automatically exclude the presence of an OAC. At the same time, a check-blowing test with a hissing sound could be helpful for the diagnosis, even if the risk of spreading the infection into the sinus is reported. The same risk is present when a probe is inserted into the communication to assess the dimensions of the AOC.

Radiologically, 2D-dimensional imaging with a gutta-percha cone inserted inside the communication can highlight the interruption and discontinuity in the floor of the maxillary sinus, indicating the presence of the communication. Coronal sections of CT and CBCT are adjunctive diagnostic tools with particular care for sinus abnormalities (7).

Multiple factors are to be considered while treating an OAC, i.e., the size of the perforation, the time of diagnosis, the presence of inflammation, and the clinician's experience, all of which have a critical role in managing these complications. In the absence of sinus infections and limited lesions ($\leq$ 2mm), the clot formation could lead to closure of the OAC and spontaneous healing. During sinus infection and when extensive communication with epithelialized tissue is present, flap mobilization surgery (buccal flap, palatal flap, buccal pad) associated with previous treatment for the sinus pathology is mandatory for the complete healing of the condition (8, 9).

Immediate intervention generally has a very high success rate (around 95%), but if the condition is unproperly treated, 50% of patients will develop sinusitis only 48h later. In addition, if not detected, sinusitis will develop in almost 90% of patients after only 2 weeks since the AOC creation (9). Some nontrasfusional hemocomponents are an effective therapeutic option (10), especially when mechanical factors are considered for the closure of the communication and flap management (11). Sinus augmentation techniques are widely used to increase the height of the residual bone ridge for implant placement in the posterolateral areas of the upper jaw.

Implant insertion strictly depends on the bone amount between the sinus floor and the residual ridge. It can be performed at the same time (one-stage technique) or delayed (two-stage technique) to ensure the primary stability necessary for a successful osteointegration (12).

Sinus augmentation techniques, first developed in the late 1970s and later revised by Summers in the 1990s, have undergone numerous modifications in terms of protocols and surgical instrumentation (Cosci&Luccioli, MISE, CAS, Intralift, Reamer-Mediated TSFE, minimally invasive osteotome SFE, Sinus balloon technique). These techniques are considered safe and predictable, and the most common intra-operative complication reported in the literature is perforation of the Schneiderian membrane.

Some postoperative complications are reported, including sub-antral artery bleeding, hematoma, dehiscence, epistaxis, nasal congestion, infraorbital neurovascular bundle injury, implant migration into the sinus, fistulae, and sinusitis. In the literature, postoperative complications of sinus augmentation surgery appear to be relatively rare compared to intraoperative complications (13).

Perforation of the Schneiderian membrane has been investigated in numerous studies as a factor influencing implant stability. Still, such analyses and evaluations would appear to be much more complex when examining post-operative complications with more limited casuistry (14-16). This short review aims to define the incidence of OACs secondary to sinus augmentation surgery and to define the technique associated with the highest incidence.

MATERIALS AND METHODS

Search strategy

The following short review attempts to answer the questions: "What is the incidence of oroantral communications secondary to sinus lift surgery? Which technique appears to be associated with the greatest risk of this complication?"

By conducting an electronic search on the MEDLINE bibliographic database (Pubmed), 63 articles with a time span from 1994 to 2021 were selected using the following algorithm: "sinus lift " OR "sinus augmentation " OR "sinus graft" OR "maxillary sinus floor elevation" OR "sinus floor augmentation" AND "oro-antral communication" OR "antro-oral communication" OR " oroantral communication" OR "oro-antral fistula" OR "oroantral fistula" OR "oro-sinusal communication" OR "antro-alveolar fistula" OR "fistula" OR "oro-sinusal fistula" OR "sinus-oral fistula" OR "sinus communication" OR "OAF".

Titles and abstracts of the articles were subjected to an initial selection process considering relevance, type of study, and population considered. A hand search was conducted for the resulting studies by analyzing the complete articles and their relevance and adherence to the inclusion and exclusion criteria.

Selection Of Studies

The choice of studies considered fell on cohort studies. Having different purposes than RCTs, CCTs, case series, and case reports, cohort studies provide a direct quantitative measure of the possible complications associated with the interventions examined.

Here we investigated the incidence of postoperative complications during different sinus lift techniques. Specifically, the incidence of oroantral communication was considered. No restrictions were placed on the surgical technique used. The following inclusion criteria were applied for the selection of studies:

-studies reporting data on the incidence of OAC after sinus lift surgery (at least 1 OAC);

-number of patients considered > 10;

-post-operative follow-up;

-absence of systemic and pre-operatory sinus pathologies.

In the same way, the following exclusion criteria were applied:

-systemic pathologies contraindicating surgery or preoperative sinus conditions;

-number of patients ≤ 10;

-absence of data on postoperative complications (incomplete clinical and/or radiographic documentation) concerning AOC;

-no antibiotic treatment prescribed.

Data extraction

The following data were extracted from the selected studies: 1) year of publication, 2) study design, 3) sample size, 4) mean age, 5) number of sinuses treated, 6) technique used, and 7) number of AOC recorded during follow-up.

Risk assessment bias

The Newcastle-Ottawa Scale (NOS) for cohort studies was used to assess the risk of bias in the individual studies considered. This scale includes a questionnaire divided into three categories: selection, comparability, and outcome. The included studies were classified as good, fair, or poor quality.

Data and statistical analysis

The individual incidence was considered to assess the overall incidence of complications and compare the techniques. The overall incidence was calculated by the sum of the total number of complications and patients for each technique. Then the hypothesis test for difference in proportions was applied to determine whether there was a significant difference between techniques. The null hypothesis was that there was no significant difference between the techniques. An alpha significance level of 0.05 was adopted to establish the threshold for statistical significance, and the value of the Z test statistic was obtained.

RESULTS

Description of studies

The electronic search yielded 63 articles. No language restrictions were applied, and only cohort studies were considered, excluding case series, case reports, RCTs, and CCTs. Titles and abstracts were examined using the previously defined inclusion and exclusion criteria.

After thorough analysis, 21 articles were excluded, and 3 studies were included in the qualitative and quantitative data synthesis. The flow chart in Fig. 1 summarizes the study selection process (17-40).

