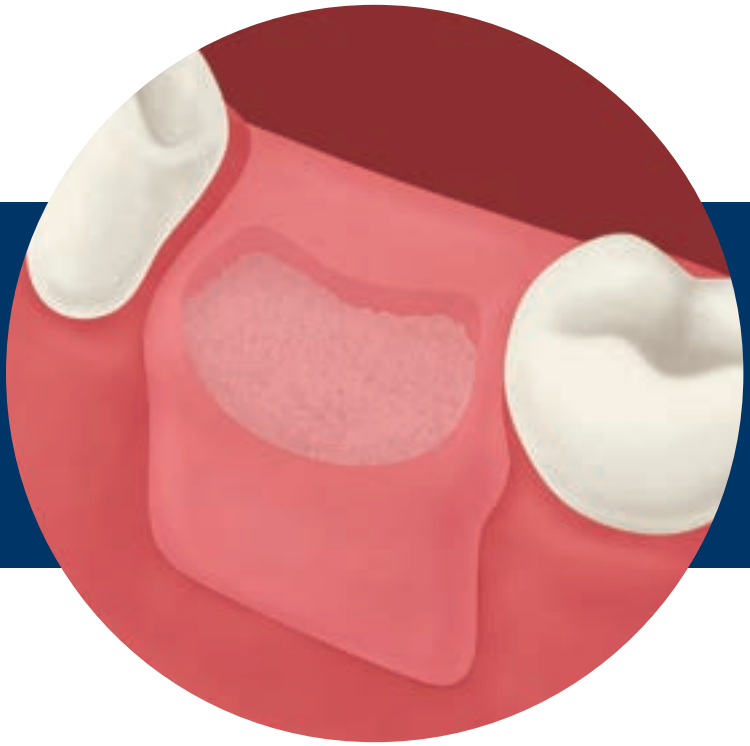
OraCell®

Decelluralized Dermis for Dental & Maxillofacial Applications



The performance you need, with the **safety** and **convenience** you trust

LifeNet Health®
Saving Lives. Restoring Health. Giving Hope.

Overview

Oracell® is a human acellular dermal matrix (ADM) that serves as a scaffold to reinforce damaged or inadequate soft tissue at the surgical site. Using LifeNet Health's proprietary and validated Matracell® decellularization technology, epidermal and dermal cells are removed, while preserving the remaining components (e.g. cytokines, growth factors, collagen, elastin, etc.) in the extracellular matrix (ECM) that aid and are vital in the healing cascade. What is left following this validated process is a decellularized, regenerative human matrix with over 97% of donor DNA removed. Next, a terminal sterilization step utilizing a low dose of gamma irradiation at ultra-low temperatures sterilizes the product to a Sterility Assurance Level (SAL) of 10^{-6}, the same SAL as traditional medical devices. All of this is achieved without compromising the desired biomechanical or biochemical properties of the allograft for its intended surgical application. Taken together, Oracell provides an advanced healing solution through:

Biohospitality

Matracell technology enables Oracell to provide an intact framework and structural integrity to damaged skin, while native growth factors such as collagen and elastin are retained. This supports and promotes rapid cell infiltration, cell proliferation, and neo-vascularization.

Safety

A high Sterility Assurance Level (SAL) in combination with a thoroughly decellularized dermal matrix with over 97% of donor DNA removed is desired to avoid and resist infection, reduce immunological response in the recipient, and lower complications. Oracell is sterilized to an SAL of 10^{-6}, or a 1 in 1 million chance of the presence of a single viable microorganism on the graft.

Convenience

Convenience is an important factor to both the surgeon and hospital. LifeNet Health's proprietary and validated technology allows for ambient storage without the need for rehydration in your operatory, leaving a product that is ready to use out of the package.

> *"With your loved one's gift, I can feel truly beautiful and normal at my wedding this summer, and not feel self-conscious about the way my smile looks."*

Clinical Efficacy

The clinical efficacy of Matracell treated dermis is supported by numerous peer-reviewed and published articles in its intended field of use.

- Gilot GJ, Attia AK, Alvarez AM. "Arthroscopic Repair of Rotator Cuff Tears using Extra-Cellular Matrix (ECM) graft." Arthrosc Tech., 2014 Aug;3(4):e487-9.
- Wallace S. "Guided bone regeneration for socket preservation in molar extraction sites: Histomorphometric and 3D computerized tomography analysis." J Oral Implantol. 2013;29(4):503-9.
- Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. "Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers." Eplasty. 2016 Feb 4;16:e10. eCollection 2016.

MATRACELL®
The FUTURE Of Allograft Bio-Implant DECELLULARIZATION

This patented and validated Matracell process renders allografts acellular, while retaining the desired physiological properties for its intended surgical application.

- Short processing time reduces the opportunity for water-mediated lysis of the natural collagen and elastin scaffold
- Utilizes multiple disinfecting agents to provide for comprehensive tissue disinfection prior to terminal sterilization
- Does not utilize any animal-derived reagents
- Uses validated DNA assessment methods able to detect as little as one nanogram of nucleic acid to validate that the tissue has been decellularized

Complete Decellurization

Matracell removes cells and ›97% DNA from the dermal matrix.*

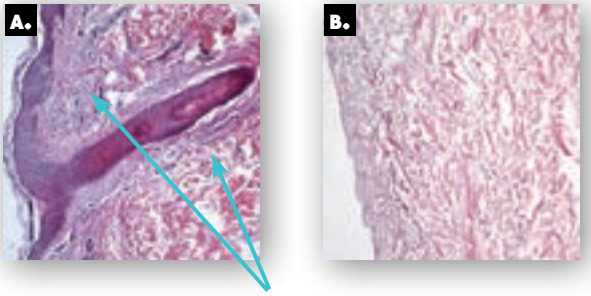


Figure 1: Human skin pre (a.) and post (b.) decellularization (Hematoxylin and Eosin staining). (b.) Note absence of cellular components in Oracell

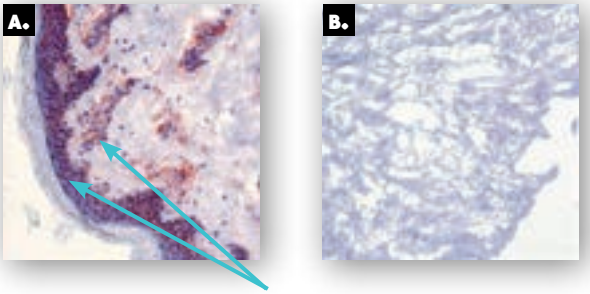
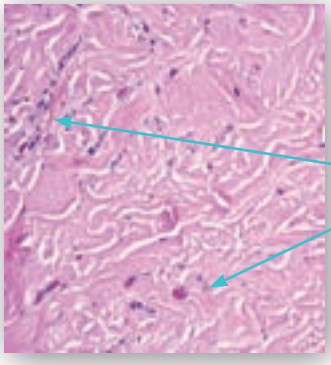


Figure 2: Human skin pre (a.) and post (b.) decellularization (Major Histocompatibility Complex 1 staining). (a.) Brick red staining demonstrates MHC I presence (b.) Note absence of MHC I in Oracell

Recipient Response[2]

An intact acellular matrix of collagen, elastin and growth factors provides a clean scaffold needed for proper healing.**

