

BIOACTIVE DELIVERY SYSTEMS IN MAXILLARY SINUS BONE REGENERATION: GROWTH FACTORS, BIOLOGICAL SCAFFOLDS, AND THE SCHNEIDERIAN MEMBRANE

Short Title: BIOACTIVE SYSTEMS IN MAXILLARY SINUS REGENERATION

Wamiq Musheer Fareed^{1*}, Mohammad Hasan Alshammari², Meshal Habis Alrshidi², Abdulaziz Qasem Alanazi², Nawaf Abdulaziz Alshebre², Sultan Faleh Al-Rashidi², Emad Ammar M. Alrashidi², Waseem Samih Matar², Mohammed Nasir Kamaluddin Inamdar³, Sheeba Khan⁴

¹ Department of Oral and Maxillofacial Diagnostic Sciences, Division of Oral and Maxillofacial Surgery, College of Dentistry and Pharmacy, Buraydah Colleges, Buraydah, Saudi Arabia.

² Dentistry Student, College of Dentistry and Pharmacy, Buraydah Colleges, Buraydah, King Abdulaziz Road, Al-Qassim, Kingdom of Saudi Arabia.

³ Department of Preventive Dental Sciences, College of Dentistry & Pharmacy, Buraydah Colleges, Buraydah 51418, Saudi Arabia.

⁴ Department of Restorative Dental Sciences, College of Dentistry & Pharmacy, Buraydah Colleges, Buraydah 51418, Saudi Arabia.

*Corresponding Author:

Dr. Wamiq Musheer Fareed, BDS, MDS

Department of Oral and Maxillofacial Diagnostic Sciences
Division of Oral and Maxillofacial Surgery
College of Dentistry and Pharmacy, Buraydah Colleges
Buraydah, Saudi Arabia

E-mail: Wamiq.Fareed@bpc.edu.sa; Wmfareed@gmail.com

ORCID: 0000-0002-5576-6236

ABSTRACT

Maxillary sinus pneumatization may contribute to deficient alveolar height and limit implant placement in the posterior maxilla. Maxillary sinus floor augmentation has been performed with autogenous bone, bone substitutes, and techniques in which the sinus membrane is elevated without grafting material. The reviewed literature describes spontaneous bone formation after elevation of the Schneiderian membrane, the contribution of a subperiosteal coagulum, local cytokines and growth factors, blood clotting, fibrin scaffold formation, osteoprogenitor cells, and the importance of maintaining a stable space beneath the elevated membrane. Studies also describe platelet-rich plasma and concentrated growth factors in relation to sinus bone formation. The available observations indicate that new bone may form beneath an elevated sinus membrane without bone grafting material when a blood-filled space is created and maintained. The Schneiderian membrane has been described as having periosteum-like and osteoinductive potential, while the blood clot provides a natural scaffold for bone repair. Bone grafting materials may contribute to space maintenance and scaffolding, but the reviewed literature indicates that graft material is not always necessary for new bone formation.^{7,10-12,14,17-20}

Keywords: maxillary sinus; Schneiderian membrane; bone regeneration; growth factors; blood clot; scaffold; bone graft; concentrated growth factors

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Dental implants are frequently used for prosthodontic rehabilitation in partially and completely edentulous patients. In the posterior maxilla, pneumatization of the maxillary sinus may contribute to deficient alveolar height and reduce the amount of bone available for implant placement. Maxillary sinus augmentation is therefore performed to increase the quantity of bone beneath the sinus

BIOACTIVE DELIVERY SYSTEMS IN MAXILLARY SINUS BONE REGENERATION: GROWTH FACTORS, BIOLOGICAL SCAFFOLDS, AND THE SCHNEIDERIAN MEMBRANE

membrane and improve the residual bone height available for implant-supported rehabilitation. ¹⁻³Various surgical and grafting procedures have been introduced to establish adequate bone volume in the atrophic posterior maxilla. Early sinus augmentation procedures involved elevation of the sinus membrane and placement of autogenous particulate cancellous bone and marrow within the confined space created at the sinus floor. Autogenous bone was subsequently regarded as an acceptable grafting material because of its osteoinductive, osteoconductive, and non-immunogenic properties. Other approaches have included allografts, xenografts, alloplasts, and combinations of bone substitutes with autogenous bone. ^{1,2,6,7}