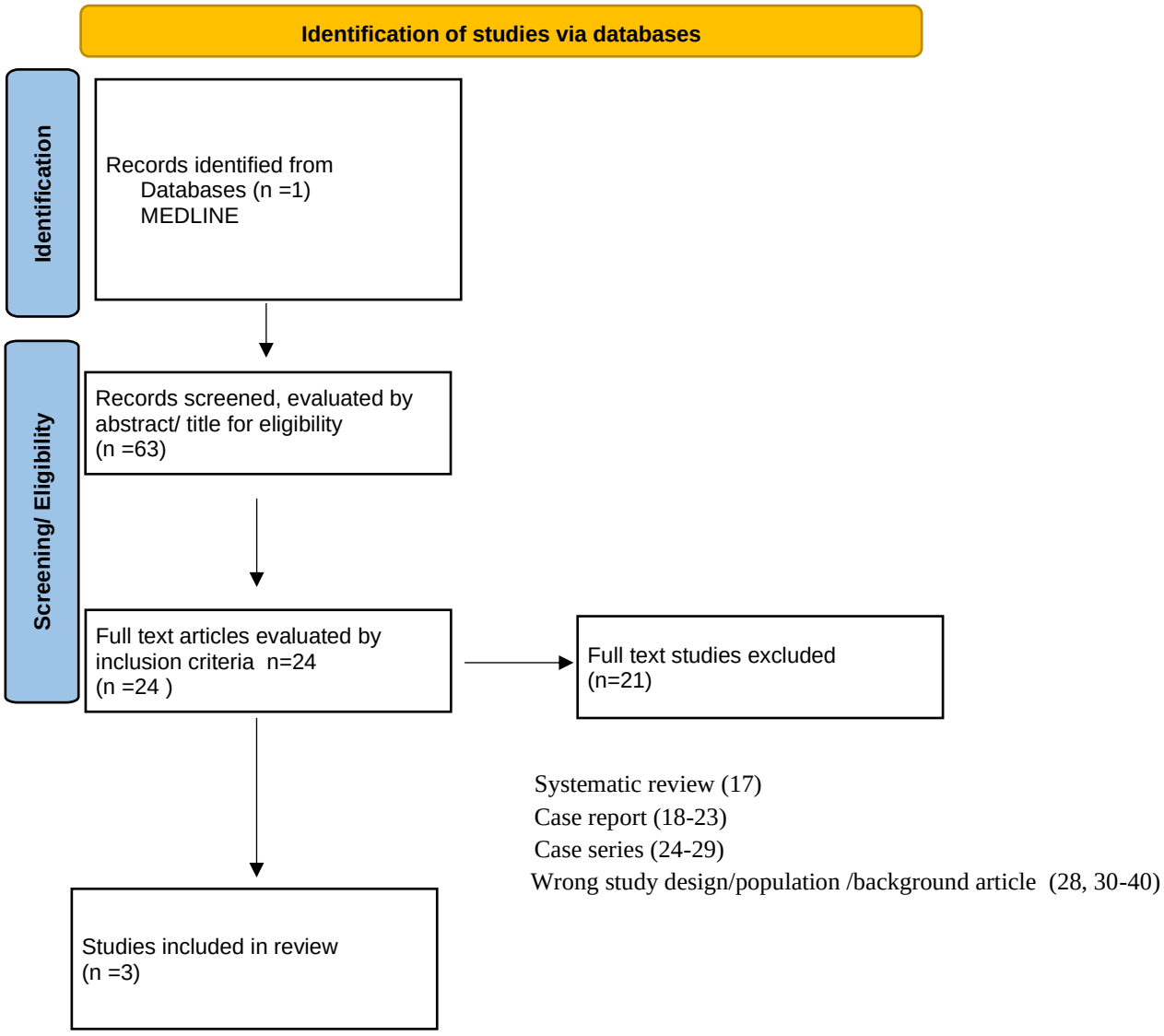

Fig. 1. *Summary of the study selection process.*

One of the studies (40), although falling within the inclusion criteria, was not considered due to a probable bias related to the biomaterial utilized (natural polysaccharides polymers-coated bovine bone, PBB) that could affect the accurate estimation of the incidence of AOC. After the selection process, therefore, 2 studies (38, 39) were analyzed.

Population

The sample size of the studies considered ranged from 116 to a maximum of 430 patients. The total number of patients treated was 546 (283 M and 263 F). The average overall age was 51.9 years. The age ranged from 26 to 84 years. The total number of sinuses treated was 580.

Operative techniques

The sinus augmentation techniques considered in the two studies involved lateral and crestal approaches. In the first study (39), a one-stage lateral elevation technique was performed on patients with 5/3 mm residual alveolar bone height and 6 mm thickness in the bucco-palatal direction. A crestal incision, a vertical release incision at the level of the

canine, and a distal incision at the level of the second/third molar were made, and a full-thickness flap was performed, which, when flipped over, allowed access to the anterolateral wall of the upper jaw.

An osteotomy was performed using low-speed burs with copious sterile saline irrigation. The sinus membrane and the anterolateral and medial walls of the maxillary sinus were carefully lifted from the floor using dedicated curettes. After membrane elevation, the implant sites were then prepared with calibrated low-speed burs specific to the implant system used. The graft material was inserted under the sinus membrane, and the implants were inserted with a torque value of 30 to 50 N/cm.

The graft materials used were a combination of heterologous, homologous, or alloplastic grafts, and the implant diameters ranged from 3.75 to 5.5 mm with lengths from 10 to 13 mm. A total of 81 patients were treated with unilateral techniques, in 35 patients, the operation involved both sinuses.

The second study under analysis considered a unilateral crestal approach in patients with residual bone height ≤ 5mm with contextual insertion of a single implant (38). Sinus access was performed with subtractive techniques using specific drills (Cosci&Luccioli) or by bone compaction using osteotomes (Smart lift technique, Summers' technique). Antibiotic therapy was conducted before and after surgery, and patients were monitored over time at the various follow-ups considered in the studies.

