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Regeneration of combined severe periodontal defects and vertical ridge defects using recombinant human platelet-derived growth factor-BB: A case series

KEYWORDS
case report/series, complications, growth factors, guided bone regeneration, surgical

ABSTRACT
Dental implants are a reliable treatment option for restoring missing teeth, but adequate bone quantity and quality are crucial for success. This case series presents four cases treated by different clinicians, all following very similar concepts for combined periodontal and vertical ridge augmentation using recombinant human platelet-derived growth factor-BB. All cases involved a severe periodontal defect requiring either extraction of the adjacent tooth or periodontal regeneration. Different bone grafts and membrane types were utilised. Although true periodontal regeneration cannot be said categorically to have occurred due to a lack of histological evidence, the clinical and radiographic findings suggest almost complete bone fill in all cases. This case series demonstrates that combined periodontal and vertical ridge augmentation using recombinant human platelet-derived growth factor-BB could be successful, but proper case selection and patient preparation for the possibility of multiple surgical procedures are recommended.

Conflict-of-interest statement: *At the time of preparing this manuscript, Dr Saleh was a clinical advisor for Lynch Biologics, Franklin, TN, USA. The other authors declare that they have no conflicts of interest relating to this study.*

Introduction

Dental implants are considered a reliable treatment option for restoring missing teeth. Successful implant treatment requires adequate bone quantity and quality. Ridge volume is one of the most significant criteria for achieving aesthetic success with implant-supported restorations, particularly in the aesthetic zone.[1] Patients with atrophied ridges often require hard and/or soft tissue augmentation prior to implant placement.[2]

Vertical alveolar ridge defects are considered challenging since they are usually 3D, one-wall defects often accompanied by collapsed soft tissue.[3] This clinical scenario regularly results in heightened technique sensitivity and numerous intra- and postoperative complications. Crafting aesthetic and functional prostheses in such cases poses considerable challenges and requires multiple surgical procedures.[1-3] Additionally, flap vascularisation and increased wound dehiscence due to extensive soft tissue mobilisation make soft tissue augmentation essential alongside bone augmentation, particularly in significant vertical defects.[2] Regardless of the technique employed, successful regeneration relies on four key principles: primary wound closure, angiogenesis, space maintenance and wound stability.[4-6]

Several other factors influence the expected healing dynamics following guided bone regeneration (GBR).[7,8] One of these is the periodontal health of the adjacent teeth and their interproximal bone level. Reduced proximal bone height may compromise the outcome of alveolar ridge augmentation; thus, attempting to regenerate periodontal defects while performing ridge augmentation is rather challenging and requires a proper technique, high-level surgical skills and selection of appropriate biomaterials.[8,9] Regeneration of periodontal intrabony defects has high predictability that enables long-term maintenance of severely compromised teeth in stage III and IV periodontitis.[10] Over the years, the introduction of novel, biologically guided surgical approaches and biomaterials has resulted in a continuous expansion of indications in terms of the severity and morphology of defects.[11,12]

Recombinant human platelet-derived growth factor-BB (rhPDGF-BB) has potent biological effects on chemotaxis and mesenchymal cell migration; it upregulates vascular endothelial growth factor (VEGF) expression and supports angiogenesis.[9] A case report showed favourable clinical outcomes for combined severe periodontal defects and vertical ridge defects using a combination of GBR and rhPDGF-BB.[8] It was hypothesised that such a protocol might be suitable for further implementation for the regeneration of combined severe periodontal defects and vertical ridge defects, and might enable recovery of the lost 3D architecture in such extreme cases.[8,13] Hence, the present article aims to outline different cases involving the treatment of severe periodontal defects adjacent to vertical ridge defects by different clinicians.

Case 1

A healthy 55-year-old man presented in a private practice setting (Budapest, Hungary; primary operator IU) with a failing single-tooth implant in the maxillary left central incisor site that had been placed 10 years earlier, immediately after tooth extraction. Clinical examination revealed deep probing depth (> 15 mm) and bleeding and suppuration on probing; severe peri-implant bone loss was visible on the periapical radiograph. The implant was removed and the maxillary left lateral incisor was retained (Fig 1a and b). Four months after implant removal, the patient had a severe, combined ridge defect (Seibert Class III) (Fig 1c and d).[14] A full-thickness safety flap[15] was elevated from the mesial aspect of the maxillary right canine to the left second premolar (Fig 1e). A decision was made to perform periodontal regeneration and save the maxillary left lateral incisor after thorough debridement of the mesial root surface.

A perforated, non-resorbable, titanium-reinforced, high-density polytetrafluoroethylene (PTFE) barrier membrane (RPM, Osteogenics Biomedical, Lubbock, TX, USA) was trimmed, adapted and fixed to the palatal bone using titanium pins (Master-Pin-Control Kit, Meisinger, Neuss, Germany). Bovine bone xenogeneic graft particles (Bio-Oss, Geistlich, Wolhusen, Switzerland) were soaked in 0.3 mg/ml rhPDGF-BB (GEM 21S, Lynch Biologics, Franklin, TN, USA) for approximately 20 minutes. A 1:1 mixture of autogenous bone chips harvested from the mandibular ramus and the bovine bone was employed for ridge augmentation. The border of the dense PTFE (d-PTFE) barrier adjacent to the maxillary left lateral incisor was trimmed and the partially exposed bone graft was covered with a resorbable porcine collagen membrane (Bio-Gide, Geistlich), which was secured using one titanium pin and a single sling suture (7-0 PGA Resorba Suture, Osteogenics Biomedical). Prior to flap closure, additional rhPDGF-BB was applied topically over the root surface of the maxillary left lateral incisor. The facial and palatal flaps were secured using multiple simple interrupted and horizontal mattress sutures (3-0 PTFE and 6-0 Resorba Resolon sutures, Osteogenics Biomedical) (Fig 1f and g).