However, observations of bone formation following elevation of the Schneiderian membrane without grafting material introduced an alternative biological concept for maxillary sinus regeneration. Bone formation has been reported around implants placed after careful elevation of the sinus membrane, while formation of a subperiosteal coagulum has also been associated with subsequent new bone formation. Establishment of a void containing a blood clot beneath the elevated membrane may promote bone formation according to the principle of guided tissue regeneration. ³⁻⁵

The biological environment created during sinus membrane elevation appears to be important in this regenerative process. Surgical implant placement has been described as eliciting an osteogenic response largely driven by local cytokines and growth factors. Blood clot formation may further contribute to regeneration, with the clot occupying the newly created compartment and providing a natural environment for subsequent bone formation. ¹⁰⁻¹³

The Schneiderian membrane may also contribute directly to the regenerative response. Sinus mucosa has been reported to contain mesenchymal progenitor cells and cells committed to the osteogenic lineage. The membrane has additionally been described as having periosteum-like and osteoinductive potential. Following surgical trauma and mechanical stimulation, bleeding from the vascularized membrane produces a fibrin network, while activated progenitor cells within the fibrin clot may form a natural scaffold for the initiation of new bone formation. ^{14,19,20}

The role of biologically active blood-derived components has also been considered in sinus augmentation. Platelet-rich plasma has been investigated in relation to new bone formation, while concentrated growth factors without a bone substitute have been described as capable of accelerating new bone formation following elevation of the sinus membrane. These observations further support investigation of the local biological environment in sinus regeneration. ^{15,18}

In addition to biological activity, maintenance of the space created beneath the elevated membrane is considered important. The source literature indicates that a blood clot alone may not always possess sufficient integrity to maintain membrane elevation for the required period. The tenting effect provided by implants and the space-making or scaffolding effect of graft materials may therefore contribute to maintaining a stable environment for new bone formation. ^{17,18,20}

DEVELOPMENT OF MAXILLARY SINUS AUGMENTATION

Boyne reported bone grafting of the maxillary sinus as a means of increasing available bone in long-standing edentulous cases complicated by sinus pneumatization. Boyne and colleagues later described elevation of the sinus membrane through a lateral approach and placement of autogenous particulate cancellous bone and marrow grafts into the confined space created at the sinus floor. ^{1,2}

Branemark and colleagues reported bone formation around the apical portion of implants placed after careful elevation of the Schneiderian membrane. They subsequently described elevation of the mucoperiosteal membrane and formation of a subperiosteal coagulum that could later contribute to new bone formation. ^{3,4}

Dahlin and colleagues reported that lifting the sinus membrane and establishing a void containing a blood clot may produce new bone according to the principle of guided tissue regeneration. This observation provided an important basis for later graft-free sinus elevation procedures. ⁵

BONE GRAFTS AND BONE SUBSTITUTES

Autogenous bone was considered an acceptable material for sinus grafting, and it was described as the gold standard because of its osteoinductive, osteoconductive, and non-immunogenic properties. Other materials discussed in the source include allografts, xenografts, alloplasts, and combinations of bone substitutes with autogenous bone. ^{6,7}

The grafting materials and graft-free approach described in the reviewed literature are summarized in Table 1.

Graft type	Material/example described in the source	Role/findings reported in the source
Autogenous bone	Autogenous particulate cancellous bone and marrow	Considered the gold standard; described as osteoinductive, osteoconductive, and non-immunogenic.

BIOACTIVE DELIVERY SYSTEMS IN MAXILLARY SINUS BONE REGENERATION: GROWTH FACTORS, BIOLOGICAL SCAFFOLDS, AND THE SCHNEIDERIAN MEMBRANE

Allograft	Demineralized freeze-dried bone allograft	Described as a bone substitute used in sinus augmentation, including in combination with other graft materials.
Xenograft	Bovine-derived bone	Used as a bone substitute; bovine bone was also described as a space maker providing a scaffolding effect.
Alloplast	Alloplastic graft material	Listed among the bone substitutes used for sinus augmentation.
Combined grafts	Autogenous bone combined with bone substitutes, xenografts, or combinations involving demineralized freeze-dried bone allograft	The source reports increased bone formation when autogenous bone was added to these substitute materials.
No graft (graft-free)	Blood clot beneath the elevated Schneiderian membrane	New bone formation was reported without grafting material when the created space was maintained.