Incidence Of OAC

In the study involving lateral techniques with a total of 151 sinuses and 116 patients, the complication was reported only once with an incidence of 0.8 % (0.6 % based on the number of sinuses treated). Even for crestal techniques for a total of 430 patients and 430 sinuses treated, the presence of an oroantral communication was reported in only one patient, with an incidence of 0.2%.

Risk of bias in included studies

The NOS scores were considered as a rough indicator of the methodological quality of the studies along with other factors, such as the completeness of the reported data. Studies with higher scores were considered to be of good quality, while those with lower scores indicated a potential risk of bias. The two studies were considered both of fair quality.

DISCUSSION

OAC is a pathological pathway connecting the oral cavity and maxillary sinus. Patients with AOC and a developed OAF are prone to acute or chronic sinus infection. OAC complications may occur early after implant placement but rarely long after, and they seldom concern osseointegrated implants (7, 41, 42). It was observed that implant perforation of the Schneiderian membrane is not associated with sinus complications or pathologies, regardless of the extension of the implant protrusion into the sinus (43). There is a lack of clear and defined data in the literature regarding sinus lift procedures.

In the sinus lift group with the lateral approach, the postoperative incidence occurred in only one patient, corresponding to an incidence of 0.8%. In the crestal approach group, on the other hand, there was again only one case of complication, with an incidence of 0.2%. The hypothesis test for difference in proportions was used to determine whether there was a significant difference between the two incidences. The test produced a value of Z =- 0.699. Considering a significance level $\alpha = 0.05$, the value of Z did not reach the critical threshold to reject the null hypothesis. Consequently, the assumption that one sinus-lift technique has a significantly different incidence than the other is not supported. Considering the two techniques and the reported incidences, the overall incidence calculated taking into account complications and total patients is 0.3%.

Limits

This systematic review has several limitations, particularly the presence of confounding factors that could play a substantial role in the development of the complications examined (i.e., patient age, surgeon experience, contextual or delayed insertion of implants, and biological complications).

The search strategy may also have introduced a potential selection bias into the studies, leading to an overestimation of the overall incidences observed, excluding from the search articles that did not explicitly mention AOC as a possible post-operative complication or articles in which no post-operative complications were reported. Limiting the bibliographic coverage to one database (Medline) similarly could affect the representativeness of the review.

CONCLUSIONS

The incidence of AOC, regardless of the technique used, appears to be a relatively rare complication. Depending on the type of technique considered, the incidence ranges reported in the literature vary from 0.2% to 0.8%. However, the trend of greater incidence observed in the lateral approach does not seem statistically supported. The lack of statistical significance could be influenced by various factors and limitations of the present short review, including the sample size. The actual rarity of this complication would necessitate a larger sample size to determine a direct comparison between the techniques. Furthermore, the surgical protocols used, the surgeon's experience, implant management, and intra-operative complications could play an active role in the occurrence of post-operative complications. Further studies are needed to establish a comparison between the techniques.

REFERENCES

1. Iwata E, Hasegawa T, Kobayashi M, et al. Can CT predict the development of oroantral fistula in patients undergoing maxillary third molar removal? *Oral and Maxillofacial Surgery*. 2021;25(1):7-17. doi:https://doi.org/10.1007/s10006-020-00878-z
2. Watzak G, Tepper G, Zechner W, Monov G, Busenlechner D, Watzek G. Bony Press-Fit Closure of Oro-Antral Fistulas: A Technique for Pre-Sinus Lift Repair and Secondary Closure. *Journal of Oral and Maxillofacial Surgery*. 2005;63(9):1288-1294. doi:https://doi.org/10.1016/j.joms.2005.05.299
3. Khandelwal P, Hajira N. Management of Oro-antral Communication and Fistula: Various Surgical Options. *World Journal of Plastic Surgery*. 2017;6(1):3-8.
4. Kiran Kumar Krishanappa S, Prashanti E, Sumanth KN, et al. Interventions for treating oro-antral communications and fistulae due to dental procedures. *Cochrane Database of Systematic Reviews*. 2016. doi:https://doi.org/10.1002/14651858.cd011784.pub2
5. Parvini P, Obreja K, Begic A, et al. Decision-making in closure of oroantral communication and fistula. *International Journal of Implant Dentistry*. 2019;5(1). doi:https://doi.org/10.1186/s40729-019-0165-7
6. Bilginaylar K. The Use of Platelet-Rich Fibrin for Immediate Closure of Acute Oroantral Communications: An Alternative Approach. *Journal of Oral and Maxillofacial Surgery*. 2018;76(2):278-286. doi:https://doi.org/10.1016/j.joms.2017.07.168
7. Nedir R, Nurdin N, Paris M, El Hage M, Abi Najm S, Bischof M. Unusual Etiology and Diagnosis of Oroantral Communication due to Late Implant Failure. *Case Reports in Dentistry*. 2017;2017(1):1-5. doi:https://doi.org/10.1155/2017/2595036
8. Borgonovo AE, Berardinelli FV, Favale M, Maiorana C. Surgical Options In Oroantral Fistula Treatment. *The Open Dentistry Journal*. 2012;6(1):94-98. doi:https://doi.org/10.2174/1874210601206010094
9. Procacci P, Alfonsi F, Tonelli P, et al. Surgical Treatment of Oroantral Communications. *Journal of Craniofacial Surgery*. 2016;27(5):1190-1196. doi:https://doi.org/10.1097/scs.0000000000002706
10. Demetoglu U, Ocak H, Bilge S. Closure of Oroantral Communication With Plasma-Rich Fibrin Membrane. *J Craniofac Surg*. 2018;29(4):e367-e370. doi:10.1097/SCS.0000000000004360
11. Scarano A, Bugea C, Leo L, Santos de Oliveira P, Lorusso F. Autologous Platelet Gel (APG): A Preliminary Evaluation of the Mechanical Properties after Activation with Autologous Thrombin and Calcium Chloride. *Materials*. 2021;14(14):3941. doi:https://doi.org/10.3390/ma14143941
12. Esposito M, Grusovin MG, Chew YS, Coulthard P, Worthington HV. Interventions for replacing missing teeth: 1-versus 2-stage implant placement. *Cochrane Database of Systematic Reviews*. Published online July 8, 2009. doi:https://doi.org/10.1002/14651858.cd006698.pub2
13. Stacchi C, Andolsek F, Berton F, Perinetti G, Navarra C, Di Lenarda R. Intraoperative Complications During Sinus Floor Elevation with Lateral Approach: A Systematic Review. *The International Journal of Oral & Maxillofacial Implants*. 2017;32(3):e107-e118. doi:https://doi.org/10.11607/jomi.4884
14. Al-Moraissi E, Elsharkawy A, Abotaleb B, Alkebsi K, Al-Motwakel H. Does intraoperative perforation of Schneiderian membrane during sinus lift surgery cause an increased the risk of implants failure?: A systematic review and meta regression analysis. *Clinical Implant Dentistry and Related Research*. 2018;20(5):882-889. doi:https://doi.org/10.1111/cid.12660
15. Scarano A, Cholakis A, Piattelli A. Histologic Evaluation of Sinus Grafting Materials After Peri-implantitis–Induced Failure: A Case Series. *The International Journal of Oral & Maxillofacial Implants*. 2017;32(2):e36-e75. doi:https://doi.org/10.11607/jomi.5303
16. Huang JQ, Hu CQ, Xia X, Guo SG, Gong JM, Wei HW. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2020;38(6):667-671. doi:10.7518/hxkq.2020.06.011
17. Ghasemi S, Fotouhi A, Moslemi N, Chinipardaz Z, Kolahi J, Paknejad M. Intra- and Postoperative Complications of Lateral Maxillary Sinus Augmentation in Smokers vs Nonsmokers: A Systematic Review and Meta-Analysis. *The*

