Tissue Engineering of the Bladder—Reality or Myth? A Systematic Review

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Purpose: We systematically reviewed preclinical studies in the literature to evaluate the potential of tissue engineering of the bladder. Study outcomes were compared to the available clinical evidence to assess the feasibility of tissue engineering for future clinical use.

Materials and Methods: Preclinical studies of tissue engineering for bladder augmentation were identified through a systematic search of PubMed and Embase™ from January 1, 1980 to January 1, 2014. Primary studies in English were included if bladder reconstruction after partial cystectomy was performed using a tissue engineered biomaterial in any animal species, with cystometric bladder capacity as an outcome measure. Outcomes were compared to clinical studies available at http://www.clinicaltrials.gov and published clinical studies.

Results: A total of 28 preclinical studies are included, demonstrating remarkable heterogeneity in study characteristics and design. Studies in which preoperative bladder volumes were compared to postoperative volumes were considered the most clinically relevant (18 studies). Bladder augmentation through tissue engineering resulted in a normal bladder volume in healthy animals, with the influence of a cellular component being negligible. Furthermore, experiments in large animal models (pigs and dogs) approximated the desired bladder volume more accurately than in smaller species. The initial clinical experience was based on seemingly predictive healthy animal models with a promising outcome. Unfortunately these results were not substantiated in all clinical trials, revealing dissimilar outcomes in different clinical/disease backgrounds. Thus, the translational predictability of a model using healthy animals might be questioned.

Conclusions: Through this systematic approach we present an unbiased overview of all published preclinical studies investigating the effect of bladder tissue engineering on cystometric bladder capacity. Preclinical research in healthy animals appears to show the feasibility of bladder augmentation by tissue engineering. However, in view of the disappointing clinical results based on healthy animal models new approaches should also be evaluated in preclinical models using dysfunctional/diseased bladders. This endeavor may aid in the development of clinically applicable tissue engineered bladder augmentation with satisfactory long-term outcome.

Key Words: meta-analysis; models, animal; reconstructive surgical procedures; tissue engineering; urinary bladder

Abbreviations and Acronyms

PLGA = poly(lactic-co-glycolic) acid

SIS = small intestinal submucosa

SMC = smooth muscle cell

UC = urothelial cell

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Decreased bladder compliance and/or capacity due to bladder dysfunction, eg neurogenic bladder, may require bladder augmentation. Current surgical techniques mainly involve the use of gastrointestinal tissues. Due to the physical properties of the tissue, complications may develop, including metabolic disorders, bladder perforation, stone formation, infections and hematuria-dysuria syndrome, as well as cancer due to metaplasia.[1,2] To avoid these complications and extensive operations, new therapeutic alternatives are needed. Tissue engineering approaches could offer innovative options for bladder reconstruction by use of biomaterials supplemented with cells and/or growth factors. This application might result in the regeneration of bladder tissue or in the construction of a neobladder, which has been pioneered by Atala et al.[3]

In this systematic review we present a comprehensive overview of the current literature regarding preclinical bladder tissue engineering, with a quantitative and unbiased comparison of study outcomes. Cystometric bladder volume was used as an outcome measure to assess the effect of tissue engineering since bladder volume is of paramount importance in the clinical situation. We also discuss the available information concerning clinical experience with tissue engineered bladders.

MATERIALS AND METHODS

Search Strategy

We systematically searched PubMed and Embase (OvidSP) through January 1, 2014 to systematically identify preclinical studies of tissue engineering and bladder reconstruction.[4,5] Synonyms for tissue engineering were combined with synonyms for bladder reconstruction using MeSH (PubMed) and Emtree terms (Embase), as well as free text words from titles or abstracts ([tiab] or /ti,ab, supplementary fig. 1, http://jurology.com/). Subsequently results were filtered for animal studies using previously designed animal filters.[6,7] The bibliographies of included series and relevant reviews were screened for any missing studies. Furthermore, clinical trials regarding this subject were manually identified using www.clinicaltrials.gov and PubMed.

Study Inclusion

After removal of duplicates and triplicates in EndNote, X5 (Thomson Reuters, Philadelphia, Pennsylvania) 2 reviewers (VS, MS) excluded studies based on titles that clearly were not related to the subject. Next, they independently screened the abstracts of the remaining studies using Early Review Organizing Software (http://www.eros-systematic-review.org), excluding 1) review articles, 2) studies in which bladder reconstruction was not performed after partial cystectomy, 3) studies in which tissue engineered biomaterial was not used and 4) studies without an animal model. Review articles were labeled but not included for further analysis. Thereafter, the eligibility of studies was investigated by a full text assessment. Studies were also excluded if they 1) were not an original article (eg conference abstracts, editorial comments), 2) were not published after 1980, 3) had no cystometry data available and lacked mean, standard deviation/standard error and number, 4) had no disease background and 5) were not published in English. In all stages of the process discrepancies were discussed until consensus was reached.