After a 7-month healing period, successful vertical ridge augmentation and periodontal regeneration were achieved (Fig 2a and b), and computer-aided implant placement with partial guidance was performed according to the manufacturer's recommendations (N1 implant, NobelGuide, Nobel Biocare, Kloten, Switzerland) in an adequate prosthetic position (Fig 2c). Autogenous bone chips were scraped from an apical region of the surgical field, combined with 0.5 ml rhPDGF-BB and added to

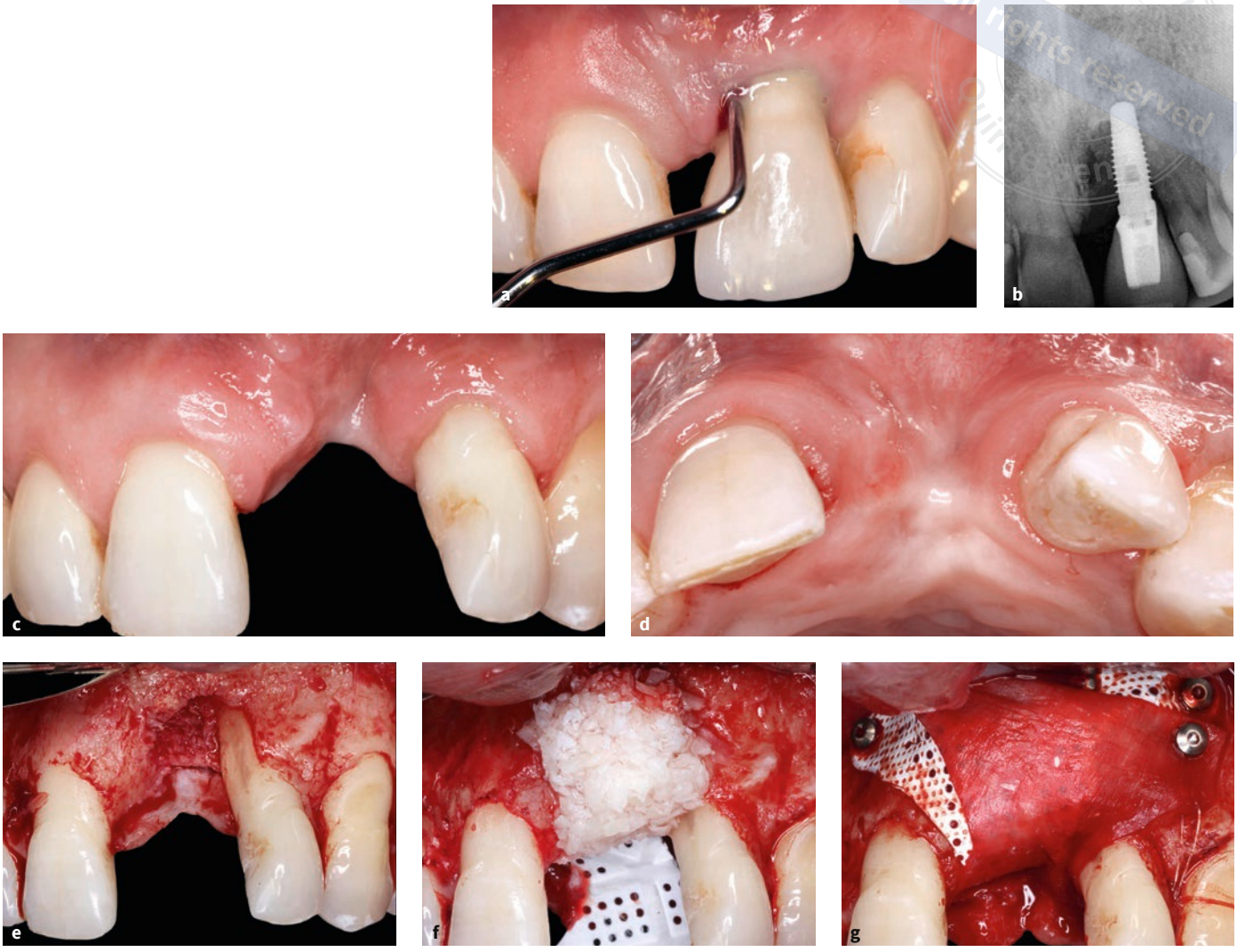

Fig 1a to g A failing single-tooth implant in the maxillary left central incisor site **(a)**. Periapical radiograph of the failing implant **(b)**. A severe, combined ridge defect (Seibert Class III) 4 months after implant removal **(c and d)**. A full-thickness safe flap as described by Urban et al[15] **(e)**. A perforated, nonresorbable, titanium-reinforced membrane fixed to the palatal bone using titanium pins and a 1:1 mixture of autogenous bone chips and bovine bone xenogeneic graft particles and rhPDGF-BB **(f)**. Resorbable porcine collagen membrane was secured on top **(g)**. Reprinted with permission from Urban et al.[8]

augment the dehiscence during implant placement. Bovine bone xenogeneic graft particles (Bio-Oss) and autogenous bone were placed on the crestal aspect in a ratio of 1:1. A thick connective tissue graft (CTG) was harvested from the palatal mucosa, and then covered with a non-resorbable d-PTFE barrier along with a resorbable porcine collagen membrane (Bio-Gide) (Fig 2d to f).

After a 3-month healing period, the keratinised mucosa width (KMW) and vestibular depth were found to have been reduced significantly due to displacement of the mucogingival junction. A partial-thickness flap was elevated on the facial aspect of the ridge to create a recipient bed and increase the vestibular depth. Two labial strip gingival grafts were harvested from the contralateral region of the buccal maxillary mucosa and the mandibular anterior sextant. After a further 3 months of healing, abundant augmented KMW was noted, signifying excellent tissue integration. The probing depth on the mesial aspect of the maxillary left lateral incisor was 3 mm, indicating a substantial amount of clinical attachment gain, and the final implant-supported prosthesis was inserted 8 weeks after implant uncovering (Fig 2g to i).