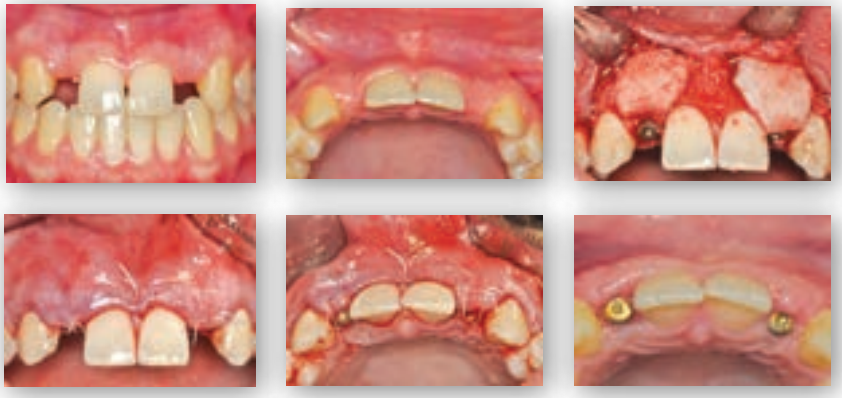


New vasculature and host repopulation

Figure 1: *Oracell explanted after Day 16 in a mouse excisional skin model.*

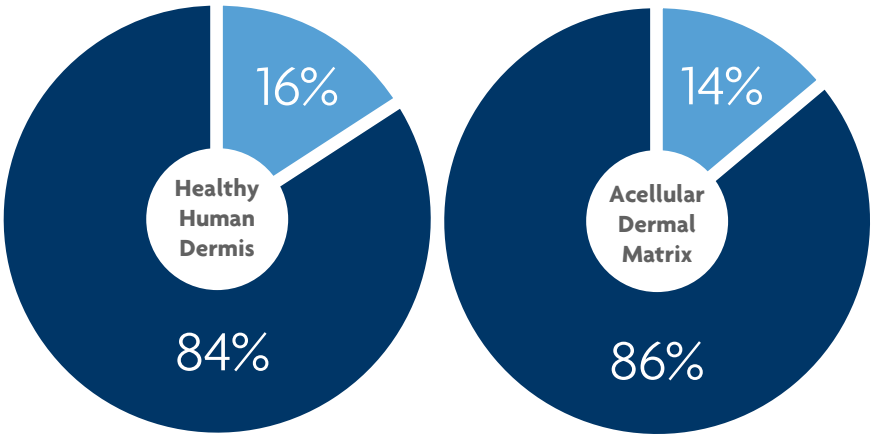
Case Study[2]

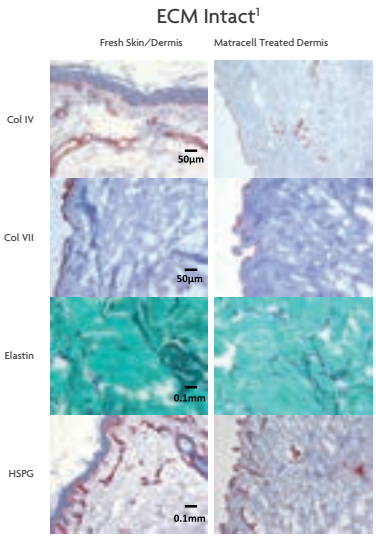
A surgery performed for implant placement at the sites of congenitally missing lateral incisors. A combination of OraGraft® mineralized cortical particulate and Oracell decellularized dermis were required on the labial to correct for the thin bone support and to increase the soft tissue profile in these areas.

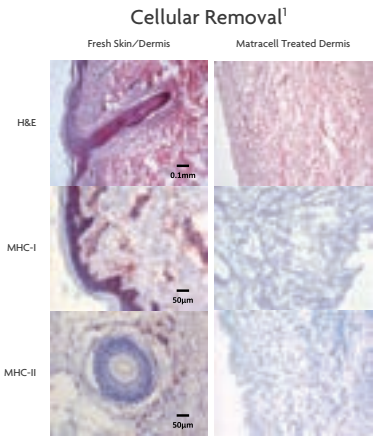


This surgical case was generously provided by Paul S. Rosen, DMD, MS. Dr. Rosen maintains a private practice limited to Periodontics and Implants in Yardley, PA.

** Data on file at LifeNet Health*







Biohospitality

Intact Framework

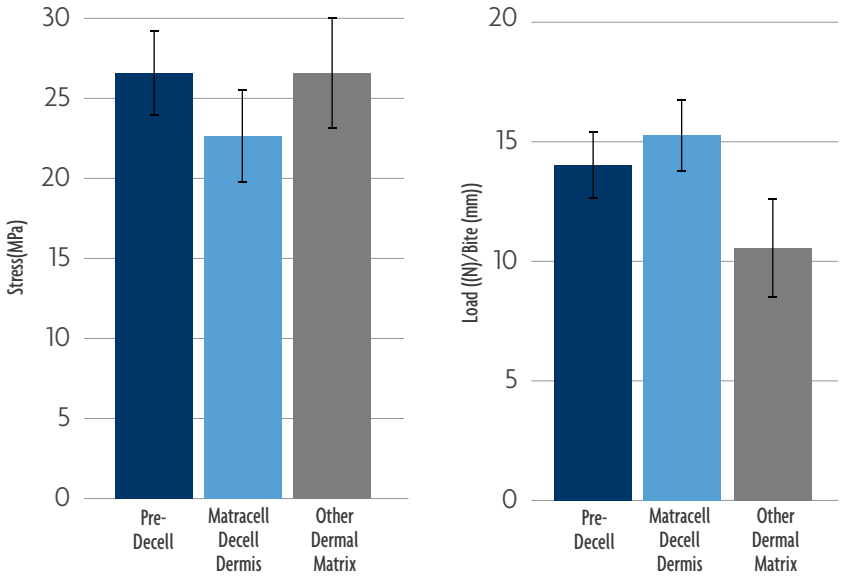
The intact framework of Oracell provides structural integrity to damaged tissue by supplying human extracellular matrix (ECM) that chronic wounds lack or are unable to properly synthesize. Oracell retains ECM components, matrikines, growth factors and cytokines consistent with healthy living tissue and relevant to the natural repair of damaged tissue. **Additionally, ECM proteins that regulate growth factor activity are preserved in the processing of Oracell. Native growth factors such as collagen and elastin are retained while providing structural support for host cells. This support promotes rapid cell infiltration, cell proliferation, and neo-vascularization.**

- The H&E staining shows removal of epidermis and dermal fibroblasts (cell nuclei: blue; ECM: pink).
- The MHC-I and MHC-II staining (brick red) shows the efficient removal of potentially immunogenic cell surface antigens.
- Collagen type IV (brick red) is an essential component of basement membrane and collagen type VII functions as an anchoring fibril between dermis and epidermis.
- Elastin is essential for skin elasticity (dark purple).
- Heparan sulfate proteoglycan (HSPG) (brick red) are integral components of the basement membrane in dermis. HSPG can modulate growth factor activities and influence cell growth and differentiation.
- The Matracell process maintains Collagen I and III, as well as the collagen ratio of I:III seen in healthy human dermis.