International Journal of Oral & Maxillofacial Implants. 2017;32(4):759-767. doi:https://doi.org/10.11607/jomi.5364

18. DePoi R, Vanchit J, Y Paez de Mendoza, C, Gossweiler MK. Development of an oro-antral fistula following sinus elevation surgery: a case report on management using platelet-rich plasma. *PubMed*. 2008;86(4):10-16.
19. Jo KH, Yoon KH, Cheong JK, Jeon IS. Postoperative Perforation of the Schneiderian Membrane in Maxillary Sinus Augmentation: A Case Report. *Journal of Oral Implantology*. 2014;40(S1):375-379. doi:https://doi.org/10.1563/aaid-joi-d-11-00201
20. Stasko SB, Kolhatkar S, Bhola M. Sinus Floor Elevation and Implant Placement via the Crestal and Lateral Approach in Patients With Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome: Report of Two Cases. *Clinical advances in periodontics*. 2014;4(4):217-225. doi:https://doi.org/10.1902/cap.2013.120092
21. Park JS, Chul Kim B, Choi B, Lee J. Facial skin fistula as a postoperative complication related to maxillary sinus grafting: A case report. *Quintessence international*. 2015;46(2):145-148. doi:https://doi.org/10.3290/j.qi.a32640
22. Han YS. Postoperative Maxillary Cyst Developing After Sinus Augmentation for Dental Implants. *Implant Dentistry*. 2018;27(2):1. doi:https://doi.org/10.1097/id.0000000000000752
23. Florio S, Suzuki T, Cho SC. The Palatal Window for Treating an Incompletely Augmented Maxillary Sinus. *Implant Dent*. 2017;26(2):328-331. doi:10.1097/ID.0000000000000563
24. Engelke W, Deckwer I. Endoscopically controlled sinus floor augmentation. A preliminary report. *Clinical Oral Implants Research*. 1997;8(6):527-531. doi:https://doi.org/10.1034/j.1600-0501.1997.080612.x
25. Anavi Y, Allon DM, Avishai G, Calderon S. Complications of maxillary sinus augmentations in a selective series of patients. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2008;106(1):34-38. doi:https://doi.org/10.1016/j.tripleo.2007.09.021
26. Khoury F, Javed F, Romanos G. Sinus Augmentation Failure and Postoperative Infections Associated with Prophylactic Clindamycin Therapy: An Observational Case Series. *The International Journal of Oral & Maxillofacial Implants*. 2018;33(5):1136-1139. doi:https://doi.org/10.11607/jomi.6517
27. Giovannetti F, Raponi I, Priore P, Macciocchi A, Barbera G, Valentini V. Minimally-Invasive Endoscopic-Assisted Sinus Augmentation. *Journal of Craniofacial Surgery*. 2019;30(4):e359-e362. doi:https://doi.org/10.1097/scs.0000000000005365
28. Kim YK, Kim SG. A Retrospective Analysis of the Retreatment of Failed Sinus Bone Grafts. *Implant Dentistry*. 2016;25(3):450-454. doi:https://doi.org/10.1097/ID.0000000000000420
29. Marin S, Kirnbauer B, Rugani P, Payer M, Jakse N. Potential risk factors for maxillary sinus membrane perforation and treatment outcome analysis. *Clinical Implant Dentistry and Related Research*. 2018;21(1):66-72. doi:https://doi.org/10.1111/cid.12699
30. Davis BR, Sándor GK. Use of fibrin glue in maxillofacial surgery. *J Otolaryngol*. 1998;27(2):107-112.
31. Liversedge RL, Wong K. Use of the buccal fat pad in maxillary and sinus grafting of the severely atrophic maxilla preparatory to implant reconstruction of the partially or completely edentulous patient: technical note. *PubMed*. 2002;17(3):424-428.
32. Hinze M, Vrielinck L, Thalmair T, Wachtel H, Bolz W. Zygomatic Implant Placement in Conjunction with Sinus Bone Grafting: The "Extended Sinus Elevation Technique." A Case-Cohort Study. *The International Journal of Oral & Maxillofacial Implants*. 2013;28(6):e376-e385. doi:https://doi.org/10.11607/jomi.te18
33. Giovannetti F, Priore P, Raponi I, Valentini V. Endoscopic Sinus Surgery in Sinus-Oral Pathology. *Journal of Craniofacial Surgery*. 2014;25(3):991-994. doi:https://doi.org/10.1097/scs.0000000000000608
34. Manor Y, Anavi Y, Gershonovitch R, Lorean A, Mijiritsky E. Complications and Management of Implants Migrated into the Maxillary Sinus. *The International Journal of Periodontics & Restorative Dentistry*. 2018;38(6):e112-e118. doi:https://doi.org/10.11607/prd.3328
35. Zimbler MS, Lebowitz RA, Glickman R, Brecht LE, Jacobs J. Antral Augmentation, Osseointegration, and Sinusitis: The Otolaryngologist's Perspective. *Am J Rhinol Ekim*. 1998;12(5):311-316. doi:https://doi.org/10.2500/105065898780182381
36. Kraut RA. Maxillary Sinus Augmentation: Concerns and Preparedness. *Implant Dentistry*. 2011;20(6):397. doi:https://doi.org/10.1097/id.0b013e3182372683
37. Kim SW, Lee IH, Kim SW, Kim DH. Points to consider before the insertion of maxillary implants: the otolaryngologist's perspective. *Journal of Periodontal & Implant Science*. 2019;49(6):346-354. doi:https://doi.org/10.5051/jpis.2019.49.6.346
38. Shi JY, Gu YX, Zhuang LF, Lai HC. Survival of Implants Using the Osteotome Technique With or Without Grafting in the Posterior Maxilla: A Systematic Review. *Int J Oral Maxillofac Implants*. 2016;31(5):1077-1088. doi:10.11607/jomi.4321
39. Chirilă L, Rotaru C, Filipov I, Săndulescu M. Management of acute maxillary sinusitis after sinus bone grafting procedures with simultaneous dental implants placement – a retrospective study. *BMC Infectious Diseases*. 2016;16(S1). doi:https://doi.org/10.1186/s12879-016-1398-1
40. Ben-Dor A, Gabay E, Horwitz J, Zigdon-Giladi H, Machtei E, Mayer Y. Severe Complications Following Maxillary Sinus Augmentation Using Poly L-lactide-co-ε-caprolactone–Coated Bovine Bone: A Retrospective Study. *The International Journal of Oral & Maxillofacial Implants*. 2021;36(5):1024-1031. doi:https://doi.org/10.11607/jomi.8792

