OSSIX® and OSSIX® PLUS Literature Review

The goal of this review is to summarize the biocompatibility and efficacy data reported in the scientific literature on the OSSIX® line of dental membranes (OSSIX® and OSSIX® PLUS) since launching in 2001.

Barrier Membranes for Guided Bone Regeneration (GBR)

GBR is a well-documented technique for bone augmentation (Hammerle and Karring, 2000; McAllister and Haghighat 2007). It requires a long enough exclusion of unwanted soft tissues (connective tissue and epithelium) from occupying a space where bone is needed. The secluded space should allow cells from bony origin or mesenchymal stem cells to proliferate migrate and differentiate into bone forming cells (Owens and Yukna 2001; Oh et al 2003). This secluded space should be maintained for the new bone to mature and become stable with minimal resorption. All this may be achieved by using a barrier that will ideally block cell passage and will still allow fluids and nutrients to reach and nourish the regenerated tissue (Friedmann et al 2008).

Non resorbable barriers are ideal for the above and thus Gortex e-PTFE (expanded poly tetra fluoro ethylene) membranes are still considered to be the golden standard in GBR. However, these are difficult to handle, require advanced surgical skills and studies have shown a high complication rate in these cases. When prematurely exposed they usually require immediate surgical removal and their effectiveness is significantly hindered (Simion et al 1994). To overcome these shortcomings there is a continuous effort to develop an ideal resorbable barrier. Among these, collagen based barriers are most commonly used worldwide. A major shortcoming of most collagen membranes is the absence or low level of collagen cross-linking, which links adjacent collagen molecules to one another and stabilizes the collagen fibrils. Non or poorly cross-linked collagen membranes are less resistant to tissue or bacterial enzymes that degrade implanted collagen devices and compromise their role as a physical barrier. Collagen cross-linking may be achieved by physical or chemical methods however; this limits the degree of cross-linking far below the desired device longevity.

GBR References

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The OSSIX® Family of Biomaterials

The OSSIX® line of collagen membranes (OSSIX® and OSSIX® PLUS) is based on a natural cross-linking process known as glycation in which collagen is cross-linked by natural sugars. This unique, patented technology owned by Datum Biotech allows the production of controlled cross-linked matrices to be custom made for each medical device while preserving the excellent biological properties of the collagen. OSSIX® and OSSIX® PLUS are both ribose cross-linked membranes. OSSIX® PLUS, which was launched in 2006, is based on porcine Type I collagen and is a second generation product to OSSIX® which was a bovine based product and was launched in 2001. In this review both versions are referred to as OSSIX®.

The advantages of using OSSIX® membranes have been established in many preclinical and clinical studies over the last decade. Clinically, over 350,000 membranes have been implanted in patients worldwide.

Biocompatibility

Rothamel et al (2004) reported on the ability of OSSIX® to promote in vitro cells adherence and proliferation. In this study four collagen membranes (OSSIX, BioGide, Tutodent and BioMend) were tested and it was concluded that OSSIX, BioGide, and Tutodent promoted, and BioMend (a glutharaldehyde based cross-linked membrane) inhibited the attachment and proliferation of human fibroblasts and human osteoblasts.

Rothamel et al (2005) used the rat subcutaneous implantation model and compared 8 membranes (5 commercially available and 3 experimental chemically cross-linked porcine collagen). They concluded that chemical cross-linking resulted in foreign body reaction (BioMend, BioMend Extend, Tutodent and 2 experimental prototypes). OSSIX showed prolonged bio degradation and low tissue integration but no foreign body reaction.

Ogawa et al (2008) compared non-metal surfaces including OSSIX to different titanium surfaces prepared with nano structuring to test the hypothesis that the latter will enhance bone to implant contact. They concluded that the discovered titanium nano-nodular self-structuring has been proven feasible on biocompatible materials other than titanium, offering new avenues for the development of implant surfaces and other implantable materials for better bone-generative and regenerative potential.

Friedmann et al (2008) evaluated the cytobiocompatability of human osteoblast-like cells to proliferate on surfaces of OSSIX, BioGide and Gortex e-PTFE membranes. They concluded that cell morphology and spatial arrangement indicated that vitality was maintained. Diffusion through the three membranes evaluated in this study was sufficient to support osteoblast-like cell differentiation.

Warnke et al (2009) tested the ability of OSSIX, Tutodent, BioGide and Condro-Gide to support and promote the proliferation of human periosteal cells. They found that: "Collagen membranes can be used as scaffolds for the cultivation of periosteum layers with a view to creating cortical bone using tissue-engineering methods".