Biohospitality

Retained Biomechanical Properties

The Matracell process allows the dermis to maintain its biomechanical integrity. In both suture pull-out and tensile strength testing, Matracell-processed acellular products exhibited no significant difference from fresh dermis. The Matracell process, low-dose gamma irradiation at ultra-low temperature, and room temperature storage have no negative impact on suture pull out strength or maximum tensile stress.

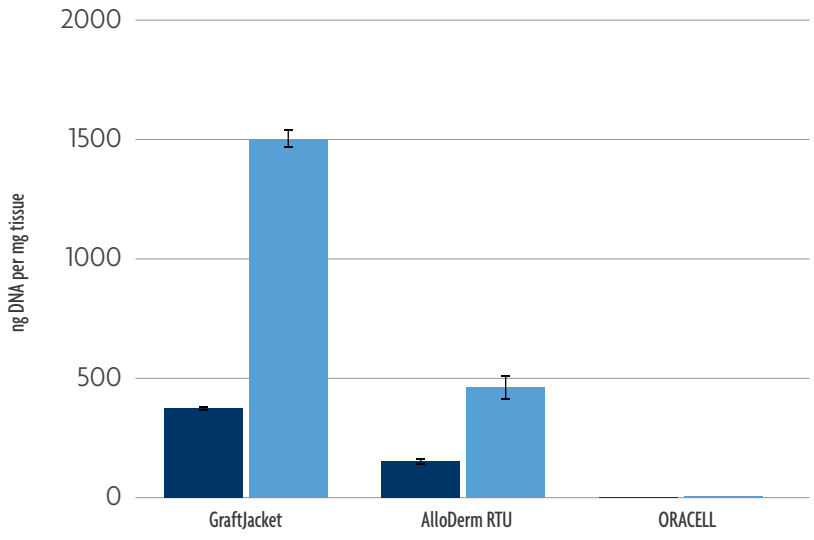


**Data on File at LifeNet Health*

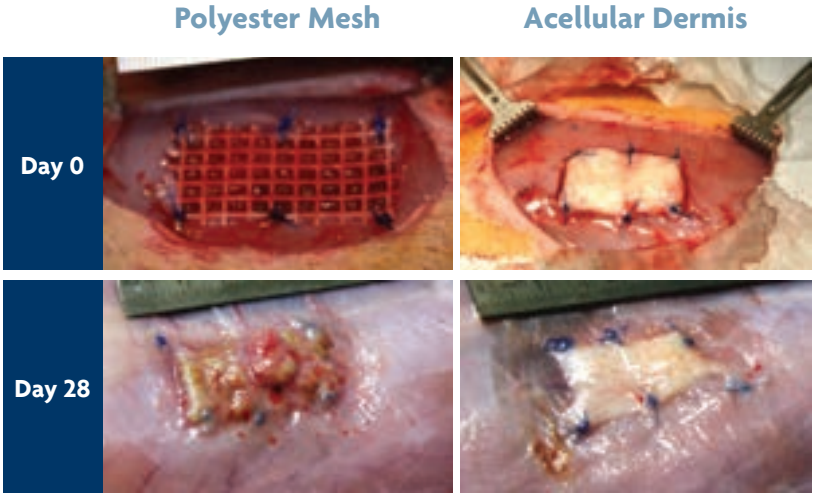
≥ 97% Donor DNA Removal

Effective removal of cellular components from dermis can helpprevent an inflammatory or immunogenic response. Over 97% of donor DNA is removed with Matracell technology. To remove the donor DNA, Benzonase®, a recombinant endonuclease, is applied to efficiently degrade the DNA without introducing the risk associated with other endonucleases. Thus, Matracell technology renders allografts acellular without compromising the biomechanical or biochemical properties, such as suture pull-out strength and retained growth factors, collagen, and elastin, that are desired by the surgeon when treating a patient.[2]

Based on dry weight, GraftJacket® has more than 150 times the residual DNA than Matracell treated dermis and AlloDerm RTU® has more than 50 times the residual DNA than Matracell treated dermis.



**Data on File at LifeNet Health*



*Both were seeded with 105 S. aureus and implanted subcutaneously in a rat.**

3. In vivo assessment of bacteria infection clearance of an acellular dermal matrix and a synthetic mesh. Rosines E, Qin X, Chen S. A symposium on advanced wound care and wound healing society. 27th Annual Mtg. Apr 23-28, 2014.

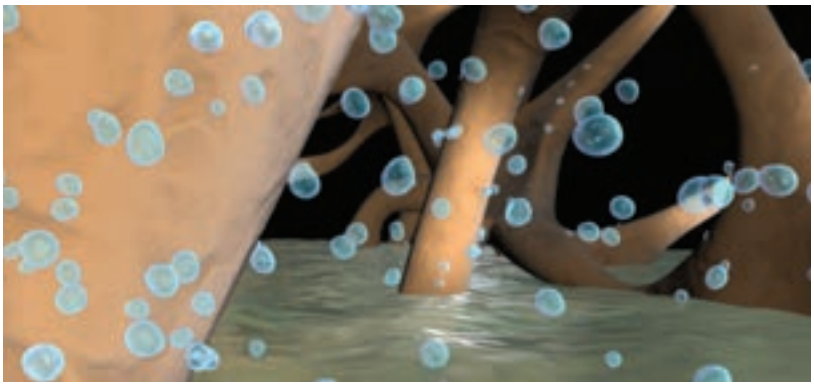
Safety

Sterility Assurance Level (SAL) of 10^{-6}

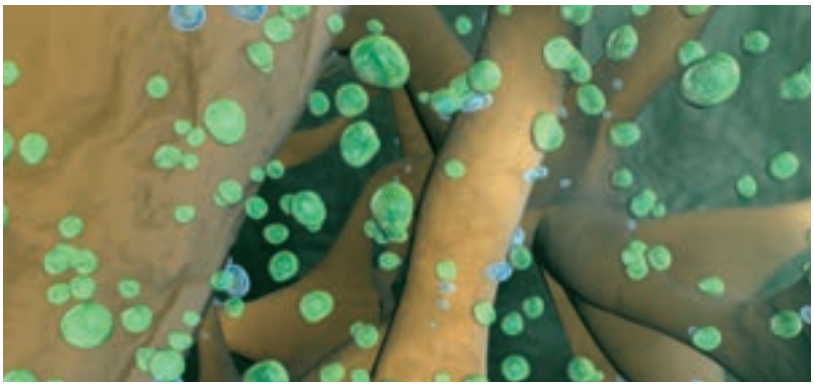
A high SAL, in combination with a thoroughly decellularized dermal matrix is desired to avoid infection or other complications. Not all tissue, however, is sterilized to the same level. Oracell is sterilized to an SAL of 10^{-6}, or a 1 in 1 million chance of the presence of a single viable microorganism on the graft. A SAL of 10^{-6} is achieved using low-dose gamma irradiation performed at ultra-low temperatures, rendering the tissue sterile without compromising the biomechanical or desired biochemical properties.

Resistance to Infection

Matracell-treated dermis ("Acellular Dermis") and polyester mesh were both seeded with 105 CFU S. aureus and implanted in rats to assess their ability to resist and clear the infection. Matracell-treated decellularized dermis resisted infection, while polyester-mesh became highly infected.[3]



Treated allograft bio-implants are immersed into a glycerol-based solution.



