Oral Mucosa Harvest: An Overview of Anatomic and Biologic Considerations

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Abstract

Objectives: The authors review the biologic characteristics of the oral mucosa. In addition, the authors report a contemporary harvesting technique of the oral mucosa for urethral transplantation, using biologically sound principles, modified by current literature.

Methods: We reviewed pertinent English literature from January 1966 through January 1, 2007 regarding the biologic properties of the oral mucosa.

Results: The oral mucosa is made up of a thick, nonkeratinized, squamous cell epithelium, overlying a thin lamina propria. It hosts a number of microorganisms, yet, the tissue's inflammatory response to these organisms is minimal. There are multiple immunologic processes intrinsic to the oral mucosa that makes it impervious to native oral flora colonization. Histologic studies have demonstrated that the oral mucosa is highly compatible with the urethral recipient site, at times being indistinguishable from the surrounding tissue. The harvesting surgeon should closely inspect the oral mucosa for any abnormalities prior to considering harvest. Wound healing in the oral mucosa isameliorated by sound surgical principles, yet is mediated by biologic processes beyond the surgeon's control. When harvesting oral mucosa, the surgeon is advised to stay well away from pertinent anatomic landmarks to defer any aesthetic or functional defect to the donor site.

Conclusions: Success of the oral mucosa graft for urethral surgery can be partially attributed to the tissue's biologic properties. When harvesting the tissue, anatomic landmarks should be considered to provide the best possible treatment for the patient while minimizing morbidity to the donor site.
1. Introduction

It has been widely suggested that oral mucosa is now the preeminent donor tissue for the reconstruction of urethral defects [1]. Its versatility is confirmed by the vast use of the tissue for the reconstruction of a variety of urethral defects such as hypospadias [2], epispadias [3], and stricture [4] among others. Although Humby reported the first use of oral mucosa for urethroplastic repair [5], it was not until a report by Burger et al. [6], closely followed by a report from Dessanti et al. [7], that use of the oral mucosa in reconstructive urology came into widespread use.

The purpose of this overview is to provide the reader with an understanding of the biologic traits of the oral mucosa and its anatomic features that make it such a versatile tissue for urethral reconstruction. A secondary objective is to report a novel technique for oral mucosa harvest modified by using sound biologic principles identified through a review of the literature.

2. Methods

We reviewed the English literature using the databases MEDLINE/PubMed (January 1966 through January 1, 2007), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase Drugs and Pharmacology (January 1974 through January 1, 2007). The Medical Subjects Headings (MeSH): oral mucosa graft and buccal mucosa graft were used to search these databases for abstracts that reported the anatomic, histologic, and biologic features, as well as novel tissue engineering methods and harvesting techniques of the oral mucosa. The bibliographies of pertinent articles were examined for additional references.

3. Results

3.1. The Biology of the oral mucosa

3.1.1. Characteristics common to labial and buccal mucosa

The two most common sites of oral mucosa harvest for urethral repair are the:

- Mandibular (lower jaw) labial alveolar mucosa.
- Mucosa of inner cheek—the buccal mucosa.

Oral mucosa is approximately 500 μm in depth [8]. Mucosal thickness is directly associated with male gender and indirectly associated with age [9]. Nonkeratinized mucosa is significantly thicker then keratinized mucosa and successfully withstands the rigorous shearing forces of a prosthesis following oral mucosa transplantation in the oral cavity [8,10]. Furthermore, nonkeratinized mucosa contains more elastic fibers than keratinized mucosa [11].

Anatomically, the oral mucosa is located between the mucosal lining of the gastrointestinal tract and the skin of the outer face displaying properties of both tissues. As shown in Fig. 1, it consists of a:

- Thick nonkeratinized stratified squamous avascular epithelium
- Slightly vascular underlying lamina propria [12]

These properties contrast the bladder mucosa and the penile skin, both of which have a thin epithelium and a thick lamina propria [12].

Take Home Message:

The oral mucosa is architecturally similar to the stratified squamous epithelium of the penile and glanular urethra, making it exceptionally adaptable for urethral substitution.