41. Scarano A, Pecora G, Piattelli M, Piattelli A. Osseointegration in a Sinus Augmented With Bovine Porous Bone Mineral: Histological Results in an Implant Retrieved 4 Years After Insertion. A Case Report. *Journal of Periodontology*. 2004;75(8):1161-1166. doi:https://doi.org/10.1902/jop.2004.75.8.1161
42. Al-Moraissi E, Elsharkawy A, Abotaleb B, Alkebsi K, Al-Motwakel H. Does intraoperative perforation of Schneiderian membrane during sinus lift surgery causes an increased the risk of implants failure?: A systematic review and meta regression analysis. *Clin Implant Dent Relat Res*. 2018;20(5):882-889. doi:10.1111/cid.12660
43. Jung JH, Choi BH, Zhu SJ, et al. The effects of exposing dental implants to the maxillary sinus cavity on sinus complications. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2006;102(5):602-605. doi:https://doi.org/10.1016/j.tripleo.2005.10.061

Review

DENTAL IMPLANT PLACEMENT IN HYPERDENSE BONE AREA OF THE JAW: A NARRATIVE MINIREVIEW

V. Lofrano[1], S. Cardillo[1], D. Ravot Licheri[1], C. Bugea[1*] and A. Lanciani[1]

[1]Department of Innovative Technologies in Medicine & Dentistry, University of Chieti-Pescara, Chieti, Italy

[*]*Correspondence to*:
Calogero Bugea, DDS
Department of Innovative Technologies in Medicine & Dentistry,
University of Chieti-Pescara,
Chieti, Italy
e-mail: calogerobugea@yahoo.it

ABSTRACT

Dental implant placement has become one of the safest surgical procedures in oral surgery; when the jawbone is enough in height and width, dental implant placement is easy, and implant primary stability is predictable. However, one of the most important elements of success in dental implants is primarily bone density. Bone tissue quality can vary depending on patient health, previous tooth extraction, or odontogenic or non-odontogenic lesions in the jaws, which should be removed before dental implant placement into edentulous areas. Among lesions of the jaw bones, the radiopaque ones are less frequent and less studied. This mini literature review aims to evaluate the reliability of dental implant placement in the hyperdense bone area of the jaws, avoiding, when possible, lesion removal. Material and methods: the research was performed manually on PubMed, Google Scholar, and Scopus databases by typing the exact search string; among 114 scientific articles, only 8 matched the eligibility criteria. These studies show how radiopaque lesions should always be investigated to understand their origins: radiological investigation and eventual clinical symptoms reported by the patient should be considered for differential diagnosis; anyway, according to these reported cases, implant placement can be successfully performed also when these types of lesions are present, even if further research is needed to develop new and specific surgical protocols.

KEYWORDS: *hyperdense lesions, dental implants, jawbone, idiopathic osteosclerosis, condensing osteitis, cemento-osseous-dysplasia*

INTRODUCTION

Radiolucent lesions of the jaws, such as periapical cysts or odontogenic tumors, correspond to 80% of bony lesions and are widely described in the literature. Therefore, many clinical protocols have been used from diagnosis to treatment (1). Otherwise, radiopaque lesions are less investigated and outlined in the literature. They are often incidental findings in radiography or computed tomography exams. They can occur in different regions of the jaws, and no treatment is required if they are located in areas of no surgical interest (1, 2).

Literature is poor in guidelines and protocols regarding diagnosing and managing hyperdense lesions. They are usually well-defined unilocular or multilocular masses and represent a benign or inflammatory process. Moreover, dental implant placement in these areas is often problematic, and the scientific literature on intra-operative and post-operative complications is unclear (2, 3).

Received: 10 May 2022
Accepted: 02 June 2022

Many types of radiopaque lesions described in the literature can be related to benign bone and cartilage tumors and mesenchymal odontogenic tumors (4). Abnormal radiopacities could often be found during CBCT exams accidentally; those could be more often related to remaining endodontic materials, remaining dental roots after a complicated extraction, and fractured bone pieces. Less commonly, these findings could be related to dental elements and other odontogenic tissue, moving the diagnosis to different types of pathological lesions, such as odontogenic and non-odontogenic tumors and benign or malignant tumors (5, 6).