Glycerol molecules in the solution replace free-standing water content of the dermal matrix, while collagen fibers retain water molecules.

Convenience

Ready to Use Out of the Package

Oracell is preserved with LifeNet Health's proprietary technology; a solution comprised of USP glycerol and USP saline. This allows the decellularized dermis to be stored at room temperature and is ready to use out of the package. Freeze-dried or frozen allografts can require lengthy thawing or rehydration steps. Using the patented technology, the need to thaw and rehydrate dermal allografts is eliminated, reducing allograft prep time to as little as 30 seconds and saving valuable operating room time without compromising product integrity.

LEGEND

= water

= glycerol

Possible Application	Oracell (OCELL) Code
Membrane (bone graft containment)	**150, 250**
Gingival Recession	**100, 101, 151, 200, 201**
Soft Tissue Correction (insufficient gingiva)	**100, 101, 151, 200, 201**
Implant Preparation	**200, 201, 250, 251**

Clinically Efficacious

LifeNet Health (2011). Early Clinical Success Utilizing Decellularized Dermis [Power Point Slides]. Data on File at LifeNet Health (68-10-104).

Holtzclaw D. Guided bone regeneration in the maxillary anterior.

Rosen PS. Congenitally missing maxillary lateral incisors

Holtzclaw D. Correction of root exposure in the maxillary arch.

Holtzclaw D. Combination extraction socket grafting and horizontal augmentation of resorbed ridge.

Holtzclaw D. Simultaneous extraction with open sinus lift.

A case series by Wallace et al. (2013) analyzed bone regeneration using histomorphometric and 3D computerized tomography analysis. Mineralized cancellous bone allograft was used to fill each socket and decellularized dermal matrix was applied over each socket site. Results showed 28.7% new bone formation using these materials.

In this series, Sindler (2014) describes the use of decellularized dermis in four separate cases. In each case, soft tissue healing and expectations for aesthetics were achieved.

Clinical Applications

Guided Bone Regeneration

- Extraction Socket
- Ridge Augmentation
- Sinus Augmentation

Soft Tissue

- Root Coverage
- Insufficient Attached Gingiva

Handling OrACELL®

General Instructions

- Use on a single occasion for a single patient only
- Once the packaging is opened, the dermis must be used for the current procedure or discarded
- Any unused dermis must be discarded
- Inspect the dermis, inner and outer packaging, and labels carefully
- Do not use past the expiration date as indicated on label
- Do not use if the dermis is damaged or the packaging integrity is compromised
- Do not use if there are discrepancies in label information
- When the temperature dot is present, do not use the dermis if the dot appears to be any color other than white
- Use aseptic technique at all times
- Do not sterilize
- Keep the dermis stored according to recommended storage instructions until preparing it for implantation

Preparations For Use

Orientation: Decellularized dermis has two physically distinct sides: a reticular and a papillary side. In general, when applied, the papillary side will face up while the reticular side is placed against the surgical wound or the most vascularized tissue. The dermis is packaged with the papillary side visible through the clear side of the packaging

1. Non-Sterile Team Member: Open the cardboard sleeve and retrieve the pouch from within.
2. Aseptically open the outer peel pack and present inner pouch to the Sterile Team Member.
3. Sterile Team Member: To maintain orientation of the dermis, the papillary side should be marked with a sterile marker immediately after opening the inner pouch. The dermis is packaged with the papillary side visible through the clear side the packaging.

   Dermis: Open inner peel pouch and remove the dermis with its slip sheet. Remove the slip sheet prior to application.

4. **NOTE:** Rinsing is not required prior to application, however it may improve handling. If a rinse is preferred by the physician, continue to the rinse instructions.

   If not used immediately, keep dermis moist until implantation.

Rinse Instructions (optional)

5. Non-Sterile Team Member: Prepare a sterile rinse basin with enough sterile isotonic solution (e.g., sterile saline) to completely cover the dermis. CAUTION: Ensure the rinse solution does not exceed 42°C as this may damage the dermis.
6. Sterile Team Member: After opening the packaging per the instructions above, remove the dermis from the slip sheet and immerse the dermis in sterile isotonic solution for a minimum of 1 minute . Ensure the dermis is completely submerged in solution during the rinse
7. Keep the dermis completely submerged in sterile isotonic solution until needed.

   The maximum sterile isotonic solution exposure time for decellularized dermis is 4 hours.

	OCELL 100	OCELL 101	OCELL 150	OCELL 151	OCELL 200	OCELL 201	OCELL 250	OCELL 251
Thickness	0.76-1.25mm	0.76-1.25mm	0.76-1.25mm	0.76-1.25mm	1.26-1.75mm	1.26-1.75mm	1.26-1.75mm	1.26-1.75mm
Size	15x20mm	20x40mm	10X10mm	10x40mm	15x20mm	20x40mm	10X10mm	10x40mm

CASE REPORT: SINUS LIFT BONE GRAFTING

Dan Holtzclaw, DDS, MS, Periodontist, Austin, TX, USA

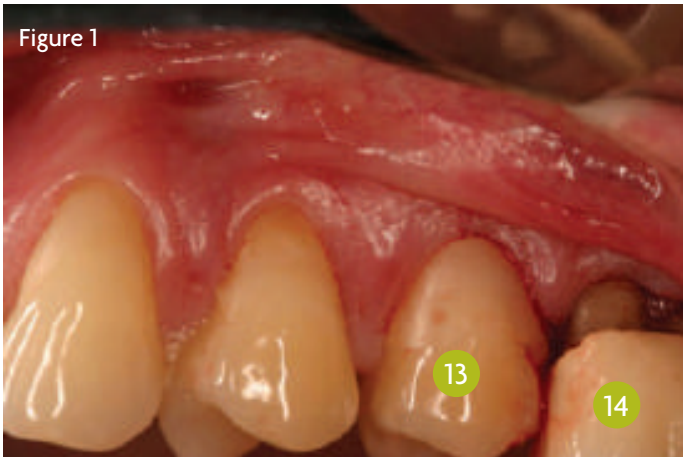
In this case a patient with a failing maxillary molar and a large maxillary sinus is grafted with subsequent implant placement.

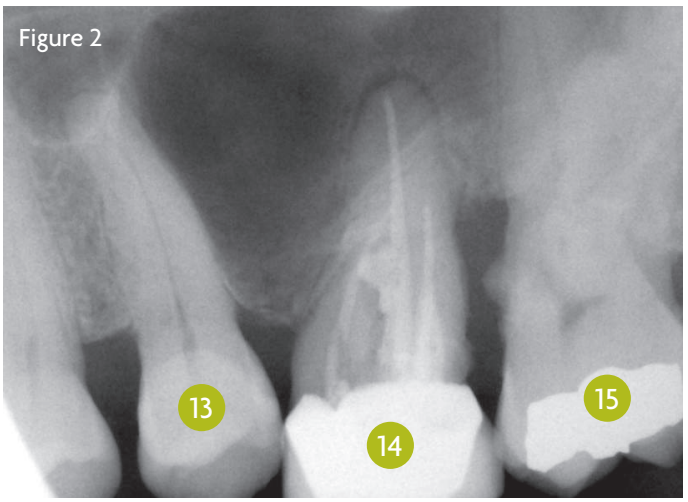
The patient presents with an endodontically treated tooth in quadrant II (#14, number 26 per FDI). The tooth has a crown, which is apparent in figure 1 from the color difference. Gum level appears normal as does soft tissue contour and color. The patient has had some discomfort with the tooth in question and wonders if the tooth should be saved. Dentists and patients are facing a perplexity between saving a compromised tooth through endodontic treatment and restoration or by extraction and replacement with an implant. Studies show that the success rate of implant placement and restoration now exceeds the success of endodontic therapy. The choice of which treatment to choose is still based on many considerations and a thorough understanding of all options.