Oral epithelial cells are infused with polymicrobial intracellular and extracellular flora, mainly streptococci, yet include other species such as [13]:

- Actinobacillus actinomycetemcomitans
- Porphyromonas gingivalis
- Tannerella forsythensis
- Fusobacterium nucleatum
- Prevotella intermedia
- Oral Campylobacter species
- Eikenella corrodens
- Treponema denticola

Despite these harsh exposures, inflammatory infiltrate is rarely witnessed under histologic examination of oral mucosa in healthy individuals [13]. Reasons for this are:

- The intracellular suppressing activity mediated between polymicrobial flora
- Production of antimicrobial peptides by the epithelia (defensins, cytokines, etc).
- Mucosal epithelial cells of the oral cavity limit microflora colonization by continued exfoliation [14] and by a specialized immune system, the mucosa-associated lymphoid tissue (MALT).

The lamina propria of a well-defatted oral mucosa graft can be considered a secondary barrier
preventing microorganisms from entering adjacent tissue layers and exhibits noteworthy antimicrobial properties including:

- Immunoglobulin-synthesizing plasma cells
- Lymphocytes
- Polymorphonuclear neutrophils
- Monocytes/macrophages
- Mast cells

Sebaceous glands, when present, are located in the lamina propria and are more prevalent in labial than buccal mucosa. Immunohistochemical staining demonstrates that blood vessels and nerve fibers from the submucosa infiltrate into the lamina propria [12] and therefore provide a mechanism for angiogenesis and revascularization of the tissue when grafting.

Frequently exposed to compression, stretching, and shearing forces, the oral mucosa is highly resilient. This can be partially attributed to the lamina propria-oral epithelium interface, which consists of extensive projections of connective tissue into the epithelial layer [15], increasing the surface area of the epithelial-lamina propria interface, and providing the oral mucosa’s ability to resist overlying forces.

In comparison to the mucosa of the gastrointestinal tract, the oral mucosa has no muscularis mucosae layer between its epithelium and lamina propria layers. Minor salivary glands, found in the submucosa, are primarily mucous secreting and are
more prevalently found in the labial mucosa. Thus, it is nearly impossible to harvest a labial mucosa graft without interfering with salivary secretion.

3.1.2. Anatomy of the labial mucosa

The mandibular labial mucosal upper and lower borders are designated by the vermilion border of the lower lip and the vestibular fold between the lower lip and the anterior border of the mandible, respectively.

The lateral borders are made up by the outer commissures of the lower lip (Fig. 1).

The mandibular labial alveolar mucosa is innervated by the mental nerve, a terminal branch of the inferior alveolar nerve of the mandibular division of the trigeminal nerve (CN V3). The mental nerve exits the mandible between the first and second premolar teeth through the mental foramen [16]. The surgeon should plan the incision for a labial mucosa harvest medial to the middle of the canines to avoid damaging the mental nerve and compromising sensation to the lower lip.

The mandibular labial alveolar mucosa receives its blood supply from the inferior labial artery (a branch of the facial artery), the mental artery (a continuation of the inferior alveolar artery), as well as anastomoses from the buccal artery. The mental and buccal arteries are both branches of the maxillary artery. Both the facial artery and the maxillary artery are divisions of the external carotid artery [16].

The blood supply of the buccal mucosa originates primarily from:

- The buccal artery—a branch of the maxillary artery
- The anterior superior alveolar artery of the infraorbital artery—a branch of the third part of the maxillary artery
- The middle and posterior superior alveolar arteries—branches of the maxillary artery
- Accessory vessels from the transverse facial artery—a branch of the superficial temporal artery [16].

The harvesting surgeon must continually be aware of the parotid (Stensen) duct. This duct originates from the parotid gland, travels across the body of the masseter muscle, turns medially at the anterior border of the masseter, crosses the buccal fat pad, pierces the buccinator muscle, and finally terminates at its orifice. This orifice is clinically visible by a papilla located on the mucosa of the inner aspect of the cheek adjacent to the maxillary second molar.

The anatomical buccal space located lateral to the buccinator muscle consists of:

- Adipose tissue (buccal fat pad)
- Stensen's duct
- The facial artery and vein
- Lymphatic vessels
- Minor salivary glands
- Branches of CN VII and CN IX

The surgeon must be aware of these structures as well as the underlying buccinator muscle as the graft is dissected from the underlying fat pad. Failure to leave the buccinator muscle intact could result in poor wound closure at the donor site and dysfunction of the buccinator muscle, which serves as a muscle of facial expression.