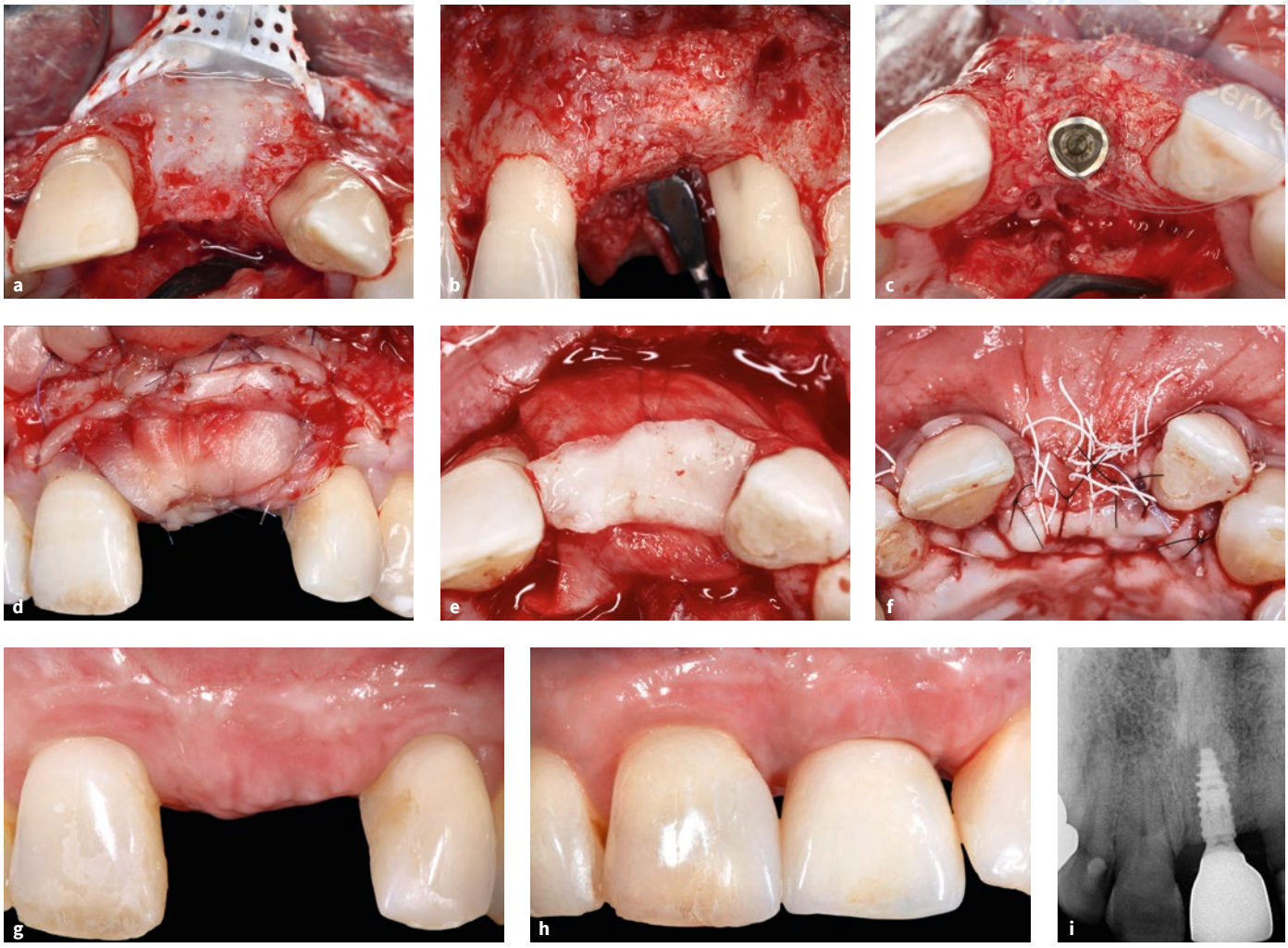

Fig 2a to i Successful vertical augmentation was clinically observed at re-entry after 7 months with the removal of the titanium-reinforced d-PTFE membrane **(a and b)**. Implant placement **(c)**. Augmentation with a bovine tissue substitute and a thick CTG harvested from the palatal mucosa **(d and e)**. Suturing **(f)**. 3 months were allowed for soft tissue healing **(g)**. Final prosthesis **(h)**. Periapical radiograph of the final restoration in the regenerated area **(i)**. Reprinted with permission from Urban et al.[8]

Case 2

A healthy 31-year-old man presented to a private practice (Bogota, Columbia; primary operator PG) seeking treatment for a mobile maxillary right central incisor. Clinical and radiographic examination revealed labial gingival recession, grade III tooth mobility, previous endodontic treatment, loss of buccal alveolar plate and external root resorption on the palatal aspect of the maxillary right central incisor. CBCT showed interproximal bone loss between the maxillary right central and lateral incisors (Fig 3a and b). After informed consent was given, the maxillary right central incisor was extracted and unassisted healing occurred (Fig 3c). After 3 months, CTG surgery was performed to improve the gingival phenotype. Orthodontic treatment was also carried out to redistribute the interdental space during healing, and an acrylic resin tooth was placed provisionally (Fig 3d).

Six months after extraction, alveolar ridge augmentation was performed to prepare the maxillary right central incisor site for implant placement. A full-thickness flap was raised, and the infrabony defect on the mesial side of the maxillary right lateral incisor was debrided using a piezoelectric handpiece (Fig 3e). Ridge augmentation and guided tissue regeneration were performed with