Degradation Resistance (Exposed)

In an in vitro study Sela et al (2009) exposed OSSIX, Bio-Gide and BioMendExtend to bacterial enzymes and concluded that cross-linking of collagen membranes significantly increased resistance to bacterial enzymes.

Tal et al (2008I) in an animal model (cat palate) compared OSSIX to Bio-Gide in intentional perforations and concluded that both membranes were undetected in perforated sites. However, it should be noticed that the well-known mechanical force of the cat's tongue was not taken into account. Thus, exposing both membranes to the destructive mechanical forces may explain the above findings.

Resistance to degradation was further investigated in a clinical human study (Klinger et al 2010). In this study OSSIX, Biomend (glutaraldehyde cross-linked) and Bio-Gide (non- cross-linked) were exposed to the oral cavity. They concluded that OSSIX was significantly more resistant to bacterial degradation under conditions mimicking post-surgical membrane exposure (a score of 5 compared to 2.25 for Biomend and 1.75 for Bio-Gide).

Degradation Resistance (Submerged)

Several animal studies compared OSSIX® degradation when submerged (covered by soft tissue).

Rothamel et al (2005) in a rat subcutaneous model reported only minute superficial degradation of OSSIX compared to all other tested membranes after 24 weeks in comparison to four other commercially available membranes.

Moses et al (2008) in the rat calvaria model, compared OSSIX to Biomend (glutaraldehyde cross-linked) and Bio-Gide (none cross-linked) and calculated the percentage of residual collagen after 28 days. They reported 91.3% in OSSIX, 24.7% in Biomend and 13.9% in Bio-Gide.

Tal et al (2008 II) in a human histological study compared OSSIX to Bio-Gide in GBR procedures 52 patients and concluded that OSSIX was present in all non-perforated sites where Bio-Gide was undetected in all 18 specimens examined.

Moses et al (2009) in a rat calvaria model examined the effect of systemic tetracycline (TC)

on resorption rate of OSSIX, BioMend and Bio-Gide. They concluded that TC reduced resorption rates of BioMend and Bio-Gide, but not OSSIX which did not resorb.

Animal Histology (Efficacy and Ossification)

Veis et al (2006) in a rabbit tibia model filled critical size defects with Biogran II and covered the defect with OSSIX®. They analyzed histological sections after 8 weeks and concluded that "new bone formation within the protected pouch interconnected with the surrounding new bone was observed exclusively in spherical particles of Biogran II".

Schwarz et al (2006) evaluated immunohistochemically angiogenesis pattern of native and cross-linked collagen membranes after subcutaneous implantation in rats. Five commercially available and three experimental membranes (VN) were included: (1) BioGide (BG), (2) BioMend (BM), (3) BioMend Extend (BME), (4) OSSIX (OS), (5) TutoDent (TD), and (6-8) VN(1-3). Specimens were randomly allocated in unconnected subcutaneous pouches (n=4) separated surgically on the back of 40 wistar rats, which were divided into five groups (2, 4, 8, 16, and 24 weeks), including eight animals each. Mean cross- and longitudinal-sectional area of blood vessels (%) was highest for VN(3) (5.27+/-2.73), followed by BG (2.45+/-0.88), VN(1) (2.07+/-0.29), VN(2) (1.91+/-0.55), TD (1.44+/-0.53), BME (0.35+/-0.29) and BM (0.25+/-0.4). In contrast to BG and VN(1-3), BM, BME and TD exhibited a homogeneous transmembraneous formation of blood vessels merely 4-8 weeks following implantation. OS, however, exhibited no signs of angiogenesis throughout the whole study period. They concluded that within the limits of the present study, it may be concluded that pattern of transmembraneous angiogenesis markedly differs among the membranes investigated.

Zubery et al (2007) in a dog jaw GBR model compared OSSIX to Bio-Gide in L-shape defects. They found that although both membranes performed well in defects closure, OSSIX itself underwent ossification. They concluded that "This is the first report on complete ossification of a collagen barrier membrane for GBR procedures".

Shwartz et al (2008) compared BioOss Collagen (BOC) alone and together with five different GBR membranes (BioGide, prototype VN, BioMend Extend, OSSIX, BioGide Titanium reinforced and GoreTex) in dehiscence type defects in implants. They harvested block biopsies After 1, 2, 4, 6, 9 and 12 weeks of submerged healing, dissected blocks were processed for immunohistochemical (osteocalcin – OC, transglutaminase II – angiogenesis) and histomorphometrical analysis [e.g., bone-to-implant contact (BIC), area of new bone fill (BF)]. They concluded that (i) angiogenesis plays a crucial role in GBR and (ii) all membranes investigated supported bone regeneration on an equivalent level.

