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Tissue Engineering of the Urethra: A Systematic Review and Meta-analysis of Preclinical and Clinical Studies

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Abstract

Context: Urethra repair by tissue engineering has been extensively studied in laboratory animals and patients, but is not routinely used in clinical practice.
Objective: To systematically investigate preclinical and clinical evidence of the efficacy of tissue engineering for urethra repair in order to stimulate translation of preclinical studies to the clinic.
Evidence acquisition: A systematic search strategy was applied in PubMed and EMBASE. Studies were independently screened for relevance by two reviewers, resulting in 80 preclinical and 23 clinical studies of which 63 and 13 were selected for meta-analysis to assess side effects, functionality, and study completion. Analyses for preclinical and clinical studies were performed separately. Full circumferential and inlay procedures were assessed independently. Evaluated parameters included seeding of cells and type of biomaterial.
Evidence synthesis: Meta-analysis revealed that cell seeding significantly reduced the probability of encountering side effects in preclinical studies. Remarkably though, cells were only sparsely used in the clinic (4/23 studies) and showed no significant reduction of side effects. ln 21 out of 23 clinical studies, decellularized templates were used, while in preclinical studies other biomaterials showed promising outcomes as well. No direct comparison to current clinical practice could be made due to the limited number of randomized controlled studies.
Conclusions: Due to a lack of controlled (pre)clinical studies, the efficacy of tissue engineering for urethra repair could not be determined. Meta-analysis outcome measures were similar to current treatment options described in literature. Surprisingly, it appeared that favorable preclinical results, that is inclusion of cells, were not translated to the clinic. Improved (pre)clinical study designs may enhance clinical translation.
Patient summary: We reviewed all available literature on urethral tissue engineering to assess the efficacy in preclinical and clinical studies. We show that improvements to (pre)clinical study design is required to improve clinical translation of tissue engineering technologies.

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1. Introduction

Congenital birth defects of the urethra, such as hypospadias (1 in every 300 births) [1,2], and acquired urethral abnormalities, such as urethral strictures (1 in every 1000 men > 65 yr of age [3]), represent major clinical entities. Treatment usually involves a surgical procedure with risk of (recurrence of) strictures or fistula requiring additional care or reintervention. Whenever possible, local tissue flaps or stricture resection in combination with end-to-end anastomosis are used for urethra reconstruction [4,5]. Generally, two surgical approaches exist for urethral reconstruction: partial replacements using onlay or inlay techniques or the full circumferential procedure, which is used in rare cases with significant urethral scarring or lichen sclerosis. Depending on patient and local factors, procedures can be performed as one-stage procedure or as planned multistage procedure [3].

Autologous tissue transplantation such as buccal mucosa or free skin grafts are the standard treatments [6–9]. However, due to the limited quantity of available donor tissue, accompanying donor site morbidity (16–32% for buccal mucosa grafts) and complications (eg, recurrences or infections), alternative treatment options are needed to improve long-term outcomes [10]. Tissue engineering may overcome some of the aforementioned disadvantages by providing a temporary template to guide tissue regeneration [11]. In general, tissue engineered templates include decellularized tissue or de-novo prepared materials from natural or synthetic origin [12–14]. Templates can be seeded with (stem) cells from the patient prior to implantation. These cells may stimulate tissue remodeling by excreting cytokines and growth factors and contributing to cellular population of the template [15,16].

Despite the potential of tissue engineering shown in in vitro research and preclinical studies, clinical translation is limited. To improve translation, an evidence-based approach, such as systematic reviews, can be applied when designing new tissue engineering strategies. This will avoid unnecessary replication of studies and will help to select the most optimal experimental design and model. We are the first to perform a comprehensive systematic review of evidence for the efficacy of urethral tissue engineering in preclinical and clinical studies. A meta-analysis was used to compare different experimental designs based on clinically relevant outcomes. This systematic review aims to improve the translation of urethral tissue engineering from bench to bedside.

2. Evidence acquisition

2.1. Literature search

To identify all available studies on urethral tissue engineering published and indexed up until June 1, 2016, a systematic search strategy was applied in PubMed (Supplementary data 1) and Embase (via OvidSP; Supplementary data 2). This strategy combined a tissue engineering search component containing synonyms for tissue engineering related terms [17] with a customized search component for urethra or urethra-related diseases. Medical Subject Headings terms and EMTREE terms were used in PubMed and Embase, respectively, together with separate words or word combinations in title or abstract. Next, either an animal filter designed by Hooijmans et al (PubMed) [18] or de Vries et al (Embase) [19] was applied (Supplementary data 1 and 2, search component 3A) or a custom filter for clinical studies (Supplementary data 1 and 2, search component 3B). In addition, retrieved reviews were screened for primary studies not found using the search strategy. Clinical studies found during animal search strategy were marked and screened for relevance and vice versa.

2.2. Study selection

Duplicates in retrieved articles were removed in EndNote (Version X7.2, Thomson Reuters, PA, USA). Studies were assessed independently by LV and PdJ. First, clearly irrelevant studies were excluded based on title. Next, titles and abstracts of the remaining articles were screened for relevance in Early Review Organizing Software (Buenos Aires, Argentina, www.eros-systematic-review.org) using the following exclusion criteria: (1) no urethra, (2) no tissue engineering, (3) no animals or patient, (4) no primary study. A study was considered to be about tissue engineering when a processed template was used. Studies on tissue transplants or reconstructive surgery without the use of a template or without a urethra defect were excluded. Of the remaining studies, full texts were screened using the same exclusion criteria. Articles not available as full text were excluded at this stage. No language restrictions were applied in the screening phase. If necessary, Google translate was used. Retrieved studies from search updates were directly screened in Endnote according to the same principles. In all stages of the selection process, discrepancies between reviewers were discussed until consensus was reached.

2.3. Study characteristics

From all included studies, general information (author, year) and study characteristics (age range of patients, animal species, sex, surgical procedure, type of biomaterial, type of cells) were extracted and listed in Table 1 for preclinical studies and Table 2 for clinical studies. For languages other than English, German, and French, Google Translate was used to retrieve study characteristics.

2.4. Extraction outcome data

Three outcome measures were used to evaluate study outcome: (1) incidence of side effects, for example, strictures, stenosis, fistulae, and infections, (2) functionality, defined as the ability to void with continence, and (3) study completion, for animals defined as survival until predetermined endpoint and for clinical studies as available for follow-up or no additional urethroplasty required. Only English, German, and French studies were

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