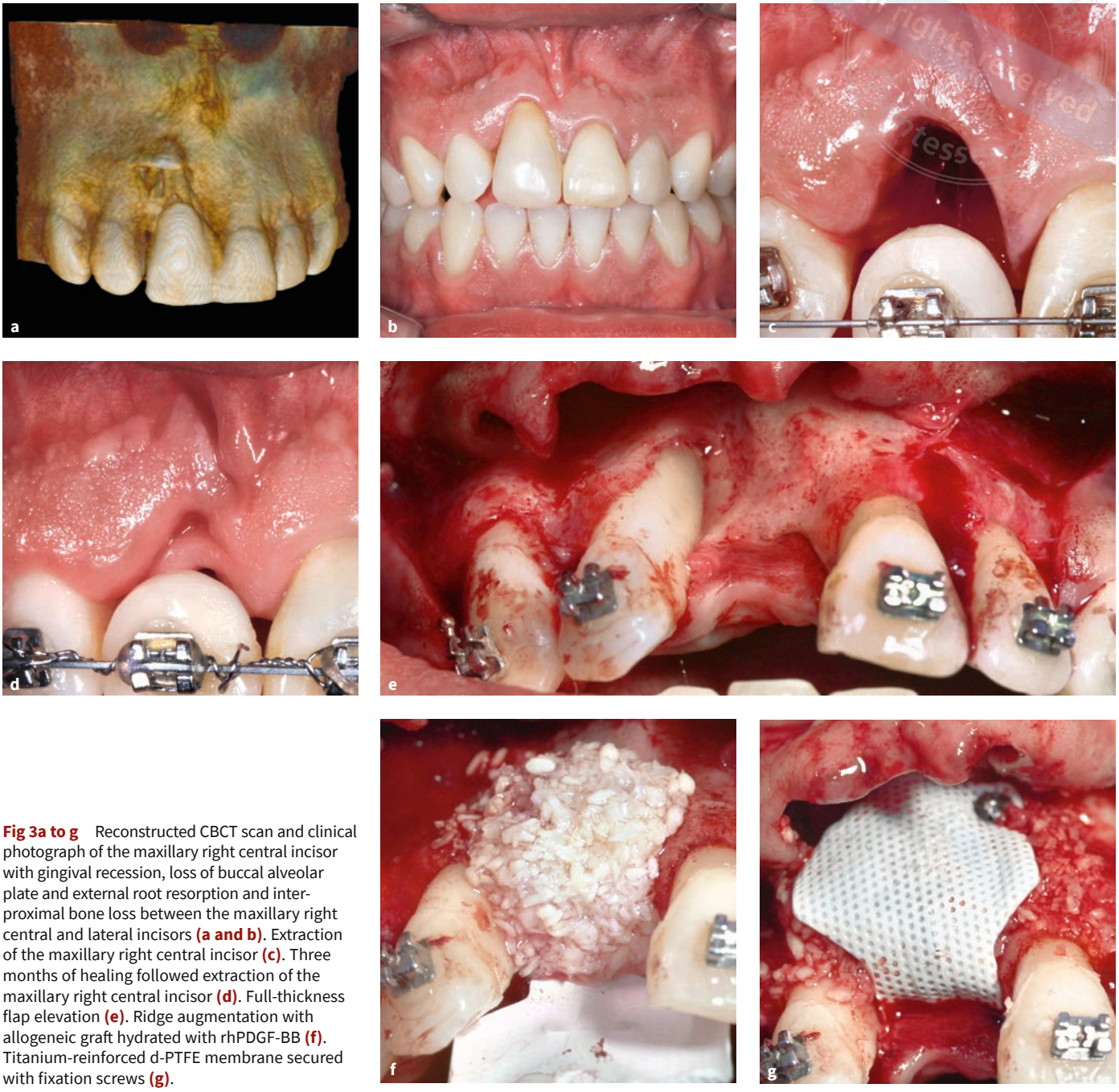

Fig 3a to g Reconstructed CBCT scan and clinical photograph of the maxillary right central incisor with gingival recession, loss of buccal alveolar plate and external root resorption and interproximal bone loss between the maxillary right central and lateral incisors **(a and b)**. Extraction of the maxillary right central incisor **(c)**. Three months of healing followed extraction of the maxillary right central incisor **(d)**. Full-thickness flap elevation **(e)**. Ridge augmentation with allogeneic graft hydrated with rhPDGF-BB **(f)**. Titanium-reinforced d-PTFE membrane secured with fixation screws **(g)**.

allogeneic graft (MinerOss; Biohorizons, Birmingham, AL, USA) hydrated with rhPDGF-BB (0.3 mg/ml GEM 21S) (Fig 3f) and covered with a titanium-reinforced d-PTFE membrane (Cytoplast, Osteogenics Biomedical) (Fig 3g). The maxillary right lateral incisor was scaled and root planed, and a thin layer of rhPDGF-BB was applied. The d-PTFE membrane was secured using three fixation miniscrews (Profil, Osteogenics Biomedical), and periosteal releasing incisions were made to facilitate tension-free primary closure, which was achieved by performing horizontal mattress sutures to ensure close contact between the inner connective tissue portions of the flaps, and then multiple single interrupted sutures (Cytoplast C-0518, Osteogenics Biomedical).