The radiograph (figure 2) shows a bleaker picture. It is easy to see that # 14 has almost no bone supporting it. In addition, the distal of #14, positioned adjacent to the mesial of #15, has severe bone loss that threatens the health of the second molar. Lastly, this sinus is very large due to a phenomena known as pneumatization. This is a normal occurrence that is loosely related to patient age but is highly variable. The size of the sinus will dictate both surgical approach and subsequent grafting.

It was decided that two procedures would be performed: 1) a sinus lift using a lateral wall approach (Caldwell-Luc) after which, 2) the endodontically treated #14 would be extracted and a socket graft would be performed. The socket of 14 would be overfilled to attempt to gain some bone height on the mesial of #15.

Radiographic Note: The widened PDL on #14 is highlighted by the blue arrow (figure 3); this is indicative of mobility in this case due to the excessive bone loss and change in center of rotation. In addition, the calculus which is mineralized plaque highlighted by the red arrow is the etiologic agent of periodontal disease, hence the bone loss.





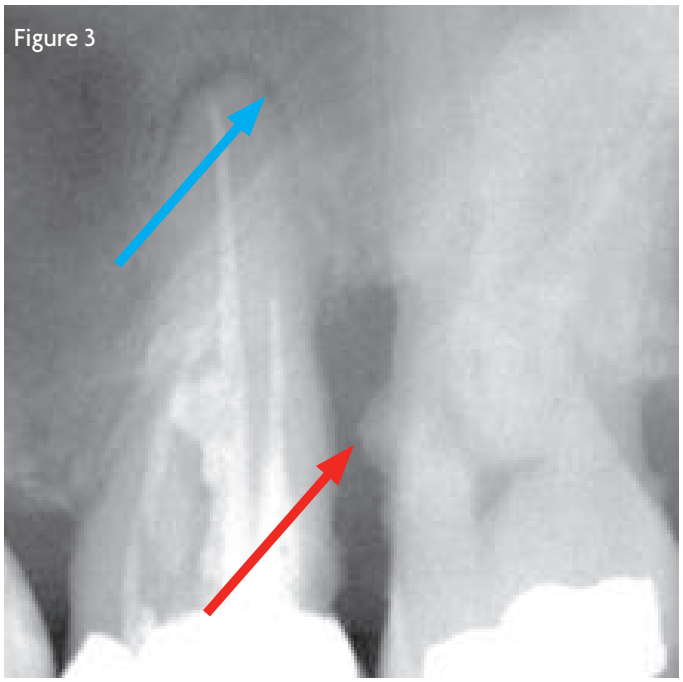


Figure 4

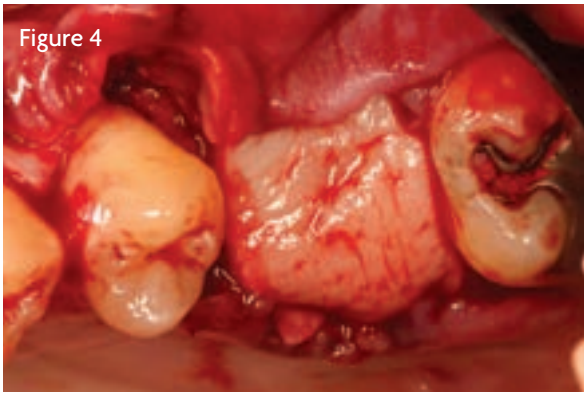


Figure 5

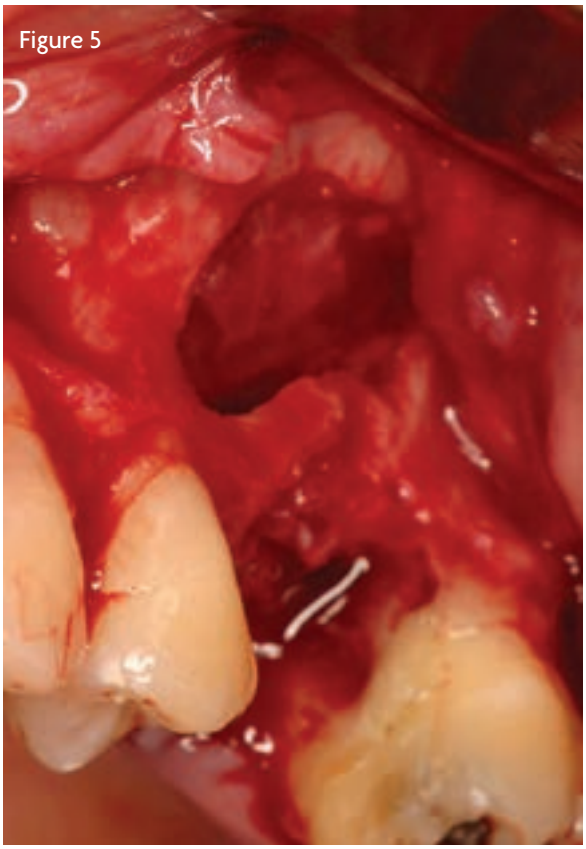
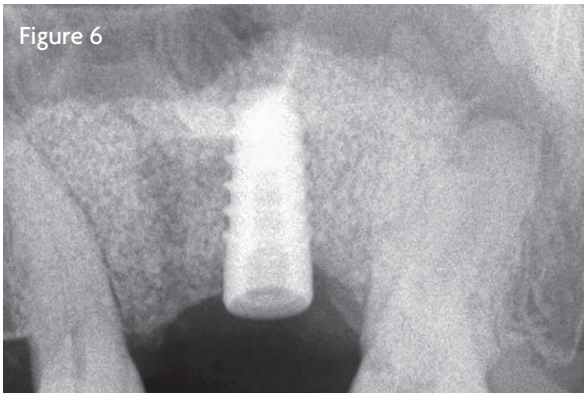


Figure 6



CASE REPORT: SINUS LIFT BONE GRAFTING

Figure 4 shows the lateral window for the sinus lift which is formed after a full thickness flap reflection over the intended surgical area. The Schneiderian membrane will be gently dissected free and reflected upward to create a new floor (inferior wall) of the patient's maxillary sinus. Bone graft material, which is usually a combination graft containing at least one component that is mineralized, is placed. The lateral access is covered with a resorbable membrane, in this case OrACELL, and the flap is replaced to its original position over the window. A normal procedure like this will require approximately 5 cc of graft material. The material(s) used is based on the clinician's experience.

The mesial of #15 was then thoroughly cleaned removing the calculus. The original flap was then extended posteriorly to allow for visualization of the area of #14. Tooth #14 was then atraumatically extracted, the socket area debrided, and grafting was performed. The socket was slightly overfilled to allow for addition bone height adjacent to #15. An acellular dermal matrix graft (OrACELL) was used to cover the bone graft (figure 5). The flap was re-approximated and sutured. A small area in the distal aspect of the suture line did not achieve primary closure – however, healing was uneventful.

