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Tissue engineered buccal mucosa for urethroplasty: Progress and future directions ☆

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ABSTRACT

Purpose: Autologous buccal mucosa is commonly utilized in the surgical treatment of urethral strictures. Extensive strictures require a larger quantity of tissue, which may lead to donor site morbidity. This review assesses progress in producing tissue engineered buccal mucosa as an alternative graft material.
Results: Few clinical studies have introduced cells onto biological or synthetic scaffolds and implanted resulting constructs in patients. The available studies show that buccal mucosa cells on acellular human dermis or on collagen matrix lead to good acute stage tissue integration. Urothelial cells on a synthetic substrate also perform well. However while some patients do well many years post-grafting, others develop stricture recurrence. Acellular biomaterials used to treat long urethral defects in animals commonly lead to fibrosis.
Conclusions: Tissue engineered buccal mucosa shows promise as a substitute for native tissue. The fibrosis which occurs months post-implantation may reflect the underlying disease process recurring in these patients.
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Contents

1. Introduction

Buccal mucosal grafts have become established as the substitution material of choice in the surgical augmentation of urethral stricture

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disease not amenable to excision and primary anastomosis (EPA) [1,2]. The first description of its use in urethral surgery was over 100 years ago [3]; however it has only gained popularity in the past 2 decades [4] as the preferred tissue of choice. Buccal mucosa has many desirable properties, which make it suited to urethral reconstruction including hairlessness, a natural compatibility with the wet environment, an ability to rapidly pick up a blood supply from the wound bed and a good resistance to contracture. It can be harvested easily from the cheek (buccal mucosa) with an acceptable degree of morbidity [5]. In the past it has been harvested from the lip (labial) where there is far greater morbidity and also from the tongue (lingual mucosa) [6,7].

Patients with very long strictures present a major challenge and require a greater length of graft. Harvesting a greater quantity of tissue increases the risk of graft related morbidity and may not be possible, particularly in patients with a history of prior grafting. Several clinical series, with small patient numbers, have assessed acellular xenografts showing short-term success in the range of 76–100% [8–11]. Conversely other series demonstrated a high risk of restricturing (up to 80%) [12]. In particular when acellular grafts were used to bridge long defects (>4 cm) all failed in the series with the longest follow-up (71 months) [8].

In order to provide a solution for men with long or recurrent strictures our group developed a methodology to culture tissue engineered buccal mucosa (TEBM) [13]. The approach consists of seeding autologous oral fibroblasts and keratinocytes onto cadaveric de-epidermized dermis sourced from a tissue bank. Grafts produce using this method were subsequently implanted into a small group of patients with complex urethral strictures [14].

Over the past decade, a variety of methodologies have been reported for the development of buccal mucosa composites [15,16]. The applications for these are not just limited to urethral surgery and intra-oral reconstruction but include providing in vitro models for oral diseases (e.g. infection, cancer), drug delivery studies and the assessment of imaging technologies [15,16]. Meanwhile, there have been further pre-clinical and clinical reports assessing the use of TEBM in urethral reconstruction (Table 1). In this article we critically analyze contemporary approaches to the production of TEBM with reference to the broader literature and discuss the key issues in using this approach in urethral reconstruction.

2. Stricture pathogenesis and surgical principles

Urethral stricture disease in the male was defined by the recent International Consultation on Urological diseases (ICUD) as "a narrowing of the urethra consequent upon ischaemic spongiofibrosis…" [17]. Strictures have an incidence of 0.6% [18] and can result from a variety of etiological factors including trauma, inflammatory, iatrogenic, and idiopathic causes resulting in ischaemic scarring of the corpus spongiosum. The epithelial injury heals by fibrosis, causing a reduction in the urethral caliber and impairment to the flow of urine.

The male urethra is divided into the posterior and anterior segments. Strictures occurring in the posterior urethra are often the result of trauma or surgical manipulation. Most strictures of the anterior urethra are idiopathic (short and soft in composition), iatrogenic or inflammatory in nature. Lichen sclerosus (LS) is an inflammatory condition of unknown etiology affecting the stratified epithelium of the anterior urethra [19]. LS results in excess dermal collagen with a hyperkeratotic epidermal layer in the urethral wall. Strictures forming from LS tend to be progressive, complex, and long and have high recurrence rates after surgical repair.