Park et al (2009) assessed four different samples of a control, OSSIX®membrane, PLGA film, and HA-PLGA/PLGA film were as periodontal barrier membranes for the calvarial critical size bone defects in SD rats. Histological and histomorphometric analyses revealed that HA-PLGA/PLGA film resulted in the most effective bone regeneration compared to other samples with a regenerated bone area of 63.1% covering the bone defect area.

Human Histology (Efficacy and Ossification)

Friedmann et al (2001) in a case series of 16 consecutive patients with atrophic edentulous ridges, treated with OSSIX for lateral augmentation prior to implant placement. Digital photographs were taken at 2 week, 4 weeks and 7 months and flap dehiscence was measured using computer software. At reentries, membrane remnants were taken for histological observation. They reported: "The collagen and bone apposition visible on the membrane remnants documents this barrier's high grade of biocompatibility".

Friedmann et al (2002) compared human histological specimens from lateral augmentation cases of OSSIX vs. e-PTFE membranes. They concluded that: "The new collagen barrier combined with the DBBM provided qualitative bone regeneration comparable to the standard e-PTFE material combined with the same mineral."

Kim et al (2007) treated peri-implants bone defects with regenaform and OSSIX membrane. At second stage surgery they removed the membranes and biopsies were taken. They reported bone density of 23-42 percent.

Tal et al (2008 II) in a human histological study compared OSSIX to Bio-Gide in GBR procedures in 52 patients and concluded that OSSIX was present in all non-perforated sites where Bio-Gide was undetected in all 18 specimens examined. They also reported that: "In non-perforated sites, OSSIX ossification at or within the membrane was occasionally observed".

Zubery et al (2008) reported in a histological human case series of 10 cases that: OSSIX maintained its barrier effect in five of seven cases for 25 weeks and induced dense new bone along its interface with underlying tissues. They concluded that: "This is the first report on OSSIX ossification in humans with direct mineral apposition on glycated collagen."

Artzi et al (2008) examined in humans the efficacy of HA/TCP bone substitute in sinus augmentation procedures. They placed OSSIX membranes over the buccal window and reported that seldom residues of the membranes were present over the grafted bone. In one case, they reported on ossification of OSSIX membrane remnants.

Friedmann et al (2009) took core biopsies from 5 patients who underwent two stage sinus augmentation, two stage lateral ridge augmentation or one stage lateral augmentation using biphasic calcium phosphate covered with OSSIX or BioGide collagen membranes. They concluded that the high scores of new bone and bone to graft contact which were similar to results of studies where non-resorbable membranes were used, may be attributed to the long barrier effect of OSSIX membrane.

Le et al (2010) in a prospective clinical trial reported on 15 cases of vertical ridge augmentation using OSSIX and tenting screws. They reported a high success rate of the implants placed in the newly formed bone. Histomorphometric analysis revealed: "Histomorphometric analysis of the 7 specimens revealed a mean bone content of 43%. Of this percent bone, the mean vital bone content was 81%."

Kim et al in 2010 reported on 14 dehiscence type defects treated with bone graft and OSSIX. They concluded that: "the use of GBR consisting of Orthoblast II and OSSIX membranes caused favorable bone formation during the 6-month healing period…Evidence of increasing

bony remodeling and maturity as well as the continuous resorption of the grafting materials".

Neiva et al (2011) reported a 10 cases series in humans where teeth were extracted and the sockets covered with OSSIX (no bone filler). 12 weeks later a core biopsy was taken and analyzed by histology and with micro CT. They concluded that: "Adequate bone formation for implant placement occurs as early as 12 weeks following exodontia, with minimal changes in alveolar ridge dimensions. No evidence of membrane ossification was observed".

Capri et al (2012) in a serious of 4 cases with insufficient implant site dimension where they placed bone graft and OSSIX membranes. They described the clinical durability of OSSIX of up to 9 months post implantation and clinical ossification in 2 cases. They obtained core biopsies prior to implant placement and observed bone apposition and remodeling of the bone graft. They concluded that their finding support the use of GBR for improved implant placement. They also noted that OSSIX degradation is slower than other collagen membranes, thus allowing a longer barrier effect.