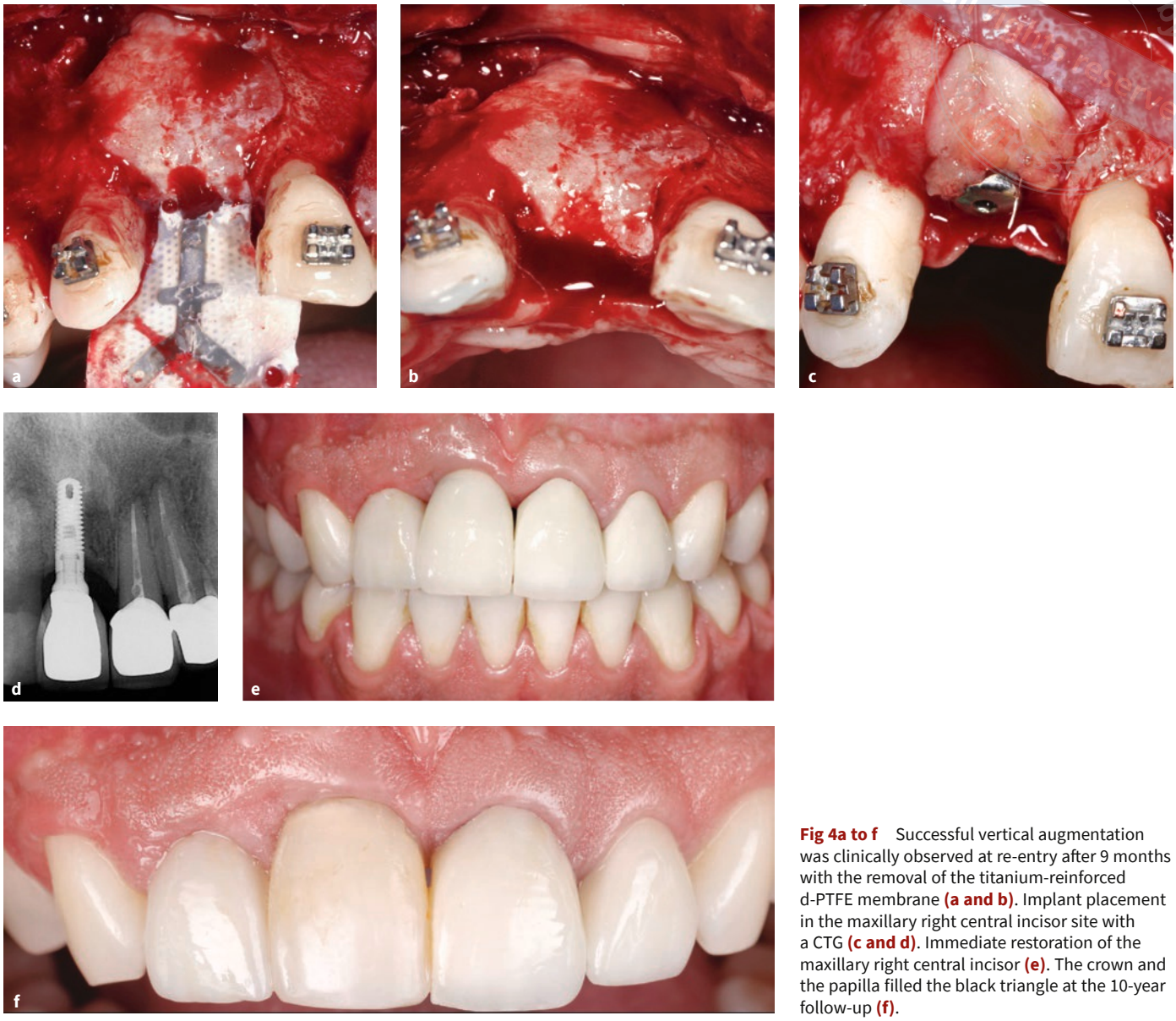

Fig 4a to f Successful vertical augmentation was clinically observed at re-entry after 9 months with the removal of the titanium-reinforced d-PTFE membrane **(a and b)**. Implant placement in the maxillary right central incisor site with a CTG **(c and d)**. Immediate restoration of the maxillary right central incisor **(e)**. The crown and the papilla filled the black triangle at the 10-year follow-up **(f)**.

Healing was uneventful, and the sutures were removed at a 2-week follow-up appointment. Six months after ridge augmentation, a small class Ib exposure[16] was evident and was monitored. Re-entry was performed 9 months after ridge augmentation, and the d-PTFE membrane was removed (Fig 4a and b). The alveolar ridge revealed significant vertical and horizontal augmentation, covering the entire mesial surface of the maxillary right lateral incisor, which was previously exposed. A Zimmer dental implant (Zimmer Biomet, Palm Beach Gardens, FL, USA) was placed in the maxillary right central incisor site (Fig 4c and d). The flaps were sutured for primary intention healing. After 6 months, stage-two surgery unveiled the implant in the maxillary right central incisor site, fitted with a porcelain-fused-to-metal crown (Fig 4e and f).