Posterior urethral strictures can successfully be treated with dilatation, endoscopic incision or excision of the diseased segment with anastomosis of the two healthy urethral ends, excision primary anastomosis (EPA). Short strictures of the proximal anterior (bulbar) urethra not due to LS can often also be treated using this method with success rates in excess of 90% in many series [20,21]. Owing to the elasticity of the urethra and periurethral tissues of the bulbar urethra and bulbomembranous junction, several maneuvers can be utilized to gain extra urethral length in order to perform EPA, which is associated with better outcomes as compared to other forms of urethroplasty. Longer strictures, or those due to LS require tissue substitution in order to prevent chordee associated with loss of urethral length or recurrence of LS respectively. Substitution urethroplasty is performed using either a flap or graft. It should be noted that as LS has the tendency to recur in urogenital skin, therefore grafts from alternative tissues sources should be used for substitution in this context. EPA cannot be performed for those strictures of the penile urethra due to the production of urethral chordee and loss of penile length if even small segments of urethra are excised. There has been increasing support for the use of buccal mucosa grafts for substitution urethroplasty [1]. A variety of other graft tissues such as bladder [22] and colonic mucosa [23] have been investigated but their harvest is more invasive. Buccal mucosa urethroplasty can achieve success rates of 85%–100% [24]. In patients who develop stricture recurrence, this can be due to the compromised wound bed, recurrence of the underlying disease process or surgical technique related factors.

3. Normal buccal mucosa

The term buccal mucosa refers to the oral mucosa that overlies the inner cheek of the oral cavity. It is architecturally similar to the epithelium of the penile urethra, making it exceptionally adaptable for urethral substitution. There are three layers; a relatively thick and avascular epithelium composed of keratinocytes, the slightly vascular fibrous connective tissue layer containing fibroblasts (Lamina propria), [25] and submucosal connective tissue, which attaches to associated structures such as fat, muscle and salivary glands [26].

The epithelium is non-keratinized stratified squamous over the cheek. Buccal mucosa is highly resilient, it is exposed to compression, stretching, and shearing forces. In areas of the mouth subject to even greater mechanical abrasion, such as the gingiva and hard palate, the epithelium is keratinized with a surface layer of dead cells containing high quantities of cytokeratin filaments. Similar to skin, buccal mucosa consists of densely packed cells at differing degrees of differentiation, attached to one another by desmosomes and tight junctions. The deepest layer contains continuously dividing progenitor cells, which differentiate into mature keratinocytes as they migrate to the surface, before eventually being shed.

The epithelium is attached to the underlying lamina propria through the basement membrane, which is composed of collagen VI, laminin, and fibronectin, as in skin. Basal epithelial cells attach to the basal lamina with hemi-desmosomes, which are in turn attached by anchoring fibrils of collagen VII to the collagen fibers of the underlying lamina propria. The lamina propria is rich in fibrillar proteins including collagens I, III, and elastin, which confer strength and elasticity to the tissue. The lamina propria also contains an extensive network of capillary loops, lymphatics, and nerve endings. The resilience of buccal mucosa can be partially attributed to the lamina propria–oral epithelium interface, consisting of many projections of connective tissue into the epithelial layer, which increases the surface area of the epithelial–lamina propria interface, and providing the oral mucosa's ability to resist overlying forces. The lamina propria is in turn attached to a submucosa of connective tissue associated with muscles, fat, and salivary glands.

4. Tissue engineered buccal mucosa

4.1. Overview

A tissue engineered oral mucosa model was first developed by Izumi et al. [27], who seeded keratinocytes onto de-epidermized dermis. A variety of three-dimensional (3D) models of oral mucosa have since been developed through tissue engineering methods [16]. These methods have included a variety of cell types, scaffolds, and culture protocols.

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