Hoang and Mealey (2012) compared bone allograft in socket preservation procedures. They used OSSIX in cases with significant bony dehiscence and left it exposed. Due to similar number of sites treated with OSSIX in both groups, no significant differences were found among the groups.

Cook and Mealey (2013) in a histological study compared a mineralized collagen sponge (HEALOS) covered with OSSIX to Bio-Oss Collagen covered by BioGide in socket preservation procedures in 44 patients. They reported that BioOss Collagen + BioGide presented with a mean of 32.83±14.72% vital bone, 13.44±11.57% residual graft material and 53.73±6.76% CT/other. HEALO + OSSIX presented with a mean of 47.03±9.09% vital bone, no detectable residual graft material and 52.97±9.09% CT/other.

Friedmann et al (2014) compared histologically biphasic calcium phosphate covered with OSSIX or BioGide. They included 12 patients in the study and placed implants in a total of 38 sites and 13 biopsies were taken. They reported a high exposure rate of all sites of 23of the total sites. They concluded that: The histological findings of this study indicate an osteoconductive nature of the BCP applied. Premature exposure of the bone substitute reduced new bone formation and may bear a risk for inflammatory and foreign body reactions.

Hans-Dieter (2014) took biopsies from a buccal sinus window covered with OSSIX membrane. He showed ossification of the membrane and dense peri-membrane new bone.

Clinical Studies

Moses et al (2005) compared OSSIX, BioGide and e-PTFE membranes in implants with buccal dehiscence defects. They reported significant reduction in defect area of 91%, 71% and 73% respectively. They concluded that in cases with premature exposure that: "OSSIX are apparently capable of supporting gingival healing even when prematurely exposed that could be advantageous in GBR procedures".

Llambes et al (2007) reported on a case series of 11 patients with vertical augmentation with OSSIX at the time dental implants' placement. In one case histology showed new trabecular bone. Minimal complications were detected and only one case failed. They concluded that: "Slow-resorption collagen membranes have the potential to promote vertical ridge augmentation when used with autogenous bone at the time of implant placement".

Ko et al (2008) evaluated evaluate survival rate of implant and bone formation, to analyze failure contribution factors. They compared OSSIX and BioMend to Gortex and BioMesh combined with autogenous bone graft or BioOss. They found that Early exposure of the membrane has significantly affected bone formation (p<0.05). Non-resorbable membrane showed more exposure of the membrane and low success rate of bone formation than resorbable membrane (p<0.05). There were no difference between success rate of bone formation and using autogenous bone or graft materials. They concluded that early exposure of the membrane, membrane type and maxilla/mandible type have influence on success rate of bone formation during GBR.

Le et al (2008) evaluated the effectiveness of using intraoral cortical block grafts in combination with particulate human mineralized allograft, in a "tenting" fashion, to augment large atrophic alveolar ridge defects for implant placement. They augmented the sites using autologous membranous cortical bone grafts from an oral donor site to tent out the soft tissue matrix and periosteum for the adjacent particulate allograft. The sites were covered with OSSIX membranes. The ridges were clinically evaluated 4 to 5 months after augmentation, and 42 implants were placed at that time. They concluded that the technique offers predictable functional and esthetic reconstruction of large-volume defects without extensive amounts of autogenous bone. This offers a superior functional and esthetic result than with either cortical or particulate grafting alone.

Kim et al (2008) reported on clinical and histological results of sinus grafting with OSTEON after 4 or 6 months in all cases OSSIX was used to cover the buccal window. Statistical analysis indicated no significant difference (p = 0.135) in the

newly formed bone fraction between the two postoperative periods. The mean LB/WB ratio after 4 months and 6 months surgery was 0.14 and 0.45, respectively, with significant difference observed between the two postoperative periods (p = 0.027). Additionally, the mean NB/GM ratio after 4 months and 6 months surgery was 1.95 and 7.72, respectively, with significant difference observed between the two postoperative periods (p = 0.046). They concluded that OSTEON is suitable for use in sinus graft application since desirable time-dependent healing was demonstrated.

Urban and Wenzel (2010) reported on pain, swelling and bleeding in patients following molar teeth extraction, immediate implant placement and augmentation with autologous bone (AB), AB with OSSIX or OSSIX alone. They reported: "Little to moderate pain in combination with marginally severe swelling and mild oozing", with no difference between the three techniques.