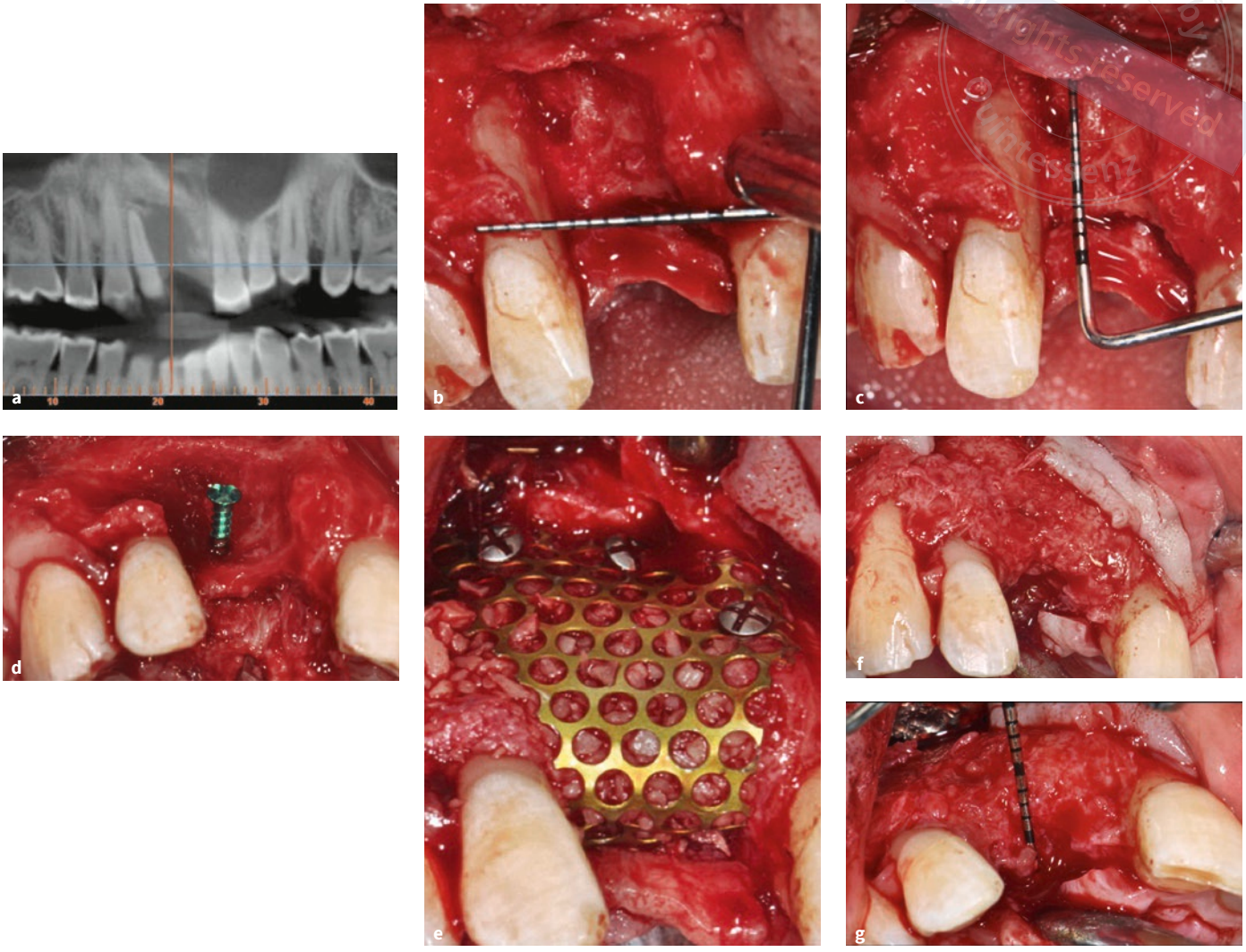

Fig 5a to g Panoramic radiograph of the severe vertical bone defect following extraction of the hopeless maxillary right lateral incisor **(a)**. Full-thickness flap elevation with a vertical bone defect with dimensions of 12 × 15 mm **(b and c)**. Fixation screw inserted buccally to create a buccal wall **(d)**. Puros bone graft was mixed and hydrated with GEM 21 and packed firmly into the defect sites over the maxillary right central and lateral incisors. Titanium mesh was then secured with fixation screws **(e)**. A 7.5-month follow-up showed successful vertical augmentation with a 7-mm gain in ridge width **(f and g)**. Reprinted with permission from Levine et al.[13]

Case 3

A healthy, non-smoking, 48-year-old man (ASA1) presented to a private practice (Philadelphia, PA, USA; primary operator RL). The maxillary right central incisor was severely discoloured due to external root resorption and endodontic involvement. A chronic, long-standing endo-perio lesion was diagnosed due to previous trauma. Initial probing depths interproximal to and buccally of the maxillary right central incisor measured 15 mm, and 14 mm on the mesial of the maxillary right lateral incisor. Following extraction and 4 months of spontaneous healing (Fig 5a), GBR with titanium mesh was planned for ridge reconstruction and implant site development for the maxillary right central incisor and guided tissue regeneration (GTR) for the maxillary right lateral incisor, as the patient wished to retain the latter if possible. His aesthetic risk profile was medium,[17] with an average lip line when smiling. After full-thickness reflection with a distal releasing incision to the maxillary right

lateral incisor and left central incisor for access to the defect (Fig 5b and c), a customised titanium mesh (DePuy Synthes, Johnson & Johnson, New Brunswick, NJ, USA) was measured and prepared to cover the maxillary right central incisor site with a 2-mm space to the adjacent teeth. Three fixation screws were placed buccally to create a "buccal wall" (Fig 5d). Clinically, the vertical bony defect measured 12 mm in height, with a periodontical defect of the same depth on the mesial of the maxillary right lateral incisor. The buccal aspect of the maxillary right lateral incisor was missing except for a small 3-mm island of bone in the coronal third attached to the distal aspect of the remaining socket bone. The mobility of this tooth was 1 degree. A tenting screw was placed on the midbuccal aspect of the maxillary right central incisor defect to maintain the regenerative space and improve mesh stability. EDTA (24%) was used for the maxillary right lateral incisor for 2 minutes after thorough root planing with hand instruments and a piezoelectric device. Puros bone graft (Zimmer Biomet) was mixed thoroughly and hydrated with rhPDGF-BB and packed firmly into the defect sites over the maxillary right lateral incisor for GTR and the maxillary right central incisor for GBR under the mesh, which was then stabilised with the initial three screws. The titanium mesh was fixed with a palatal 5-mm screw (Fig 5e) and both sites were covered with collagen tape (CollaTape, Zimmer Biomet) soaked with rhPDGF-BB. Primary passive flap closure without tension was achieved after apical periosteal releasing incisions were made, using a combination of PTFE, nylon and chromic sutures (Ethicon, Johnson & Johnson). The 7.5-month follow-up showed favourable clinical and radiographic outcomes with no mesh exposure. The CBCT scan revealed an increase in ridge width of roughly 7 mm. The periodontal defect was completely healed when the titanium mesh was removed for both the maxillary right central and lateral incisor sites. Clinically, a horizontal width of 5.5 mm was achieved (Fig 5f and g). A surgical guide was fabricated, and the implant (Straumann BL RC 4.1 × 12.0 mm) was placed with buccal contour grafting with xenogeneic graft and collagen membrane (BioOss and BioGide, respectively) with a coronally positioned flap. After 3.5 months, the implant was uncovered using a minimally invasive keyhole technique. At the 7-year follow-up, clinical photographs and a CBCT scan were taken, which showed maintenance of bone and soft tissue levels and a stable 1.3 to 2.0 mm facial bone on the maxillary right central incisor. In addition, the facial periodontal defect on the maxillary right lateral incisor demonstrated regeneration/bone fill with a buccal wall bone thickness of at least 2.0 mm.

Case 4

A 73-year-old man with an edentulous maxillary right central incisor site and a history of traumatic extraction presented to the University of Seattle, Seattle, WA, USA (primary operator EZ) for implant placement. The defect dimensions were 10 × 10 × 5 mm, classifying it as a Seibert Class III ridge defect (Fig 6a to d). The patient reported no relevant medical history. Local anaesthesia, including two cartridges of 4% articaine with 1:200,000 adrenaline, was administered via local infiltration. Full-thickness flap elevation was performed with a vertical releasing incision at the distobuccal aspect of the maxillary right lateral incisor. Decortication was achieved using a 1/2 round bur. The site was augmented horizontally and vertically with corticocancellous allogeneic graft particles (Straumann Allograft). The allogeneic graft was hydrated for 10 minutes with rhPDGF-BB. The augmented site was covered with cross-linked collagen membrane (OsseoGuard, Zimmer Biomet) after periosteal releasing incisions were made to achieve tension-free closure. 4-0 PTFE sutures were performed using horizontal mattress and simple interrupted techniques to achieve primary wound closure. After 6 months of healing, 7 × 14 mm new regenerated bone was restored to the complex defect, as confirmed on a CBCT scan (Fig 6e to h). A dental implant (Straumann Roxolid SLActive BL 4.1 × 12.0 mm) was placed using a surgical guide in an ideal prosthetic-driven position. Due to the lack of keratinised tissue on the facial side, soft tissue augmentation was performed to increase keratinised tissue width before implant restoration (Fig 7).