3.2. Histologic and animal studies

Iizuka et al conducted an experiment in a canine population in which a longitudinal incision in the urethra was repaired either by primary closure (control group) or by oral mucosa [17]. Histologically, the oral mucosa group displayed a urethral lumen completely lined by squamous epithelium with a submucosa abundant in blood vessels and smooth muscle essentially identical to the control group. Oral mucosa grafts (OMGs) exhibited a thinner lamina propria and a thicker squamous epithelium compared to penile skin [18]. Filipas et al. [19] histologically compared healing of full-thickness
skin grafts and OMGs on implantation in the bladders of mini-pigs. Full-thickness skin grafts exhibited significantly greater inflammatory cell infiltration, necrosis, and graft ulceration than OMGs on visual examination. El-Sherbiny used a canine model to compare the histologic outcomes of two different grafting procedures (tube vs. onlay), and three types of grafts (full-thickness skin graft, bladder mucosa, and oral mucosa) [20]. OMGs had an average shrinkage rate of 10%, whereas bladder mucosa and full-thickness grafts had shrunk 20–40% of their original size following transplantation. Histologically, no difference in the degree of neovascularization of the three graft tissues was observed, yet an increase in inflammation and fibrosis was more associated with the full-thickness grafts, especially in the area of hair follicles. Bladder and oral mucosa showed a more uniform graft thickness in comparison to full-thickness skin, which demonstrated an irregularity in graft thickness. Interestingly, the structural integrity of oral mucosa remained intact following transplantation to distant sites [21].

### 3.3. Wound healing in the oral mucosa

Age and female status are associated with prolonged wound healing in the oral mucosa [22]. In contrast to the healing of keratinized oral mucosa whereby the process of wound healing is more complex [23], the healing of nonkeratinized mucosa is less complicated and is much more predictable.

**Take Home Message:**

The three primary clinical factors responsible for successful healing of the oral mucosa wound are:

1. Close proximity of wound edges during primary healing
2. Minimal development of granulation tissue during secondary healing [23]
3. Properly defatting and removing all excess submucosal tissue, fat, and muscle encouraging revascularization of the graft [24, 25]

These variables can be ameliorated by using sound harvesting techniques and by the patient’s cooperation with postoperative and oral hygiene instructions from the harvesting surgeon. Healing by secondary intention was associated with less postoperative pain, discomfort, and dysfunction to patient [26].

### 3.4. Tissue engineering

Previous dental procedures, tissue trauma, infection, malignancy, or prior OMG harvest may make donor sites less than adequate for harvest. In fact, a well-known shortcoming of oral mucosa as a donor tissue is the limited quantity available compared with skin [27]. Bhargava et al developed a technique to increase the amount of tissue available for harvest called tissue-engineered buccal mucosa (TEBM) [28]. To assess graft tensile strength, the graft was exposed to shear mechanical and catheterization forces.

**Take Home Message:**

Histologic examination revealed that full-thickness TEBM was well integrated at the epidermal-dermal junction and was suitable to withstand catheterization forces without substantial epithelial changes [28].

Lauer et al described a technique facilitating primary closure of the oral mucosa harvest site [29]. Tissue grafts were engineered and resized to fit corresponding intraoral defects left by OMG harvest and were then sutured to the surrounding native mucosa. Clinical assessment of maximum jaw opening revealed that all 12 patients returned to preoperative maximum jaw opening measurements. The grafted/native mucosa interface could not be differentiated clinically 3 mo following harvest.

### 3.5. Surgical procedures for oral mucosa harvest

To facilitate access to the oral cavity, nasal endotracheal intubation is the preferred method of airway control by the harvesting surgeon [30]. When oral endotracheal intubation is used, special precautions should be taken to maintain proper tube placement during the entire harvesting procedure. This is particularly important when the urethral defect requires bilateral buccal mucosa harvests. Two separate sterile surgical instrument tables, instrument setups, prepping and draping should be used to minimize cross-contamination of the oral and urologic wounds.

#### 3.5.1. The two-team approach

The exaggerated lithotomy position has well-documented potential complications that are proportional to the length of time in surgery. By reducing the patient’s time in the lithotomy position, a
reduction in sequelae such as neurapraxia, compartment syndrome, myoglobinuria, and renal failure can be achieved [31]. When the lithotomy position is used by the reconstructive urologist, a two-team approach with separate and concurrent operating teams at the urologic and oral sites reduces lithotomy and general anesthesia time. Furthermore, it allows the transplantation team to solely concentrate on urethral reconstruction [30]. When a single operator performs both the harvesting and urethroplasty procedures, the patient’s legs should be put down, out of the lithotomy position during harvest to prevent any unpleasant complications.