Beitletum et al (2010) compared bone augmentation with a freeze-dried bone allograft with and without the addition of autogenous bone chips covered with OSSIX membrane. They concluded that: "Large vertical and/or horizontal ridge deficiencies may be treated with FDBA and ribose cross-linked collagen barrier membranes with good clinical outcome. No added effect of the application of a layer of autogenous bone in these one augmentation procedures could be demonstrated. Spontaneous membrane exposure was the only parameter to affect the degree of new calcified tissue formation".

Urban et al (2011) reported on 109 consecutive immediate implants placed in the molar region with augmentation of residual defects with autologous bone (AB), AB with OSSIX or OSSIX alone. They concluded that: "Implants placed immediately after extraction of a molar were associated with a high risk for failure at abutment operation. There was no difference in failure rate between three bone reconstructive techniques".

Nissan et al (2011) augmented atrophic maxillary ridges in 31 consecutive patients with cancellous freeze dries block allografts, the blocks were covered with 3 collagen membranes OSSIX, OSSIX PLUS and BioGide. After 6 months healing they placed 63 implants which were restored after 6 months. The reported a mean bone gain was 5 ± 0.5 mm horizontally, and 2 ± 0.5 mm vertically. Mean buccal bone resorption was 0.5 ± 0.5 mm at implant placement, and 0.2 ± 0.2 mm at second-stage surgery. Mean bone thickness buccal to the implant neck was 2.5 ± 0.5 mm at implant placement, and 2.3 ± 0.2 mm at second-stage surgery. There was no evidence of vertical bone loss between implant placement and second-

stage surgery. Block and implant survival rates were 95.6 and 98%, respectively. All patients received a fixed implant-supported prosthesis.

Nissan et al (2011) treated 12 patients with congenitally missing teeth with 19 cancellous freeze-dried block bone allografts, BioOss and OSSIX membranes. They placed 21 implants and followed for 30 ± 16 months. Bone block and implant survival rates were 100% and 95.2%, respectively. Mean bone gain was statistically significant (P < .001): 5 ± 0.5 mm horizontally and 2 ± 0.5 mm vertically. All of the patients received a fixed implant-supported prosthesis. Soft tissue complications occurred in 4 patients (30%). Complications after cementation of the crowns were seen in 1 implant (4.8%). All implants remained clinically osseointegrated at the end of the follow-up examination. There was no crestal bone loss around the implants beyond the first implant thread. They concluded that cancellous bone block-allografts can be used successfully for implant-supported restorations in patients with congenitally missing teeth.

Nissan et al (2011) augmented mandibular atrophic ridges with cancellous freeze-dried block bone allografts in the posterior atrophic mandible followed by placement of dental implants in 21 patients. They covered the blocks with BioOss and three collagen membranes that were selected randomly OSSIX, OSSIX PLUS and BioGide. The mean follow-up was 37 months. Bone block survival rate was 79.3%. Mean horizontal and vertical bone gains were 5.6 and 4.3 mm, respectively. Mean buccal bone resorption was 0.5 mm at implant placement and 0.2 mm at second-stage surgery. A total of 85 implants were placed. Mean bone thickness buccal to the implant neck was 2.5 mm at implant placement and 2.3 mm at second-stage surgery. They concluded that implant placement in the posterior atrophic mandible following augmentation with cancellous freeze-dried bone block allografts may be regarded as a viable treatment alternative.

Friedmann et al (2011) compared OSSIX to Bio-Gide in a morphometric assessment of alveolar ridge alterations 6 months after one-stage augmentation of bone dehiscence. Their results indicate that:

"Gain in clinically hard newly mineralized tissue at the crestal level was significantly higher in test group (OSSIX) in lateral (1.8 versus 0.7 mm; p=.046) and in vertical dimensions (1.1 versus 0.2 mm; p=.035) compared with controls (BG)", and that: "OSSIX supported mineralization process and remodeling even in sites showing compromised healing as indicated by morphometric outcome".

Kaner and Friedmann (2011) treated 12 patients with an osmotic tissue expander and vertical bone augmentation with autogenous blocks covered with bovine

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bone mineral and OSSIX membrane. The combined treatment resulted in comparably high vertical gain of well-structured bone and may help to further improve the outcome and predictability of implant therapy of patients showing severe bone resorption.