Table 1. Types of Grafting Materials Described for Maxillary Sinus Augmentation

Froum and colleagues reported increased bone formation when autogenous bone was added to bone substitutes, xenografts, or combinations involving demineralized freeze-dried bone allograft. Rosen and colleagues reported that the choice of graft material did not appear to influence implant survival in the bone-added osteotome sinus floor elevation technique.^{8,9}

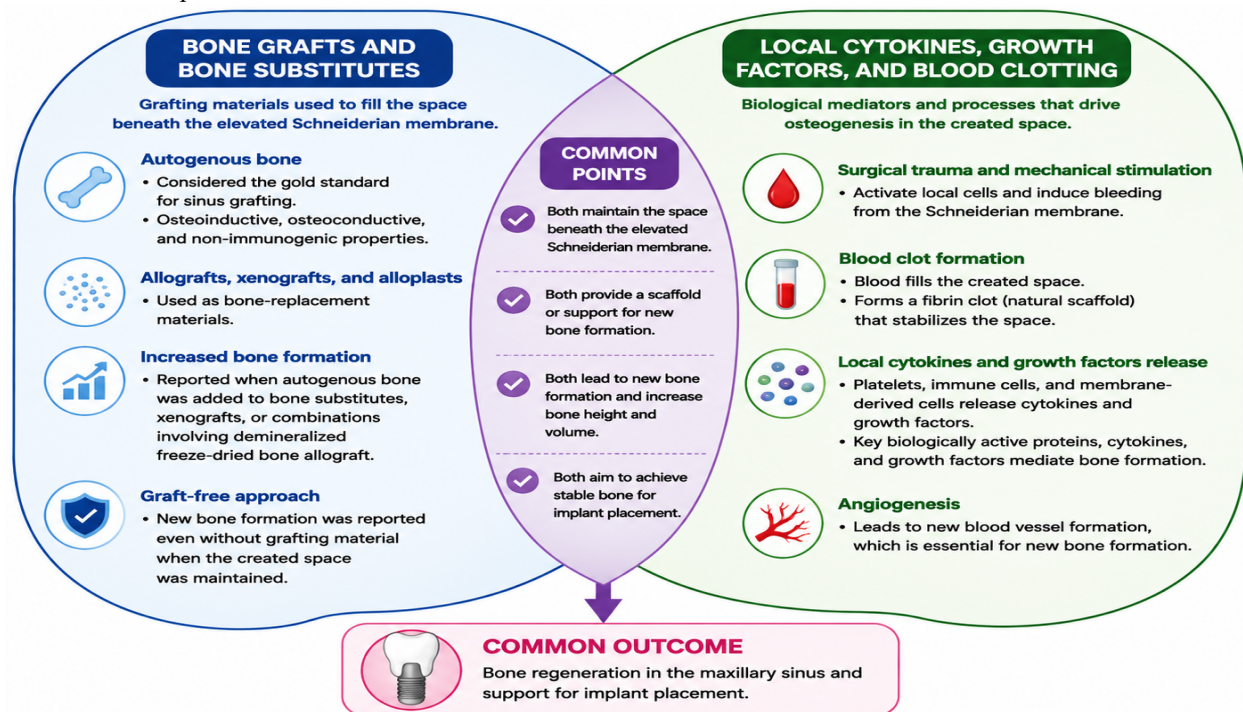


Figure 2. Relationship between bone grafts and substitutes and local biological factors involved in maxillary sinus bone regeneration.

Sohn and colleagues later described bovine bone as acting mainly as a space maker and providing a scaffolding effect. In that study, the key factor for bone reformation was described as space making beneath the elevated sinus membrane rather than the grafting material itself.¹⁸

LOCAL CYTOKINES, GROWTH FACTORS, AND BLOOD CLOTTING

Misch and colleagues stated that surgical placement of a dental implant elicits an osteogenic response that is largely driven by local cytokines and growth factors. This observation places local biological activity among the factors involved in bone formation after implant surgery.¹⁰

Hong and colleagues described the titanium surface of dental implants as markedly thrombogenic in vitro. Frost and colleagues reported that, in the sinus environment, a blood clot formed on the implant may generate thrombin that not only cleaves fibrinogen but may also contribute to activation of osteoblasts through proteinase-activated receptors.^{11,12}