3.5.2. Retraction
Several methods have been proposed to stabilize the dissection plane in oral mucosa harvest. One group has advocated use of the Steinhauser mucosa stretcher [30,32], which is designed to retract and provide hemostasis to the donor bed providing improved access and ease of harvest for the surgeon. Similar devices, initially designed for cleft palate surgery, have proven useful in oral mucosa harvest by adding the benefit of tongue and cheek retraction thereby increasing operator visibility and access to the harvest site [33].

3.5.3. Site conditions contraindicating oral mucosa harvest
A thorough head and neck examination should be undertaken to avoid potential transplantation of diseased tissue to the recipient site. There are several conditions in the oral cavity that would contraindicate oral mucosa harvest (Table 1) [34–36]. Immunocompromised patients have a higher susceptibility to all these conditions. These conditions must not be confused with variations of normal oral mucosa (Table 1) [37].

Alterations in normal mucosal anatomy increase in prevalence as one increases in age [38,39]. Functional changes increasing with age are a decreased nerve response to thermal, chemical, and mechanical stimuli and an increased susceptibility to chronic irritation, such as that caused by a removable prosthesis. This is most likely due to arteriosclerotic changes of the oral mucosa that cause a decrease in perfusion to the tissue.

A thorough social history must also be elicited from the patient. Ethanol abuse increases the permeability of the oral mucosa [40] by altering the lipid composition of oral mucosa cells [41]. In addition, chronic exposure to alcohol may induce dysplastic change in the oral mucosa, contraindicating its harvest [42]. A social history positive for heavy smoking warrants careful examination of the oral mucosa for dysplastic change because smoking is more associated with malignancy than alcohol abuse. Although smoking and periodontal disease in unison may be contraindications for oral mucosa harvest, when combined these patient-oriented factors increase the prevalence of pathogens in the tissues possibly leading to a poor outcome at the recipient site [43].

Medications, whether prescription or over the counter, herbal supplements, or vitamins, can affect the condition of the oral mucosa [44]. Patients on anticoagulants, antithrombotic therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and herbal supplements such as ginger, gingko biloba, and garlic are at risk for increased bleeding at the harvest site. Commonly used medications directly affecting the oral mucosa causing erythema multiforme or lichenoid lesions include clindamycin, ibuprofen, barbiturates, and Captopril among others. In addition, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and NSAIDs have been associated with angioedema of the oral mucosa. Both of these conditions would contraindicate oral mucosa harvest.

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<tr>
<th>Normal oral conditions [37]</th>
<th>Pathologic oral conditions</th>
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<tbody>
<tr>
<td>Ephelis (cutaneous freckle)</td>
<td>Leukemia [35]</td>
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<tr>
<td>Fordyce granules (ectopic sebaceous glands)</td>
<td>Leukoedema [35]</td>
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<tr>
<td>Linea alba buccalis (white streak on buccal mucosa following the occlusal plane)</td>
<td>Mucositis associated with head and neck radiation therapy, chemotherapy, and cancer surgery [34]</td>
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<tr>
<td>Morsicatio buccarum (cheek chewing)</td>
<td>Pemphigus vulgaris</td>
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<td>Mucous membrane pemphigoid</td>
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<td>Erythema multiforme</td>
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<td>Leukoedema [37]</td>
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<td></td>
<td>Oral lichen planus</td>
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<td></td>
<td>Recurrent aphthous stomatitis (canker sores) [36]</td>
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The first column list oral conditions that may necessitate the need to delay oral mucosa harvest until site conditions improve. The second column lists oral conditions that would be strict contraindications for oral mucosa harvesting.
3.5.4. Graft harvest

Similar surgical procedures should be undertaken when harvesting from both labial and buccal sites. In the operating room, the patient is prepped and draped in a fashion typical for oral and maxillofacial surgical procedures: a pharyngeal throat screen is placed, and beta-iodine solution is used to cleanse the oral cavity.

Once the urologist determines the quantity of graft needed, either by preoperative urethrography examination or by measuring the defect intraoperatively, a surgical marking pen is used to outline the extent and shape of the graft, staying several millimeters inferior to the papilla of the Stensen duct orifice in the buccal harvest site. The outline should compensate for predicted shrinkage of the graft because one group reported that OMGs shrink up to 20% of their original size at harvest [29]. Anatomic variations such as extensive frenial (muscle) attachments extending toward the vermillion border of the lip and poor periodontal status contraindicate labial mucosa harvest, whereas variations such as an unusually inferiorly located Stensen's duct or anteriorly located anterior pillar and tonsillar tissue contradict buccal mucosa harvest. The graft can be outlined as an elliptical shape (Fig. 1). This design allows for ease in primary closure of the anterior and posterior aspects of the donor site without compromising graft size or viability [26].