The presence of radiopaque or radiolucent lesions of the bone could make the placement of dental implants challenging. In these cases, it is often needed to wait for the healing of the interested area after their surgical removal: bone regeneration requires time, and it takes at least 3-4 months to have good bone quality to place an implant with an acceptable primary stability (7-9). But is surgical resection always needed when a radiopaque lesion occurs?

First, understanding its nature is the most crucial thing when a radiopaque lesion is found during the radiographical investigation. Radiologists play a vital role in identifying and diagnosing mandibular and maxilla lesions. CBCT is the gold standard imaging modality to detect information about the characteristics of the lesions and their anatomical boundaries in the maxillofacial district (10).

The relationship of densely sclerotic lesions to adjacent teeth and cortical bone and the assessment of lesion margins often allows the clinician to arrive at a single diagnosis. Moreover, a final diagnosis can frequently be made to assess extragnathic bone findings when these lesions occur as a systematic disorder sign (11, 12). Usually, a radiopaque lesion can be described as a densely sclerotic, ground glass, or mixed lytic-sclerotic, with each category representing different lesions that can help in differential diagnosis. This is a general guide to the diagnostic process, as many lesions demonstrate considerable radiologic variability (11).

Similar clinical and radiographical manifestations can be seen when densely sclerotic lesions occur. They are usually benign with a homogeneous radiopaque pattern, and among these, we can find:

- *Idiopathic osteosclerosis (IO)* can be described as a well-defined, more radiopaque area in cancellous bone and can be associated or not to dental elements; when associated with teeth, it can be found in the periapical or interradicular region, especially lower molars. The lesion can present an irregular or rounded shape, measuring from 1 to 3-4 mm. Its etiology is unknown; inflammation or trauma should be considered. Normally, lesions do not grow in size but decrease. Patients do not show symptoms or clinical signs. No biopsy is needed, and the diagnosis is based on radiological presentation (6, 11).
- *Condensing osteitis (CO)* is a radiopaque asymptomatic lesion usually localized in the posterior region of the mandible in the root region of the tooth. Its etiology is linked to a persistent apical infection due to tooth bacterial invasion or bone exposure to necrotic substances such as the material used for root canal treatment. The necrosis of surrounding soft and periodontal tissue near the root can lead to bone remodeling with excess bone matrix deposition, resulting in a more dense bone area (13, 14).
- *Cemento-Osseus-Dysplasia (COD)* describes a spectrum of idiopathic odontogenic fibro-osseous lesions in which a mixture of cementum, bone, and fibrous connective tissue replaces normal bone. There are subtypes based on the affected region and diffusion: periapical, focal, or florid. Periapical COD is usually described adjacent to the roots of vital teeth in the anterior sextant of the mandible. Focal COD occurs away from the periapical region, in the posterior jaw. Florid COD shows multifocal lesions affecting multiple regions of the mouth. COD has a strong female predilection in the 4th and 5th decades of life. A narrow radiolucent halo at imaging distinguishes COD from condensing osteitis and idiopathic osteosclerosis. However, at early stages, COD can be confused for a periapical inflammatory lesion (11, 15, 16).

MATERIALS AND METHODS

Literature research has been performed, including PubMed, Google Scholar, and Scopus databases typing the same research string adapted according to their respective advanced research criteria: "*Radiopaque Lesions OR Hyperdense Jaws Lesions OR Cemento-Osseus Dysplasia OR Idiopathic Osteosclerosis OR Condensing Osteitis AND Dental Implant*". A total of 114 scientific articles were found.

The inclusion criteria were case reports, case series, or RCTs related to human cases of dental implant placement in hyperdense bone areas.

The exclusion criteria were: studies containing keywords but not relevant to the research topic, articles that included radiopaque odontogenic tumors such as odontoma, cementoblastoma, osteoid osteoma, articles that did not include a description of clinical cases of dental implants placement in the lesion area, articles not available in full-text, articles not available in English. According to these criteria, only 8 articles were included in this review.

RESULTS

A total of 114 articles was found published from 1991 to 2021 (30 on PubMed, 67 on Google Scholar, and 17 on Scopus, respectively): doubles, articles that did not include description of clinical cases and articles not written in English were excluded for a total of 94 remanent studies; only 8 articles were electable for this review published from 2018 to 2021. Among these, 6 reported cases of Florid-Cemento-Osseus-Dysplasia (FCOD) and two reported Condensing Osteitis (CO). In 2 articles, dental implant placement was scheduled without involving the radiopaque mass, and the first decided to perform the lesion removal plus Guided Bone Regeneration (GBR) before implant surgery at 6 months with a follow-up of 18 months after function (3, 13). Alqahtani et al. reported a dental basal implant placement in a CO lesion after the tooth extraction; no follow-up is available (17, 18). All the remaining articles reported cases of dental implant placement directly in the radiopaque areas, and only 4 of these (19-22) reported respectively 2, 8, and 16 years of follow-up after surgery and a case of osteomyelitis after surgery. The most recent study reported a case of dental implant placement in the radiopaque lesion describing a new 3-step surgery protocol (23).

DISCUSSION

The management of radiopaque lesions is always confusing and unclear for the clinician. The studies included in this mini-review reported different approaches. Treatment of this kind of lesion is often “wait and see”, avoiding the removal when there are no evident signs or symptoms. The avascular nature of these lesions is often related to a major risk of bone infection, resulting in necrosis and osteomyelitis (20). Implant placement in these areas is rarely performed because the lack of vessels and marrow bone could lead to unsuccessful osseointegration. The exposure of lesion tissue during extraction of the involved tooth or lesion removal or implant bed preparation could lead to a bacterial invasion and, consequently, osteomyelitis (21). According to the articles included in this mini-review, the management could be differentiated into:

- a more conservative approach, which provides the dental implant placement in a safe area near the radiopaque mass without involving it,
- a second option is not removing the lesion and placing the dental implant directly into the radiopaque mass,
- and finally, a more invasive approach that removes the entire lesion and, if necessary, a GBR before implant placement.