Ropen and colleagues reported in an animal model that blood clotting enhanced new bone formation. These observations support the importance assigned to the coagulum in the source review.¹³

BLOOD CLOT AND FIBRIN AS A NATURAL SCAFFOLD

Several observations in the source document indicate that the space created by sinus membrane elevation fills with a blood clot and that healing progresses within this compartment. The clot has therefore been considered an important component of graft-free sinus regeneration.^{5,13,16}

Srouji and colleagues proposed a sequence in non-grafted sinus lift procedures in which surgical trauma and mechanical stimulation of the Schneiderian membrane activate osteoprogenitor cells. Injury to the highly vascularized membrane produces bleeding and formation of a fibrin network or scaffold. The activated progenitor cells within the fibrin clot were described as creating a natural scaffold construct that becomes an initiation center for new bone formation beneath the membrane.²⁰

The source discussion similarly states that surgical lifting of the Schneiderian membrane causes formation of a blood clot that provides a natural scaffold for bone repair. The clot therefore has both a space-filling role and a scaffold role in the regenerative concept presented in the source.²⁰

OSTEOGENIC POTENTIAL OF THE SCHNEIDERIAN MEMBRANE

Gruber and colleagues reported that sinus mucosa contains mesenchymal progenitor cells and cells committed to the osteogenic lineage. This observation was used in the source review to support the concept that the sinus membrane may participate directly in bone formation.¹⁴

Srouji and colleagues reported that the sinus membrane acts as periosteum and shows osteoinductive potential. The source discussion further proposes that lifting of the Schneiderian membrane may stimulate a periosteum-like structure and activate osteoprogenitor cells associated with the membrane.^{19,20}

Shokier and colleagues observed increased bone density and height below the sinus lining in both grafted and ungrafted sides and attributed the gradual increase to osteogenic activity of the periosteal layer of the sinus lining in response to stimulation produced by closed sinus lift with simultaneous implantation.¹⁷

PLATELET-RICH PLASMA AND CONCENTRATED GROWTH FACTORS

Steigmann and colleagues compared bilateral sinus lift procedures in which platelet-rich plasma was used on one side and an alloplastic graft reconstituted with blood on the other. The source review reports a higher percentage of new bone where platelet-rich plasma alone was used.¹⁵

Sohn reported that concentrated growth factors without a bone substitute can accelerate new bone formation in the sinus after elevation of the sinus membrane. The study was cited in the source as supporting the statement that a bone graft may not be a prerequisite for sinus augmentation.¹⁸

GRAFT-FREE SINUS MEMBRANE ELEVATION

Clinical and experimental reports cited in the source describe new bone formation after elevation of the sinus membrane without grafting material. Bone formation was reported around implants protruding into the sinus, and localized management of the sinus floor was described as combining bone regeneration and osseointegration without the use of bone grafts or membranes.^{3,16}

Palma and colleagues reported new bone formation in coagulum-only sites and observed bone in contact with the Schneiderian membrane. Nedir and colleagues reported bone formation beyond the original limits of the sinus floor after elevation of the membrane without the addition of grafting material.^{16,17}

Sohn and colleagues reported new bone formation in the maxillary sinus without bone grafts. The source review uses these findings, together with other graft-free studies, to support the view that bone formation may occur in a maintained space beneath the elevated membrane.¹⁸

SPACE MAINTENANCE AND TENTING EFFECT

Although the blood clot is important, the source document also emphasizes that the newly created space must remain stable. Kim and colleagues stated that blood clots do not have sufficient integrity to keep the sinus membrane elevated for therapeutically effective periods when greater bone formation is required.¹⁸

Jeong and colleagues reported tent-like bone formation around implants after sinus membrane elevation. The source states that new bone forms in the space created by the sinus membrane tent and emphasizes the importance of keeping the membrane elevated in its new position.¹⁷

The discussion also cites an animal study in which shrinkage of the blood clot and instability of newly formed bone occurred when only the clot was used as a space holder. The source therefore describes the tent-pole effect of an implant as important for maintaining a stable situation.²⁰

DISCUSSION

Augmentation of the maxillary sinus is described in the source as a predictable method for increasing posterior maxillary bone height and permitting implant placement when residual alveolar bone volume is deficient. The original protocol used autogenous bone, while bone substitutes were later used to avoid the disadvantages associated with harvesting autogenous bone.^{2,6-9}