At 90 days post-op, clinical and radiographic evaluation (figure 6) showed sufficient bone mass and maturity to allow for placement of a dental implant. Compare the bone level in this radiograph to the pre-operative radiograph shown earlier. The clinician was now able to place the implant in the correct position for proper occlusion. After placement, the implant was allowed to osseointegrate for approximately 4 months prior to fabrication and placement of the final restoration.

Soft Tissue Grafting: Materials for Guided Tissue Regeneration (GTR)

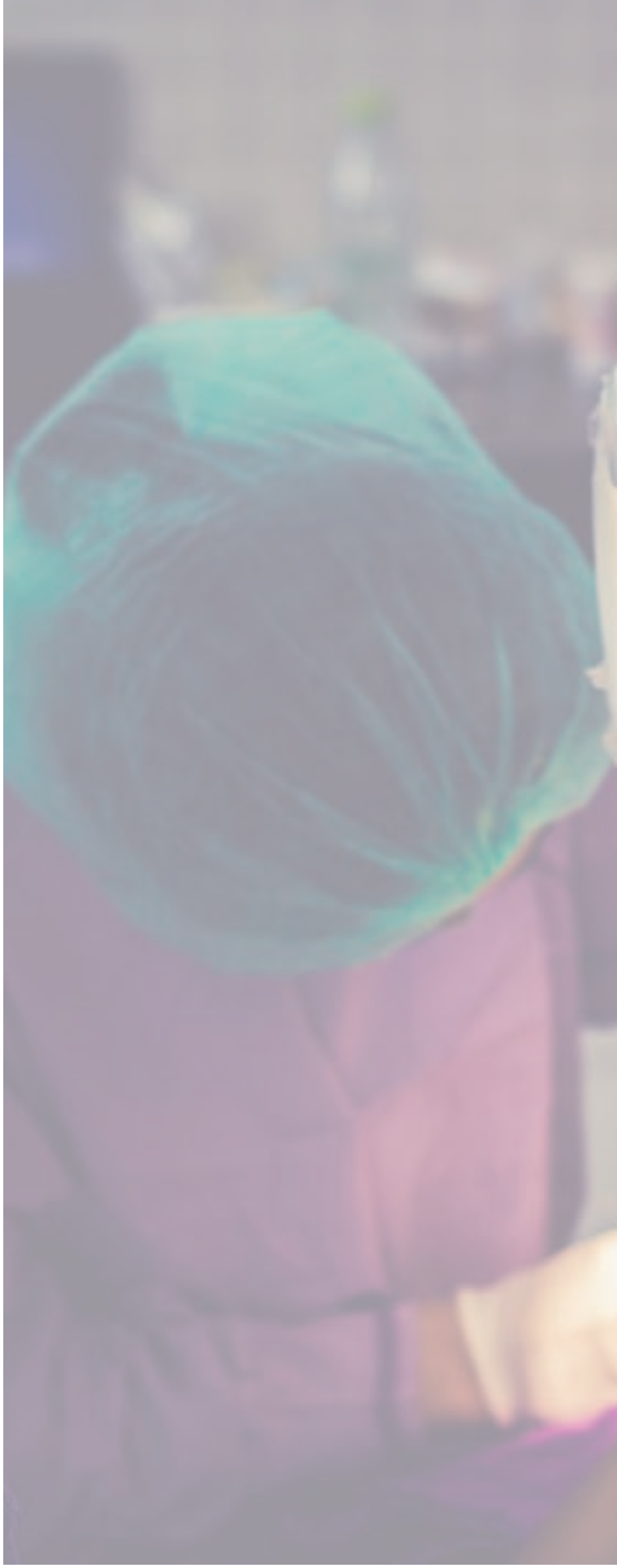
A soft tissue graft serves as a barrier membrane. Specifically, the purpose is to prevent the gum tissue from growing into the bone cavity, or to hold grafting material in place. While there are many different types of dental membranes, they can be divided into two categories: resorbable (dissolvable) membranes and non-resorbable (non-dissolvable) membranes. Membranes for GTR should meet basic requirements to function successfully, easy to manipulate and biocompatible. The ideal membrane will also be easy to trim to ensure a precise fit over the defect.

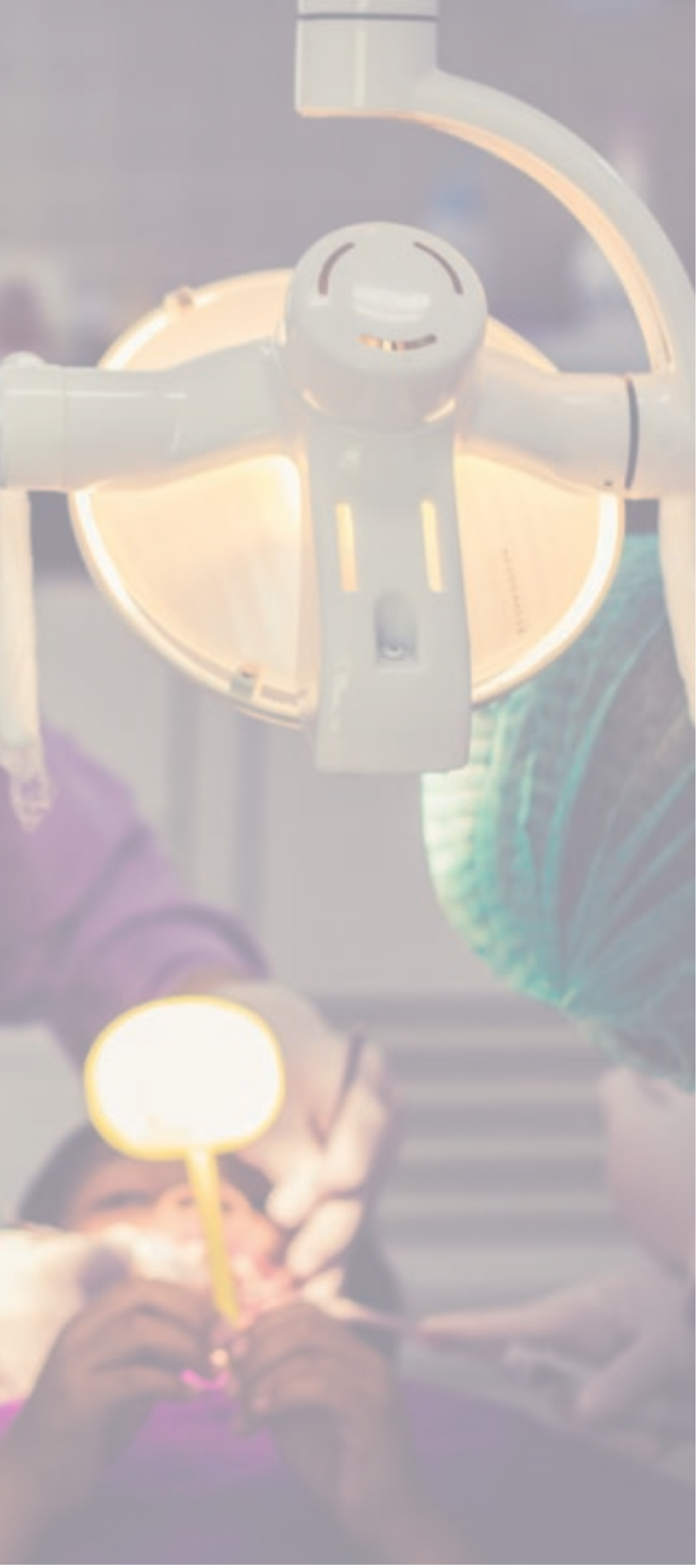
Resorbable Material

A resorbable, or dissolvable membrane will dissolve on its own. Most of the resorbable membranes are compromised of collagen, which is a protein. They are generally made from bovine or porcine tissue and they generally resorb in as little as a few days, or as long as four months. There are also several allograft options for resorbable membranes including pericardium, fascia lata, and decellularized dermis. These allograft options are easy to manipulate, can be trimmed to match the defect, and are biocompatible. The most accepted, published, and widely used allograft membrane is decellularized dermis.