Esfahanizadeh et al. (3) describe a case of dental implant placement near a hyperdense bone area of the mandible identified as a Florid-Cemento-Osseus-Dysplasia (FCOD). In this case, Esfahanizadeh et al. decided to perform dental implant insertion without removing the FCOD lesion: two dental implants were placed respectively on the mesial and the distal edge of the lesion. Orthopantomography was taken at 12 and 18 months after surgery. The other studies describe two cases of Condensing Osteitis (CO) associated with erupted teeth. Rass et al. (13) opted for a less conservative surgery: the mandibular left second molar (4.5) was extracted together with the CO lesion, and the wide bone defect was treated with a Guided Bone Regeneration using a bone graft and a resorbable membrane; two dental implants were placed after 6 months, and no follow-up controls were available. Alqahtani et al. (17) reported a case of CO associated with a first mandibular molar in which the involved tooth was extracted to immediately place a basal implant without removing the radiopaque lesion.

In all these studies, clinicians opted not to involve the radiopaque mass during dental implant insertion. This choice can be explained by the results shown by other studies, such as Gerlach et al. (24), in which implant failure is reported following implant placement in patients with FCOD: patients returned with swelling, pain, and implant mobility after only 26 months of function. The FCOD lesion was grown and involved all the surrounding implant bone. The moving implant and lesion were removed, followed by histological exams that confirmed FCOD diagnosis.

Another approach could involve the removal of the lesion before the implantation procedure: the surgical procedure is recommended for those patients with pain, swelling, and deformities; otherwise, no treatment is required since these lesions usually remain non-aggressive (4, 11). Moreover, when surgical removal is performed, the avascular nature of the lesion contributes to susceptibility to severe infection, bone sequestration, and osteomyelitis (25), which do not lead to adequate bone healing. In addition, after the surgical removal, a GBR with bone graft and membrane is often needed to replace the absent bone volume. Alqahtani et al. (13) show how this procedure may lead to a successful implant placement after 6 months, but sadly, there is no further information about follow-up and survival after function.

A more conservative approach includes no treatment for the radiopaque mass and implant placement in the adjacent area, even very close to the lesion (3, 17). Esfahanizadeh et al. (3) show an 18-month follow-up in a patient with FCOD

where two implants were placed mesially and distally to the lesion without invading it. A contralateral edentulous area where the same lesion was spotted was not treated because a similar implant placement could not be performed without involving the radiopaque mass. Alqahtani et al. (17) show even immediate implant placement without removing the lesion, but unfortunately, there is no follow-up.

Other studies show dental implant placement involving the affected bone area: Adnot et al. (19) described a dental implant placement in an affected bone area after ostectomy treatment to adjust crestal edges. The authors showed perfect dental implant integration after 2 years of follow-up. They underlined specific recommendations during surgical and prosthetic procedures, such as drilling under abundant irrigation and delayed implant loading till dental implant osseointegration is obtained. Perez et al. (23) describe how to manage safe dental implant placement in COD lesions instead. The first step includes a drilling sequence under abundant irrigation, rinsing with betadine, hermetic wound closure, and a prescription of antibiotic therapy. The second step includes dental implant placement after 3 weeks. The third and last step includes the insertion of the healing abutment ed during the drilling sequence; this risk is higher in COD lesions made of avascular tissue. Moreover, delaying implant placement helps reduce dental implant surface contamination, placing the implant after 3 weeks during proliferative after 3 months.

The biological rationale of this protocol is to reduce bone necrosis risk due to the high-temperature reach phase with woven bone and fibrous matrix formation. Shadid et al. (20) show a case of dental implant placement in an FCOD lesion with 8 years of follow-up: classic 2-stage surgery was performed by placing implants directly in the hyperdense tissue. The patient underwent radiographic controls immediately after surgery, after one year, and every 2 years; after 8 years, dental implants showed perfect integration without bone problems. The FCOD lesion was not removed because it was asymptomatic, and it would be difficult for the clinician to discern healthy tissue from diseased tissue with the necessity of bone-guided regeneration after removal. Otherwise, FCOD lesions are made of tissue with poor vessel presence, which could lead to poor healing and osteointegration process, risk of infection, and risk of bone fracture, depending on their dimensions.

When the clinician decides to preserve the lesion, it is important to insert the patient in a maintenance protocol of hygiene and radiographic exams to highlight any changes. Park et al. (21) reported the longest follow-up of a dental implant placed into an FCOD lesion. After 16 years, implants were removed due to periimplantitis, and a micro-CT analysis was performed. The histological investigation showed how FCOD tissue is similar to dense bone, with no gap between the implant and FCOD tissue with good direct contact, no soft tissue interposition, and no blood vessels. The conclusions of this study led the clinicians to affirm that dental implant placement in FCOD tissue could be performed after endodontic and periodontal infection resolution and after complete calcification of the FCOD lesion, delaying surgery in the late stages of lesion maturation. On the other hand, Shin et al. (22) showed all the complications of placing dental implants directly into the avascular lesion: a case of osteomyelitis after dental implant placement due to drilling sequence without good cooling plus lack of blood vessels, which led to bone necrosis.

CONCLUSIONS

Implant placement in the jawbone area in which radiopaque masses are spotted can be performed following a conservative surgical procedure without consequences. When the radiopaque mass is not invaded, implant success can be reached normally. For those benign lesions, no treatment is required unless the patient complains symptoms such as pain and swelling or facial deformities. Implant placement directly into the radiopaque area is possible but not risk-free. A good drilling protocol with abundant irrigation is required in order to prevent bone necrosis as well as delaying implant loading when osteointegration is reached totally. Once diagnosis is cleared follow-up with regular radiographic exams is needed to control any possible modifications. Further studies are necessary in order to understand how to manage these cases, how to improve and facilitate differential diagnosis and how to ease implant placement even when radiopaque masses are present.