At the same time, the literature reviewed in the source contains repeated observations of successful new bone formation and osseointegration after sinus membrane elevation without bone grafts. According to the principle of guided tissue regeneration, membrane elevation together with space maintenance and blood clot formation may be sufficient for new bone formation in the created space.^{5,16-18}

The biological explanation presented in the source centers on the native osteogenic activity of the Schneiderian membrane, activation of osteoprogenitor cells, formation of a subperiosteal coagulum, and development of a fibrin scaffold. Local cytokines and growth factors are also described as drivers of the osteogenic response after implant placement.^{10,14,19,20}

Within the evidence summarized in the uploaded document, grafting materials may provide bone volume, stability, or scaffolding, while graft-free techniques depend strongly on creation and maintenance of a stable compartment. The source therefore places particular importance on space making, blood clot formation, membrane elevation, and the tenting effect of implants.^{9,17,18,20}

LIMITATIONS OF THE SOURCE LITERATURE

The studies summarized in the uploaded review include different surgical techniques, grafted and ungrafted procedures, animal observations, clinical follow-up, radiographic observations, and histologic findings. Because the source document presents these studies as a narrative review.

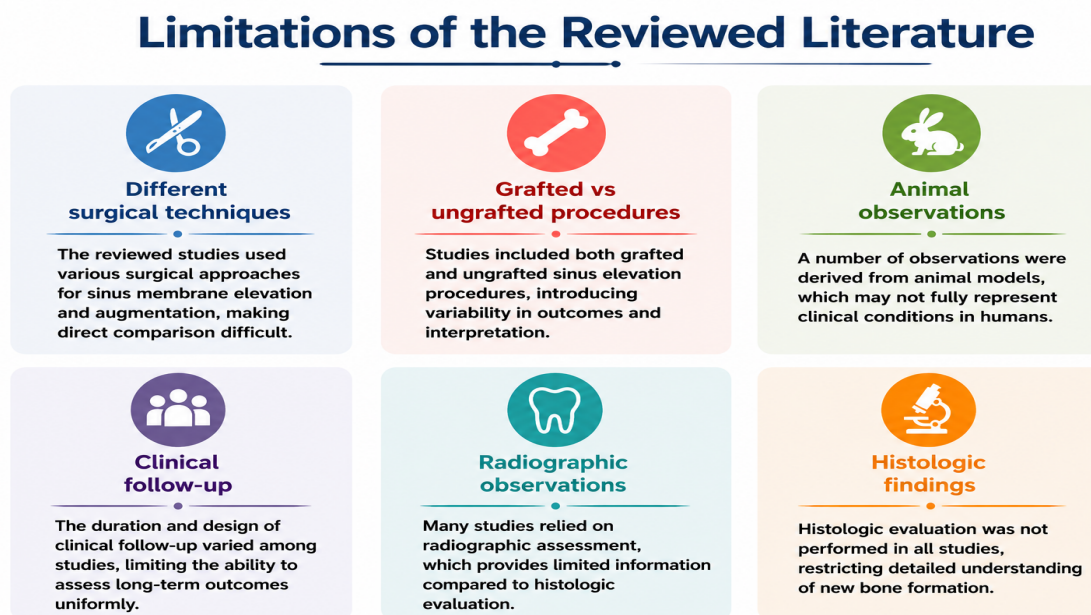


Figure 3. Limitations of the reviewed literature. The included studies showed variability in surgical techniques, grafted and ungrafted procedures, animal observations, clinical follow-up, radiographic assessment, and histologic evaluation. This heterogeneity limits direct comparison and uniform interpretation of the available evidence on maxillary sinus bone regeneration.

CONCLUSION

The reviewed literature indicates that bone grafts are not always necessary for formation of new bone beneath the sinus membrane lining. The void formed beneath the elevated sinus membrane can become filled with a subperiosteal coagulum that is subsequently replaced by new bone.^{4,5,16-20}

The source further supports a regenerative concept involving local cytokines and growth factors, blood clotting, fibrin scaffold formation, osteoprogenitor cells of the Schneiderian membrane, and maintenance of a stable space. Bone grafts and substitutes can contribute to augmentation and scaffolding, but the source identifies space maintenance and the biological activity associated with the elevated membrane and coagulum as central features of graft-free bone formation.^{10-14,18-24}

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