Le and Borzabadi-Farahani (2013) examined the relationship between the vertical buccal defect size and the outcome of single stage (non-submerged) implant placement and simultaneously augmentation of sites with mineralized particulate allograft (Puros Cancellous) using collagen membranes (OSSIX PLUS). They placed 156 tissue level Straumann implants in 108 patients with vertical buccal bone defects. They evaluated the defects pre and post surgically with CBCT scans. They reported complete defect correction occurred in 66 (61.1%) patients followed by improved ridge contours in 38 patients. They concluded that Single-stage implant placement and simultaneous grafting with mineralized particulate allograft showed promising outcome in correcting small and medium sized vertical buccal wall bone defects (<5 mm).

Kim et al (2013) evaluated implant success rate, survival rate, marginal bone resorption of implants, and material resorption of sinus bone graft in cases wherein tapered body implants were installed. They evaluated retrospectively 50 implants with a mean follow-up period of 19 months. Fourteen implants were placed in the maxillary premolar area, and 36 in the maxillary molar area; 24 sinuses were included. In 17 cases OSSIX PLUS was placed on the buccal window, 1 with TR-Gortex and 6 with no membrane. The success rate was 92%, and the survival rate was 96.0%. The mean amount of sinus augmentation was 12.35±3.27 mm. The bone graft resorption rate one year after surgery was 0.97±0.84 mm; that for the immediate implantation group was 0.91±0.86 mm, and that for the delayed implantation group was 1.16±0.77 mm. However, the difference was not statistically significant. The mean marginal bone resorption one year after restoration was 0.17±0.27 mm (immediate group: 0.12±0.23 mm; delayed group 0.40±0.33 mm); statistically significant difference was observed between the two groups. They concluded that tapered body implant can be available in the maxillary posterior edentulous ridge which sinus bone graft is necessary.

Ghaly et al (2013) compared two barrier materials calcium sulfate and OSSIX PLUS in GBR procedures. They augmented 18 bony defects with a 1:1 mixture of DFDBA covered with OSSIX PLUS or CalcigenOral. They placed implants in the augmented ridges 4-6 months later and measured horizontal and vertical bone gain. The OSSIX group showed a horizontal gain of 1.06+1.01mm and vertical gain of

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0.19+1.11mm compared to CalcigenOral with loss of horizontal bone of 0.14+0.74 mm and loss of vertical bone of 0.19+0.74 mm. They concluded that calcium sulfate has a limited use as a barrier for ridge augmentation.

Lee et al (2013) compared cross linked (OSSIX 24 defects) to non cross- linked (BioGide 25 defects) membranes in the treatment of dehiscence type defects. They evaluated defect reduction and bone reduction value on radiographs and found no difference between the groups. They concluded that "the success of guided bone regeneration was performed simultaneously for dehiscence defects around implant, was regardless whether collagen membranes were cross-linked or non cross-linked." However, they excluded early exposure cases from the analysis.

Le and Borzabadi-Farahani (2014) assessed the relationship between the vertical buccal defect size and the outcome of single-stage (non-submerged) implant placement and simultaneously augmentation of sites with mineralized particulate allograft (Puros Cancellous) using collagen membranes (OSSIX PLUS). They examined CBCT scans of 108 patients with 156 tissue level Straumann implants. They concluded that Single-stage implant placement and simultaneous grafting with mineralized particulate allograft showed promising outcome in correcting small and medium sized vertical buccal wall bone defects (<5 mm).

Case Series and Reports

Testori et al (2005) described the use of OSSIX to preserve the buccal bone following implants' placement in the esthetic zone.

Gernhart and Bekes (2006) described cases treated with OSSIX.

Nart et al (2007) described a case in which OSSIX was used to regenerate periodontium and bone following removal of lateral periodontal cyst.

Scala et al (2007) described an original method of treating oro-antrl fistula in 13 patients by means of cryoplatelet gel mixed with different types of bone grafts. In eight patients, a CT was performed after 8 to 12 months from the operation, showing a normal pneumatization with reconstruction of the floor of the maxillary sinus. OSSIX was used over the graft material in 2 patients. Although preliminary, these findings seem to suggest that the use of bioengineered materials coupled with growth factors and osteoprogenitor cells may represent a valuable alternative to autologous bone transplantation for the reconstruction of the maxillary sinus.

Adornato et al (2007) reported on 12 cases with refractory bisphosphonate-associated osteonecrosis (BON), treated with a combination of debridement, PRP and OSSIX. They reported 10 cases with complete resolution of the lesions. They concluded that treatment of refractory BON with a combination of marginal resection and PDGF has shown favorable

results, including complete wound healing in most patients. This modality has been shown to be effective in treating BON and may be a useful alternative to existing treatment strategies.