Local anesthetic (1% lidocaine with 1:100,000 epinephrine) is injected at the periphery of the marked outline and deep into the central area of the donor site to help elevate and hydro-dissect the oral mucosa from the underlying soft tissues. After an interval of 5–7 min to allow for maximum epinephrine vasoconstriction effect, an initial incision at the anterior apex of the outline is made with a steel blade or Bovie needle tip on cut mode. The incision is limited to the full thickness of the mucosa only, and a dissection plane is created above the submucosal adipose layer superficial to the buccinator muscle containing as little of the buccal fat pad as possible. Atraumatic forceps are used to handle and grasp the tissue on the submucosal side of the graft with particular care directed at avoiding trauma to the external mucosal surface of the graft. Metzenbaum scissors may be used for both sharp and blunt dissection staying above the submucosal plane, which is performed somewhat past the entire marked outline to the posterior apex of the graft. When dissecting the graft from the buccinator muscle of the buccal site, adipose tissue should be spared on the buccinator surface. Sharp and blunt submucosal dissection is then extended at least 0.5 cm beyond the superior and inferior wound edges to release tension during primary closure. Primary closure is accomplished with a single layer of 4-0 Polyglactin 910 sutures (Vicryl rapid, Ethicon Inc, Somerville, NJ, USA) with an RB-1 tapered needle to minimize mucosal tearing. Initially, two or three interrupted sutures are equally placed along the entire length of the incision to evenly segment and properly align the wound margins. The remainder of the wound is then closed with multiple simple interrupted sutures or a continuous horizontal mattress suture.

The harvested tissue is then inspected and measured. It is usually prepared by the harvesting surgeon by vigilantly removing any muscle, salivary gland, or subcutaneous adipose tissue remnants from the underside of the graft using sharp scissors. Care is taken to avoid accidental perforations and to maintain uniformity of the thickness of the tissue during this process. The graft is then placed on a sponge, rolled up, and placed in 0.9% NaCl solution and passed to the urology surgical table and stored until needed for reconstruction. All patients should be prescribed chlorhexidine oral rinses in the postoperative period to control microbiologic colonization. A second-generation cephalosporin (eg, cefotaxime) is typically administered intravenously by the urologist following surgery. This coverage is adequate to minimize incidence of infection at the donor site.

4. Conclusion

Since the initial papers by Burger et al and Dessanti et al, numerous reports have detailed the biologic reasoning for the success of the oral mucosa in reconstructive urology. Innovative techniques are being reported at a rapid pace. Paralleling the clinical success of the oral mucosa, researchers must understand the biologic basis for why one technique works better than another. The translation of this information from the bench top to the surgeon’s hands is necessary to move the field forward.

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Conflict of interests

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References

CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. The oral mucosa is composed of:
   A. A thin squamous cell epithelium and a thick lamina propria
   B. A thick squamous cell epithelium and a thin lamina propria
   C. A thin squamous cell epithelium and a thin lamina propria
   D. A thick squamous cell epithelium and a thick lamina propria

2. The most abundant microorganism(s) indigenous to the oral mucosa is (are):
   A. Streptococci
   B. Porphyromonas gingivalis
   C. Fusobacterium nucleatum
   D. Prevotella intermedia

3. The mandibular labial mucosa is innervated primarily by the:
   A. Mental nerve
   B. Buccal nerve
   C. Middle posterior alveolar nerve
   D. Facial nerve

4. One of the primary patient-oriented factors found to be directly associated with delayed wound healing in the oral mucosa of an otherwise healthy patient is:
   A. Young age
   B. Surgical harvest site (labial vs. buccal)
   C. Race
   D. Female gender status

5. Normal features of the oral mucosa may include:
   A. Leukoedema
   B. Linea alba buccalis
   C. Pemphigus vulgaris
   D. Aphthous ulcer

6. Medications that may cause erythema multiforme or lichenoid lesions of the oral mucosa include:
   A. Sertraline
   B. Loratadine
   C. Acetylsalicylic acid
   D. Ibuprofen