REFERENCES

1. Mortazavi H, Safi Y, Rahmani S, Rezaeifar K. Oral Hard Tissue Lesions: A Radiographic Diagnostic Decision Tree. *Open Access Macedonian Journal of Medical Sciences*. 2020;8(F):180-196. doi:https://doi.org/10.3889/oamjms.2020.4722
2. Mortazavi H, Baharvand M, Rahmani S, Jafari S, Parvaei P. Radiolucent rim as a possible diagnostic aid for differentiating jaw lesions. *Imaging Sci Dent*. 2015;45(4):253-261. doi:10.5624/isd.2015.45.4.253
3. Esfahanizadeh N, Yousefi H. Successful Implant Placement in a Case of Florid Cemento-Osseous Dysplasia: A Case Report and Literature Review. *Journal of Oral Implantology*. 2018;44(4):275-279. doi:https://doi.org/10.1563/aaid-joi-

d-17-00140

4. Silva BSF, Bueno MR, Yamamoto-Silva FP, et al. Differential diagnosis and clinical management of periapical radiopaque/hyperdense jaw lesions. *Brazilian Oral Research*. 2017;31. doi:https://doi.org/10.1590/1807-3107bor-2017.vol31.0052
5. Marzook HAM, Yousef EA, Elgendy AA. Endodontic remnants are found more than other radiopacities in proposed implant sites. *International Journal of Implant Dentistry*. 2021;7(1). doi:https://doi.org/10.1186/s40729-021-00307-0
6. Van Hoe S, Bladt O, Van Der Steen K, Van den Eynde H. Sclerotic Lesions of the Jaw: A Pictorial Review. *Journal of the Belgian Society of Radiology*. 2021;105(1). doi:https://doi.org/10.5334/jbsr.2208
7. Araújo MG, Lindhe J. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. *Journal of Clinical Periodontology*. 2005;32(2):212-218. doi:https://doi.org/10.1111/j.1600-051X.2005.00642.x
8. Di Dio M, De Luca M, Cammarata L, Pierazzi G. Bone regeneration after removal of a mandibular cyst and following prosthetic rehabilitation with implants. Case report. *Minerva Stomatol*. 2005;54(6):373-378.
9. Roffi A, Filardo G, Kon E, Marcacci M. Does PRP enhance bone integration with grafts, graft substitutes, or implants? A systematic review. *BMC Musculoskelet Disord*. 2013;14:330. doi:10.1186/1471-2474-14-330
10. Buch K. Invited Commentary: Differential Diagnosis for Radiopaque Jaw Lesions—An Algorithmic Approach. RadioGraphics. 2021;41(4):210034. doi:https://doi.org/10.1148/rg.2021210034
11. Holmes KR, Holmes RD, Martin M, Murray N. Practical Approach to Radiopaque Jaw Lesions. *RadioGraphics*. 2021;41(4):200187. doi:https://doi.org/10.1148/rg.2021200187
12. Holmes KR, Holmes RD, Martin M, Murray N. Practical Approach to Radiopaque Jaw Lesions. *RadioGraphics*. 2021;41(4):200187. doi:https://doi.org/10.1148/rg.2021200187
13. Rass MA. Interim endodontic therapy for alveolar socket bone regeneration of infected hopeless teeth prior to implant therapy. *J Oral Implantol*. 2010;36(1):37-59. doi:10.1563/AAID-JOI-D-09-00040
14. Green TL, Walton RE, Clark JM, Maixner D. Histologic Examination of Condensing Osteitis in Cadaver Specimens. *Journal of Endodontics*. 2013;39(8):977-979. doi:https://doi.org/10.1016/j.joen.2013.02.002
15. Alsufyani NA, Lam EWN. Osseous (cemento-osseous) dysplasia of the jaws: clinical and radiographic analysis. *Journal (Canadian Dental Association)*. 2011;77:b70.
16. MacDonald-Jankowski D. Focal cemento-osseous dysplasia: a systematic review. *Dentomaxillofacial Radiology*. 2008;37(6):350-360. doi:https://doi.org/10.1259/dmfr/31641295
17. Alqahtani F. Implant Treatment for a Patient With Large Condensing Osteitis: Case Report. *J Oral Implantol*. 2020;46(3):249-252. doi:10.1563/aaid-joi-D-19-00306
18. Patel K, Madan S, Mehta D, Shah SP, Trivedi V, Seta H. Basal Implants: An Asset for Rehabilitation of Atrophied Resorbed Maxillary and Mandibular Jaw - A Prospective Study. *Ann Maxillofac Surg*. 2021;11(1):64-69. doi:10.4103/ams.ams_446_20
19. Adnot J, Moizan H, Trost O. Dental implants in a patient with left mandibular fibrous dysplasia: Two-year outcomes on the normal and affected sides. *Journal of Stomatology Oral and Maxillofacial Surgery*. 2019;120(6):575-578. doi:https://doi.org/10.1016/j.jormas.2019.02.005
20. Shadid R, Kujan O. Success of Dental Implant Osseointegration in a Florid Cemento-Osseous Dysplasia: A Case Report with 8-Year Follow-Up. *Clinics and Practice*. 2020;10(3):1281. doi:https://doi.org/10.4081/cp.2020.1281
21. Park WB, Han JY, Jang J, Kang K, Kang P. Long-Term Implant Survivability of an Implant Having Direct Contact with Cementum-Like Tissue in a Preexisting Mandibular Intraosseous Lesion with a 16-Year Longitudinal Follow-up. *The International Journal of Periodontics & Restorative Dentistry*. 2019;39(6):895-902. doi:https://doi.org/10.11607/prd.4432
22. Shin HS, Kim BC, Lim HJ, Jo SY, Lee J. Chronic osteomyelitis induced by the placement of dental implants on cemento-osseous dysplasia. *British Journal of Oral and Maxillofacial Surgery*. 2019;57(3):268-270. doi:https://doi.org/10.1016/j.bjoms.2019.01.014
23. Perez A, Maman A, Donna ED, Lombardi T. Implant Placement in a Cemento-Osseous Dysplasia: A case report. *Discussion of Clinical Cases*. 2021;8(2):6. doi:https://doi.org/10.5430/dcc.v8n2p6
24. Gerlach RC, Dixon DR, Goksel T, Castle JT, Henry WA. Case presentation of florid cemento-osseous dysplasia with concomitant cemento-ossifying fibroma discovered during implant explantation. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2013;115(3):e44-e52. doi:https://doi.org/10.1016/j.oooo.2012.05.020
25. de Santana Sarmento DJ, de Brito Monteiro, BV, Costa de Medeiros, AM, Dantas da Silveira EJ. Severe florid cemento-osseous dysplasia: a case report treated conservatively and literature review. 2012;17(1):43-46. doi:https://doi.org/10.1007/s10006-012-0314-0