Kontovasanitis et al (2008) reported two cases where gingival recessions were treated with platelets concentrate covered with OSSIX membrane. They reported that "the use of platelet concentrate gel combined with the principle of GTR may be an effective and less invasive way of treating gingival recession defects."

Fagan et al (2008) described a regenerative technique for implants placed in the esthetic zone in 37 consecutive cases. They used OSSIX in several cases with a high success rate.

Smukler, Capri and Landi (2008) described a technique of bone augmentation in atrophic ridges with autogenous bone collected with a trephine, osseous coagulum trap and bone scrapers. This was covered with OSSIX PLUS membrane fixated with periosteal sutures. They treated 9 patients over a period of 2 years. They concluded that the technique is a safe and predictable method for augmenting deficient ridges in preparation for endosseous dental implants.

Griffin and Cheung (2009) reported the use of OSSIX in root coverage procedures in six patients. They concluded that: "Treating root recession with a GTR–based technique and a PC graft was effective and is an attractive alternative. The outcomes remained stable for 3 years".

Lupovici (2009) reviewed the ability of different combinations of resorbable barriers and bone grafts to successfully augment bone for implant placement and concluded that: "Cross-linked collagen membranes thus have the potential to provide most of the benefits of non-resorbable membranes, without their drawbacks."

Lupovici (2009) described two out of three cases where OSSIX was used with excellent clinical and histological results.

Chaushu et al (2009) reported on 28 consecutive patients with lateral window sinus elevation procedures with cancellous bone allografts and implants. Resorbable collagen membranes including OSSIX were used to cover the lateral wall of the sinus. They reported high success rate of implants with minimal complications.

Tischler (2009) in a review article described cases in which OSSIX was used in conjunction with bone grafting materials with excellent results.

Le (2010) described a technique of bone augmentation around an implant placed in one stage procedure using MinerOss and OSSIX.

Anzalone and Vastardis (2010) reported of a complication caused by a sleep apnea positive pressure mask following sinus elevation with autogenous bone and OSSIX membrane. The complication was treated successfully.

Toffler (2010) described a technique of crestal core sinus elevation. The bony spaces created by the displacement of the cores were covered by OSSIX. The choice of OSSIX was due to its long barrier effect.

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Castillo (2010) reported on two cases in the esthetic zone, where he used OSSIX as a slow resorbing barrier and covered it with Bio-Gide in two stages augmentation procedure prior to implants' placement.

Hur et al (2010) described a double flap incision design for guided bone regeneration using different barrier membranes including OSSIX. The technique, as observed by the authors, resulted in reduced frequency of side effects and especially flaps dehiscence.

Lee and Kim (2010) described cases with severe alveolar atrophy treated with augmentation procedures with OSSIX membranes.

Toscano et al (2010) described a consecutive case series of 73 lateral augmentations performed in 67 patients treated with Regenaform RT and OSSIX. They reported an average gain in horizontal ridge width of 3.5 mm (range, 3-6 mm). The density of the bone was noted to be type 2 to 3, with type 3 being the predominant finding. This retrospective case series from 5 clinical private practices suggests that the use of a composite material of demineralized freeze-dried allograft, mineralized cortical cancellous chips, and a biologically degradable thermoplastic carrier, when covered by a resorbable collagen membrane for GBR, is an effective means of horizontal ridge augmentation.

Hurzeller et al (2010) described a new technique for second stage implant surgery in the esthetic zone that involved the placement of two collagen membranes BioGide and OSSIX.

O'Neil and Al-Hezaimi (2011) described a case of odontogenic keratocyst that following its removal the defect was treated with Puros allograft and OSSIX membrane. At 1-year follow-up, the patient was comfortable and complete resolution of the radiolucent pathology was evident.

Kim et al (2013) described a series of 23 cases with guided bone regeneration with allogenic bone graft. Membranes were not used in 9 cases, but in one case with a large bone augmentation they used OSSIX PLUS membrane. They reported that AlloMatrix™ is an allograft material that can be readily manipulated. It does not require the use of barrier membranes, and good bone regeneration can be achieved with time.

Froum et al (2012) reported the results of treatment of 51 consecutive peri-implant defects using a regenerative approach with OSSIX, BioGide or Mucograft as graft containment materials and barrier function. They reported probing depth reductions at 3 to 7.5 years of follow-up were 5.4 and 5.1 mm in groups 1 and 2, respectively. Concomitant bone level gain was 3.75 mm in group 1 and 3.0 mm in group 2. No implant in either group lost bone throughout the duration of the study. The results to date with this regenerative approach for the treatment of peri-implantitis appear to be encouraging.