Non-Resorbable Material

Non-resorbable, or non dissolvable membranes can be titanium reinforced or made of PTFE (polytetrafluoroethylene). Since they do not resorb, they must be removed during a secondary procedure.





Soft Tissue Grafting: Gingival Recession

Gingival Recession (Root coverage)

In health, the attached gingiva overlying a tooth serves a protective function. As we age, or as a result of gum disease, the position of the "gum", or attached gingiva, will become more apical. Over time receding gum tissue will result in exposure of the soft root structure of the tooth. This will make the tooth susceptible to root decay, sensitivity (chemical and temperature), and periodontal problems. Once soft tissue is lost, it will not regenerate. Many surgical procedures exist to correct the loss of tissue covering the root surface. Most involve the use of autograft tissue. To successfully restore gum to its physiologically protective position, many factors must be considered: position of the tooth, available attached gingiva, amount of bone support for the soft tissue, esthetics, and health of the patient.

Decision tree

The desired outcome of gingival recession correction is the total coverage of the exposed root of the tooth. Decellularized dermis can be used as an alternative to autograft tissue in many cases.

Case Report:
Gingiva Recession

Arnold Sindler, DDS, Periodontist, Westminster, MD, USA

In this case, a patient with severe gum recession was treated with soft tissue allograft. Gum recession was seen in the upper left first bicuspid, and adjacent areas not needing immediate attention. (Fig 1)

Step one of treatment was for the patient to alter brushing technique to eliminate mechanical trauma. The next phase was surgical, including local anesthesia with aggressive cleaning of the roots of teeth 20, 21, and 22, followed by tetracycline application.

Incisions were made on the facial aspect of #s 12, and 13, extending mesially and distally on the buccal side at the base of the papillae. Partial thickness dissection carried into the vestibule for necessary extension thus releasing the muscle pull on #12.

OrACELL was sutured over the facial surface, and the buccal flap was sutured over the graft. A periodontal dressing was used to protect the graft.

Most of sutures removed at 2 weeks; however some remained functional and were left (Fig 2)

Excellent healing was seen at the 4 week follow-up; however, some OrACELL was protruding from free gingival region in area between #12 and #13 (Figs 3-4). Excellent healing at 2 & 3 months; all remaining sutures removed (Figs 5-6)