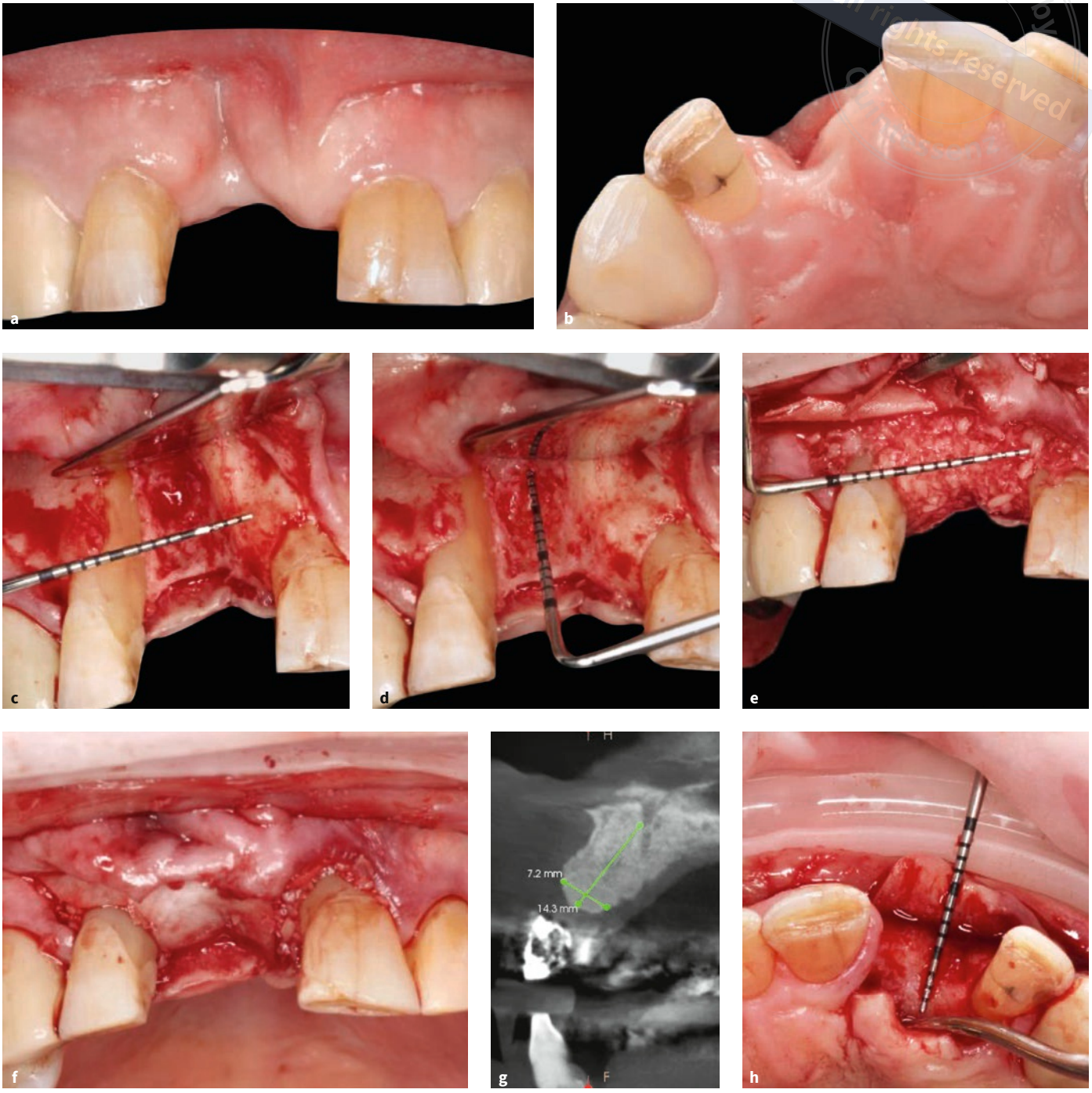

Fig 6a to h Clinical photograph of the Seibert Class III ridge defect of the maxillary right central incisor **(a and b)**. Vertical defect of the maxillary right central incisor with dimensions of 10 × 10 × 5 mm **(c and d)**. After 6 months, healing was completed and almost complete bone fill had been achieved **(e to h)**.

Discussion

Vertical ridge augmentation interventions are considered technique-sensitive; thus, understanding the biological principles of tissue regeneration is a key factor for success.[18] In this retrospective case series, all patients had a neighbouring periodontally affected tooth requiring periodontal regeneration. True periodontal regeneration cannot be declared due to a lack of histological evidence, but the clinical and radiographic findings imply that bone fill occurred.

