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Review

Overcoming scarring in the urethra: Challenges for tissue engineering

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Abstract Urethral stricture disease is increasingly common occurring in about 1% of males over the age of 55. The stricture tissue is rich in myofibroblasts and multi-nucleated giant cells which are thought to be related to stricture formation and collagen synthesis. An increase in collagen is associated with the loss of the normal vasculature of the normal urethra. The actual incidence differs based on worldwide populations, geography, and income. The stricture aetiology, location, length and patient's age and comorbidity are important in deciding the course of treatment. In this review we aim to summarise the existing knowledge of the aetiology of urethral strictures, review current treatment regimens, and present the challenges of using tissue-engineered buccal mucosa (TEBM) to repair scarring of the urethra. In asking this question we are also mindful that recurrent fibrosis occurs in other tissues—how can we learn from these other pathologies?

1. Introduction

Urethral strictures are an abnormal narrowing of the urethra. The origins of this fibrosis may be due to intrinsic conditions but commonly occur in response to damage or infection [1]. They represent a scarring of the vascular corpus spongiosum leading to fibrosis [2]. There are varying degrees of spongiofibrosis but obstruction of the urethra can cause infection, bladder calculi, fistulas, sepsis, and renal failure.

Overall the incidence of urethral strictures is about 1% in the males over the age of 55. The actual incidence differs based on worldwide populations, geography, and income [1,3].

Management of strictures varies from less invasive techniques such as urethral dilatation and urethrotomy, to

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more invasive procedures such as anastomotic and substitution urethroplasty [4]. In patients who have extensive disease, obtaining sufficient graft can be challenging. For this reason, tissue-engineered buccal mucosa (TEBM) for the treatment of complex strictures was developed [5,6].

2. Urethral stricture and histopathology

The normal urethra is lined by pseudo stratified columnar epithelium anchored to a basement membrane beneath which there is connective tissue composed of fibroblasts in an extracellular matrix composed of collagen, proteoglycans, elastic fibres and glycoproteins. Under this is the spongiosum composed of vascular sinusoids and smooth muscle. The pathological changes associated with strictures show that the normal epithelium becomes replaced with squamous metaplasia [7]. All strictures involve some injury to the epithelium of the urethra or corpus spongiosum and fibrosis occurs during the subsequent healing process.

This stricture tissue is rich in myofibroblasts and multinucleated giant cells which are thought to be related to stricture formation and collagen synthesis, respectively. An increase in collagen is associated with the loss of the normal vasculature of the normal urethra. Singh and Blandy [8] reported an experimental study in the rat to determine the role of extravasation of urine in the pathogenesis of urethral stricture. They observed that the ultrastructure of urethral stricture tissue suggested that some strictures were fibrous while others were more resilient, and the total amount of collagen increased in urethral strictures, resulting in dense fibrotic tissue with decreased smooth muscle tissue and decreased elasticity. In contrast, Baskin et al. [9] could not demonstrate an increase in the total amount of collagen in strictures compared with the normal urethra, but rather found that an alteration in the ratio of collagen type may explain the fibrotic, non-compliant nature of urethral stricture scar tissue. They found that the normal urethral spongiosum was composed of 75% type I collagen and 25% type III collagen. In contrast, the type III collagen in urethral stricture tissue was increased to 84% with a corresponding decrease in type I collagen (to 16%). These changes were accompanied by a decrease in the ratio of smooth muscle to collagen, as well as changes in the synthesis of nitric oxide in the urethral stricture tissue [10]. Glycosaminoglycans (GAGs) and collagens are major components of the extracellular matrix and they have key roles in fibrotic diseases. Da-Silva et al. [11] measured the GAG composition in the strictured urethral segment. They concluded that composition changes in GAGs could contribute to the non-compliant nature of urethral scar tissue and cause functional changes. Anterior urethral strictures normally occur after trauma or inflammation, and result in spongiofibrosis. Posterior urethral strictures generally result from iatrogenic injury or occur after pelvic fractures. These injures are contractures or stenosis of the urethra rather than true strictures.

2.1. Aetiology of urethral strictures

Urethral stricture disease can occur due to several different aetiologies (Table 1) [12]. Strictures can be due to iatrogenic, idiopathic, inflammatory or traumatic causes. The largest category is actually iatrogenic resulting from urethral manipulations, related to placing of indwelling catheters, transurethral manipulation, surgery for hypospadias, prostatectomy, and brachytherapy [13,14] (Fig. 1). Strictures can also occur due to trauma associated with pelvic fractures and in approximately 60% of patients the function of the distal sphincter mechanism and hence continence depends on the integrity of the bladder neck. Moving on to infection, untreated gonorrhoea and chlamydia causing urethritis can lead to strictures. Another inflammatory disease associated with urethral stricture is balanitis xerotica obliterans. This is a chronic inflammatory disease whose aetiology is still unknown [15].

Table 1 Stricture aetiology by location [12].

	Penile, %	Bulbar, %
Iatrogenic	40	35
Idiopathic	15	40
Inflammatory	40	10
Traumatic	5	15

3. Clinical evaluation

The first important step in the evaluation of a patient and the decision about treatment is to obtain a thorough history to get as much information as possible about the aetiology behind the urethral stricture. This requires documenting the onset and severity of obstructive and storage-related voiding symptoms. In addition to this history, uroflowmetry is widely used in the assessment of the urethral stricture. Retrograde urethrography is used to provide information on stricture location and length. Moreover, retrograde and antegrade cystourethrographies are recommended to assess posterior urethral strictures and bladder neck function [16]. Cystoscopy can show the location and degree of the stricture, but if the stricture cannot be passed, no information can be obtained. Another diagnostic procedure is ultrasonography which can be helpful in the assessment of the stricture length and the degree of spongiofibrosis [17].

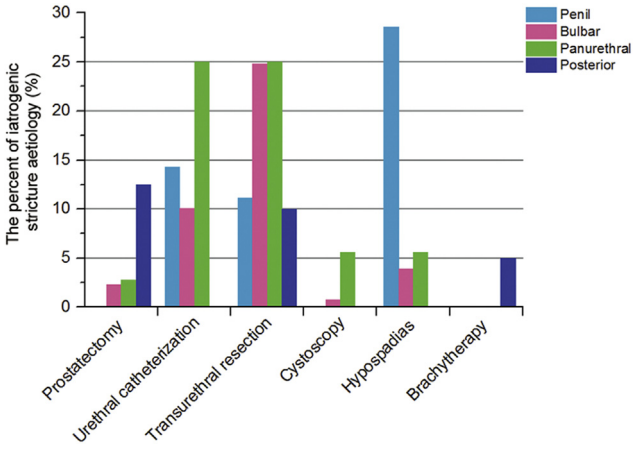

Figure 1 Iatrogenic stricture aetiology (%) by location [13].