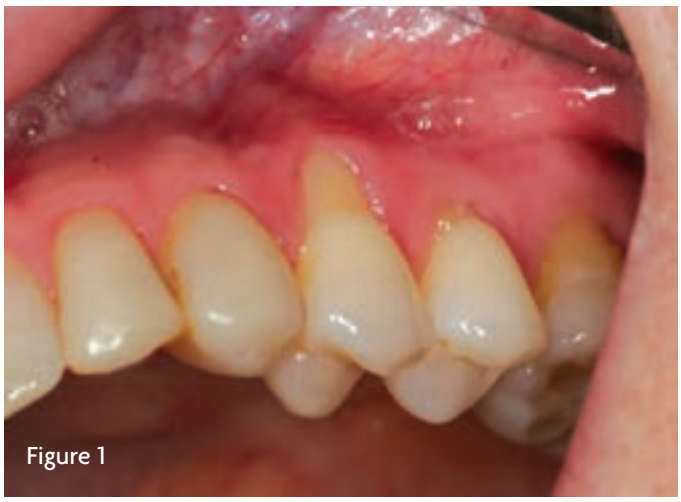


Figure 1

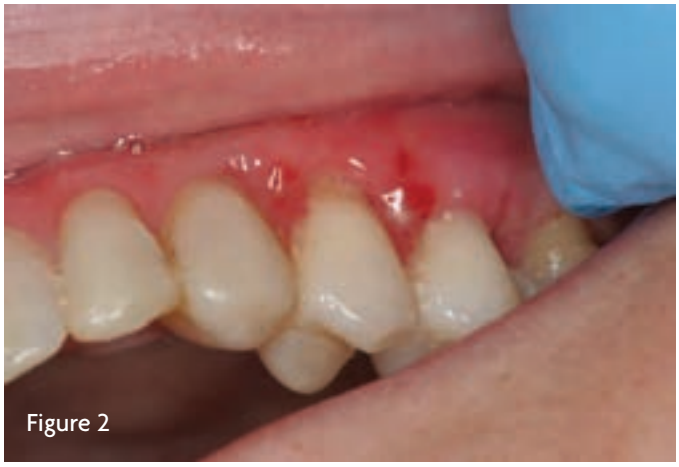


Figure 2

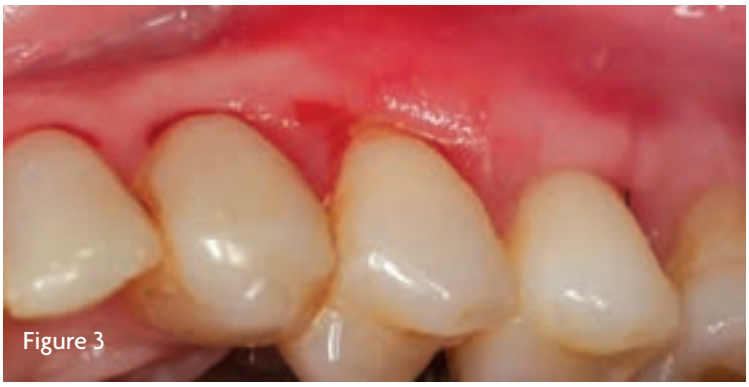


Figure 3

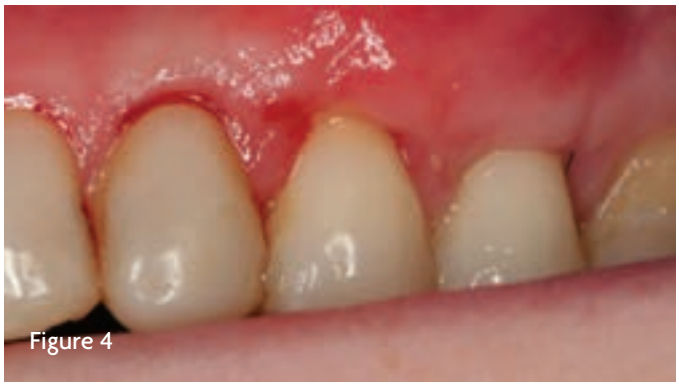


Figure 4

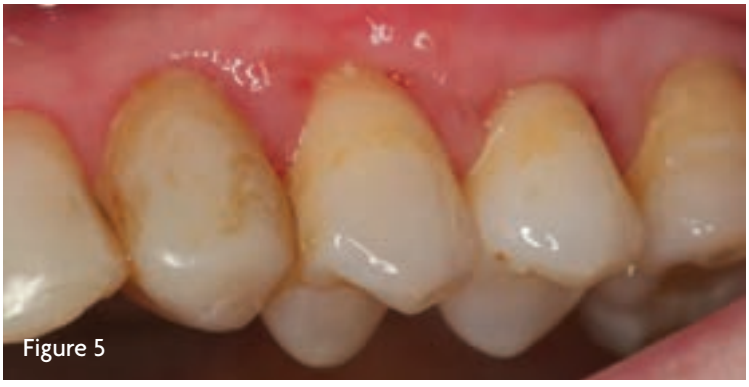


Figure 5

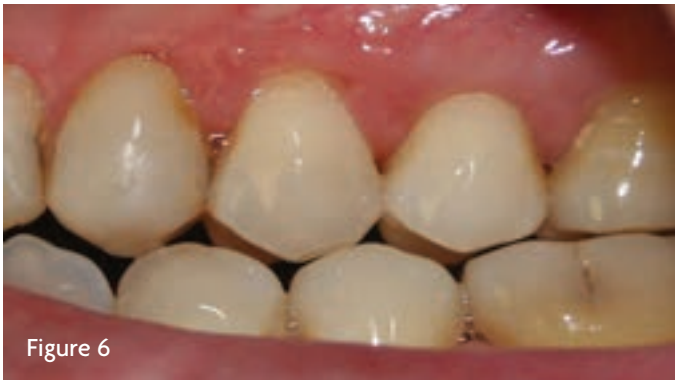


Figure 6

Soft Tissue Grafting: Insufficient Attached Gingiva

Insufficient attached gingiva (IAG) is similar to gingival recession in appearance and treatment, but the causative factors are different. IAG is generally seen where there are mechanical factors that result in either the loss of attached gingiva or an insufficient amount of it (with replacement by mucosa). Malposed muscle attachments from the tongue and lips (frenula), habits (such as picking at gumline with toothpicks or wooden sticks), infections and many other situations can result in the loss of attached gingiva adjacent to a tooth. In addition, often implants need to be placed in an area where insufficient attached gingiva exists in addition to tooth loss. The lack of gingiva will affect the success of the implant procedure. The function of attached gingiva is to protect the tooth it surrounds. Many factors must be considered prior to these procedures: position of the teeth, available attached gingiva, amount of bone support for the soft tissue, esthetics, and health of the patient.

Decision tree

The desired outcome of grafting to correct an area with insufficient attached gingiva is the restoration of the area to a healthy and functional state. Decellularized dermis can be used as an alternative to autograft tissue in many cases.

Case Report: Insufficient Attached Gingiva

Arnold Sindler, DDS, Periodontist, Westminster, MD, USA

In this case, a patent with gum recession, thin keratinized tissue, and inflammation due to muscle pull is treated with a soft tissue allograft. Other than the deficient tissue, the patient appeared to be in good health.

Gum recession and inflammation is seen in the lower left of #20, #21, and #22. Tooth numbers 20 and 22 display a 1mm recession, where #21 show a larger 4mm recession. All affected teeth show thin, minimal keratinized tissue remaining.

Step one of treatment was for the patient to alter brushing technique to eliminate mechanical trauma. The next phase was surgical, including local anesthesia with aggressive cleaning of the roots of teeth 20, 21, and 22, followed by tetracycline application.

Incisions were made around #s 20, 21, and 22, continuing beyond the mucogingival junction into the vestibule. Papillae between #20/21 and #22/23 were undermined with sharp dissection and separated from underlying tissue on the facial aspect, creating a soft tissue flap.

A piece of OrACELL decellularized dermis was used as connective tissue graft to #22; and another piece of OrACELL used for #20 and #21. Both grafts were then stabilized with sling sutures (Fig 2). Buccal, native gingival tissues were coronally positioned over OrACELL and stabilized with a secondary row of sling sutures. A periodontal dressing was used to protect graft

Post operative photo taken at 3 month follow-up, keratinized tissue and complete root coverage was achieved. (Fig 3)

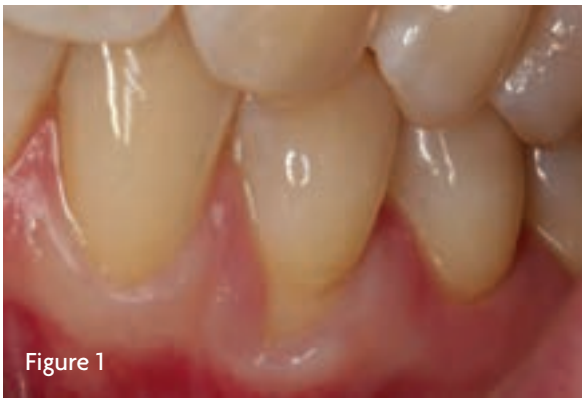


Figure 1

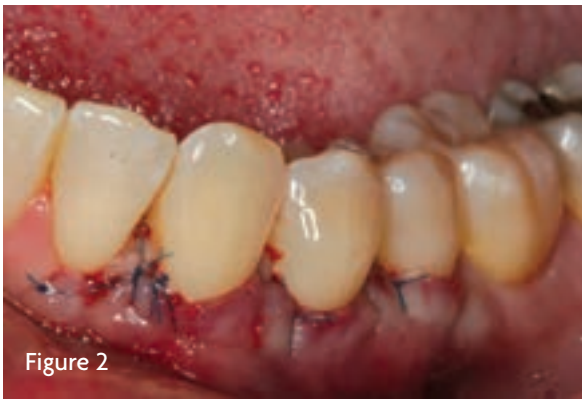


Figure 2

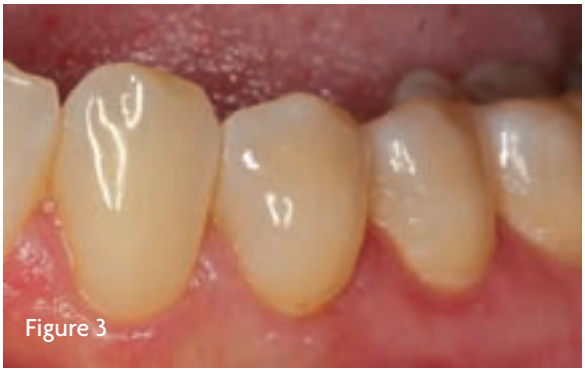


Figure 3

1864 Concert Drive
Virginia Beach, VA 23453
1-888-847-7831 (US & Canada)
1-757-464-4761 ext. 2000 (OUS)
www.LifeNetHealth.org

68-00-057.00

LifeNet Health helps to save lives, restore health and give hope to thousands of patients each year. We are the world's most trusted provider of transplant solutions, from organ procurement to new innovations in bio-implant technologies and cellular therapies—a leader in the field of regenerative medicine, while always honoring the donors and healthcare professionals that allow the healing process.

LifeNet Health®
Saving Lives. Restoring Health. Giving Hope.