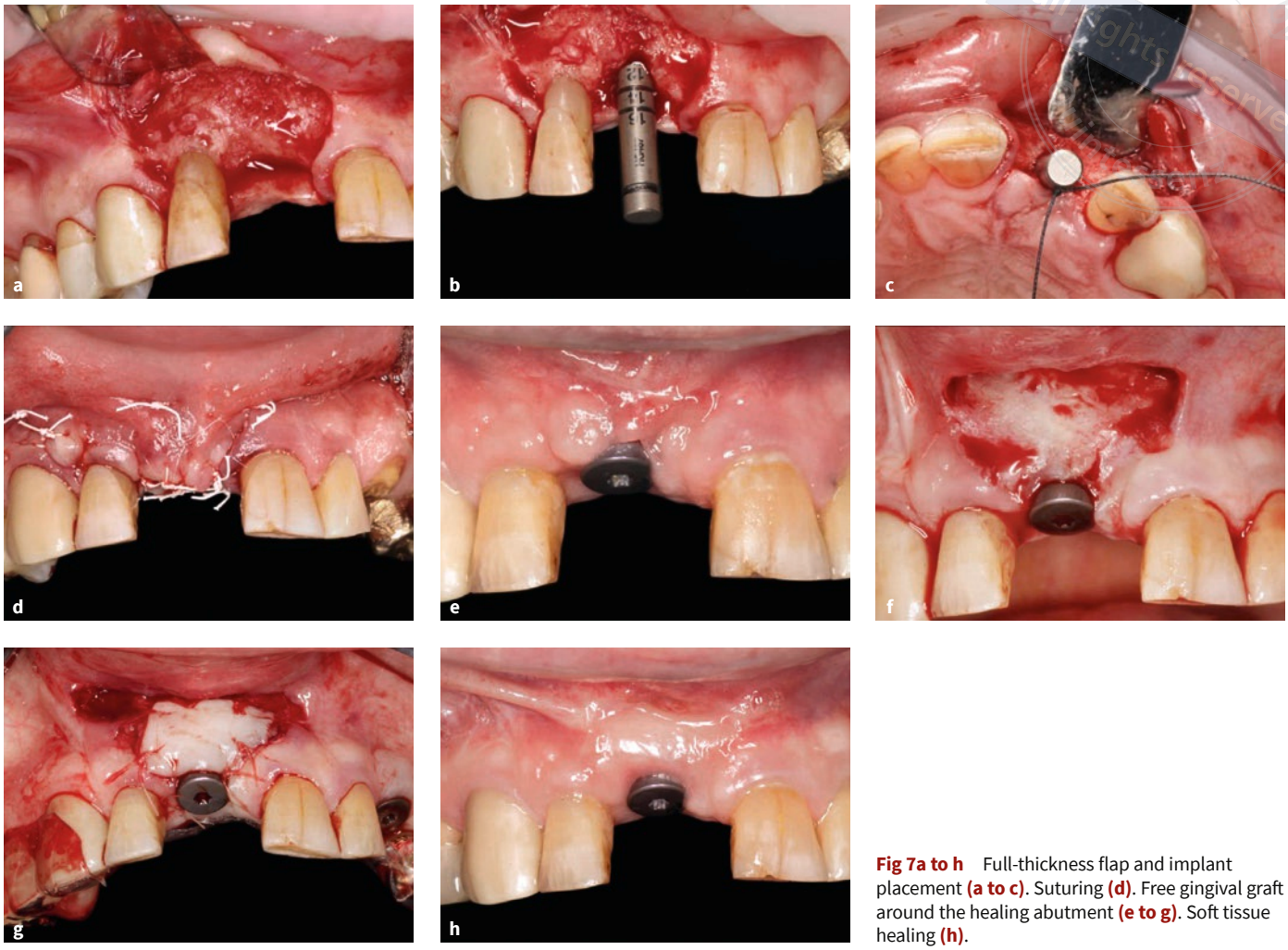

Fig 7a to h Full-thickness flap and implant placement **(a to c)**. Suturing **(d)**. Free gingival graft around the healing abutment **(e to g)**. Soft tissue healing **(h)**.

Even though periodontal regeneration could be achieved without biological materials,[19] rhPDGF-BB is considered a therapeutic resource for enhancing cellular mechanisms such as proliferation and chemotaxis, and favours periodontal regeneration.[10] A recent systematic review evaluated the beneficial effect of rhPDGF-BB in both hard and soft tissue regeneration and concluded that rhPDGF-BB, alone or in combination with bone substitutes such as xenogeneic and allogeneic graft, showed promising results in promoting periodontal regeneration, root coverage, alveolar ridge augmentation and alveolar ridge preservation.[20]

In the second stage (at re-entry during implant placement), some patients in the present study required use of a CTG to achieve optimal aesthetics and function. Depending on the complexity of the regenerative procedure, it is advisable to consider applying a CTG at the time of implant placement when a significant volume is required. This approach could potentially prevent the need for an additional surgical intervention.[8,13]

In three of the cases in the present series, a protected bone regeneration approach was used, once with a titanium mesh and twice with a titanium reinforced d-PTFE membrane. A retrospective study involving 58 cases of implant site development in the maxilla, which utilised titanium mesh in combination with various bone grafts and biological materials, was conducted in 48 patients.[13] Despite a titanium mesh exposure rate of 22%, all implants were placed successfully.[13]

In two of the cases in the present series, d-PTFE membranes were selected. These have a lower exposure rate and are easier to manage than expanded-PTFE (e-PTFE) membrane (~4% versus ~8%, respectively). This may be attributed to the large pore size and less occlusive effect of e-PTFE, which could facilitate putative bacteria penetration and result in a compromised graft healing outcome.[11]

In one case, a cross-linked collagen membrane was selected since the defect was a combined horizontal-vertical defect rather than purely vertical. The chemical process of cross-linking affects the membrane enzymatic degradation and leads to slower membrane degradation, making such membranes a suitable choice for challenging defects. However, a significant limitation of resorbable membranes is their inability to maintain space effectively, which may cause the membrane to collapse into a defect. This can result in reduced bone regeneration, particularly in vertical ridge augmentation.[12]

Different bone grafts were presented in this case report, with allogeneic graft used in three cases and autogenous bone chips employed in the other; however, the advantages of autogenous grafts in different defects are unclear.[21] A recent systematic review indicated no clinically significant differences between autogenous bone types and other bone substitutes regarding implant and prosthesis survival and success.[22]

This case series presented the management of similar defects using the same growth factors, employing similar surgical interventions and extended healing periods with follow-up examinations. Thus, proper case selection, patient preparation for surgery and surgical experience are recommended. Future randomised clinical trials investigating such challenging, complex cases will further contribute to developing optimal treatment strategies for vertical ridge defects with concomitant periodontal defects.

Conclusion

This case report presented a range of complex clinical scenarios involving vertical alveolar ridge defects and neighbouring periodontally affected teeth. The treatment approach involved the use of a combination of regenerative techniques, including employing rhPDGF-BB with various bone graft materials and different barrier membranes. Clinical and radiographic outcomes indicated successful vertical ridge augmentation with resolution of the periodontal defect.

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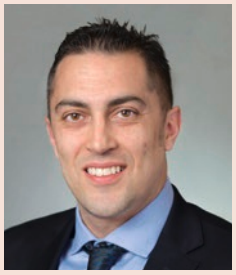

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