Jeong et al (2013) reported on treatment of alveolar cleft defects. Three cases were treated with chin bone grafts and two with AutoBT graft. They concluded that both chin bone graft and AutoBT graft showed favorable outcomes in reconstructing alveolar cleft defects. Autogenous tooth bone graft opens up the possibility of avoiding harvesting autogenous bone graft with complications and morbidities.

Kim et al (2013) A case study of 12 patients who had guided bone regeneration, extraction socket graft, sinus bone graft, and ridge augmentation procedures using autogenous tooth

block graft material. They reported that all of the cases had successful bone graft results. One patient developed wound dehiscence after surgery, although favorable secondary healing was achieved. One implant resulted in osseointegration failure. A histopathologic examination was performed after 2.5 months and showed excellent bone healing due to osteoconduction. The AutoBT block was incorporated into the upper soft tissue, aponeurosis, and lower recipient bone. They concluded that there were no notable complications associated with the bone transplant materials. The AutoBT block is clinically useful for a variety of bone grafts.

Lee et al (2013) treated 9 patients with vertical or horizontal ridge augmentation using AutoBT covered by one of 3 membranes: OSSIX, BioGide or Gortex. They reported that no complications related to bone graft material, such as infection. Average marginal bone loss after one-year loading was 0.12±0.19 mm. They therefore concluded that excellent clinical results can be said to have been obtained with vertical and horizontal ridge augmentation using autogenous tooth bone graft material.

Froum (2013) described two successful cases with regenerative procedures in implants with bone loss due to peri-implantitis. OSSIX was used as a barrier membrane in one case followed for 7 years.

Clem and Hinds (2013) described the principles of treatment of congenitally missing lateral incisors and a case where they successfully used OSSIX for bone augmentation.

Froum and Rosen (2014) described a series of 12 implants with bone loss ranging from 3-12mm that were treated with GBR procedures and examined 6-96 months later. They found in reentry 2-9mm bone fill (40%-100%). They concluded that the results are encouraging.

Sheyer and McGuire (2014) described a series of 9 consecutive cases with dehiscence type defects on buccal aspect of implants. Following implants placement, a bone graft and OSSIX membrane were placed and the patients followed for 6 months. At six-month reentry surgery all dehiscence and fenestration defects had been eliminated with newly regenerated bone covering previously exposed implant threads. No membrane exposure occurred during this study. They concluded that successful GBR outcomes may be enhanced by avoiding premature membrane exposure. Although collagen cross-linking may be associated with increased mucosal dehiscence, the ribose cross-linked membrane examined in the current study may help promote positive regenerative outcomes by sustained functional and structural integrity and a reduction in membrane exposure incidence.

Kim et al (2014) described a case series of 8 cases with large sinus membrane perforation during sinus augmentation procedures. The used a pedicle buccal fat pads and OSSIX PLUS membranes over the perforated membranes and performed 12 implants in 6 cases, 3 failed. They concluded that large sinus membrane perforations can be managed successfully with the above technique.

Kim et al (2014) reported 2 cases of bone augmentation where they used ground dentine of teeth extracted in siblings. In one case OSSIX PLUS membrane was used to cover the augmented site. They reported satisfactory results in both cases.

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Funato et al (2014) described two complex cases where they used ultraviolet light for photofunctionalization of titanium implants and Ti meshes prior to placement in sites requiring augmentation, extraction sockets, sinus elevation and the esthetic zone. They claimed that photofunctionalization facilitates the treatment outcome and allows immediate and early loading protocols.

Engler-Hamm and Heinz (2015) described 2 cases of treatment of perio-endo lesions with OSSIX. (German)

Levin (2015) described a technique for socket preservation using OSSIX with intentional exposure (German).

Zubery (2015) described cases with early exposure of GBR sites treated with OSSIX and its subsequent resistance to exposure and final healing (German).

Reviews

McAllister BS and Haghighat K. (2007).

Bashutski and Wang (2009).

Hitti RA and Kerns DG (2011).

Horowitz et al (2014)

In these reviews OSSIX is described as one of the commercially available collagen membranes for GBR and GTR procedures.

Book Chapters

Wallace et al (2006) described the role of barrier membranes on the buccal window in sinus elevation procedures.

Tal et al (2011) in two book chapters described the advantages of OSSIX in both animal models and in human studies and case reports.

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