Data Extraction

Table 1 outlines the general characteristics and outcomes of the included studies. The quality of the studies was assessed using a previously designed questionnaire (supplementary fig. 2, http://jurology.com/). Cystometric data on bladder volume (mean ± SD bladder capacity, number of animals) was used for meta-analyses. In case of more than 1 experimental group or time point the most successful group, as indicated by the authors, at the end point was used in the analyses. The parameter of bladder volume was chosen because it has the greatest clinical significance in bladder augmentation procedures, which aim at restoring bladder volume and protecting the upper urinary tract.

Meta-Analyses

Meta-analyses were performed for mean bladder volumes. Due to large differences in absolute bladder volumes between species, standardized mean differences were calculated for the individual studies.[8] Since different species and biomaterials were used, considerable heterogeneity was expected. Therefore, studies were organized according to study type (I to IV) and analyzed using a random effects model to calculate overall effect size, 95% CI and I^2 (measure of statistical heterogeneity). Type I studies compared experimental bladder volumes with volumes of healthy control animals, type II compared preoperative and postoperative measurements in the same animals, type III compared sham operated animals to outcome (although the definition of sham operated was unclear) and type IV compared augmented animals to nonaugmented animals (primary closure) after partial cystectomy. Further subgroup analyses were only performed with type II studies, and included animal species and construct type (with or without cells). ReviewManager,™ version 5.2 was used to create forest plots and perform meta-analyses.

RESULTS

Study Inclusion and Characteristics

Figure 1 outlines study inclusion and exclusion criteria. A total of 28 articles were included for data synthesis and meta-analysis.[9–36] Exclusions during full text assessment were mainly related to incomplete or missing cystometry measurements. No additional references were found in the bibliographies of the included studies or relevant reviews. Three articles were excluded from further analysis since either the control group was represented as 100% without any SD or the experimental group consisted of only 1 subject.[37–39]

Table 1. *Study characteristics*

References	Study Type	Animals				Cystectomy	Followup (mos)	Material
		Models (stock/strain)	Sex	Age	Wt			
Mauney et al[9]	I	Mice (CD-1®)		6 Wks		1 cm^2	2.5	Silk
Adamowicz et al[10]	I	Rats (Wistar)	Male			0.7 cm^2		Amniotic membrane + bone marrow stem cells
Lepper et al[11]	I	Rabbits	Male		3.1–4.2 Kg	16 cm^2	3	Collagen
Horst et al[12]	II	Rats (Lewis)	Female		200 Gm	Partial	2	PLGA/bladder acellular matrix
Jack et al[13]	II	Rats (rnu)	Female		200–250 Gm	50%	3	PLGA + adipose derived stem cells
Wefer et al[14]	II	Rats (Sprague Dawley)	Female	3 Mos		50%	3	Bladder acellular matrix
Yang et al[15]	II	Rabbits (New Zealand)	Female		2.5–3.5 Kg	40%–50%	2	Bladder acellular matrix
Zhu et al[16]	II	Rabbits (New Zealand)	Male			40%–60%	6	Bladder acellular matrix + adipose derived stem cells
Zhu et al[17]	II	Rabbits (New Zealand)				60%–70%	6	Bladder acellular matrix
Paterson et al[18]	II	Minipigs (Yucatan)			53–76 Lbs	48 cm^2	12	SIS
Portis et al[19]	II	Minipigs (Yucatan)	Female			9 cm^2	3	SIS
Jayo et al[20]	II	Dogs (mongrel)	Male + female			80%	24	Polyglycolic acid + SMCs/UCs
Jayo et al[21]	II	Dogs (mongrel)	Male + female			75%	9	PLGA + SMCs/UCs
Kambic et al[22]	II	Dogs			25 Kg	50%	4	Pericardium
Kropp et al[23]	II	Dogs (beagle)	Male		11–13 Kg	35%–45%	14	SIS
Roth et al[24]	II	Dogs (beagle)	Male		13.9 Kg	40%	2.5	SIS + nanoparticles
Sievert et al[25]	II	Dogs (mongrel)	Female	1 Yr		50%	7	Bladder acellular matrix
Zhang et al[26]	II	Dogs (beagle)	Male		12–13 Kg	90%	9	SIS + SMCs/UCs
Caione et al[27]	II	Pigs (Landrace)	Female	2 Mos		Partial	3	SIS
Hattori et al[28]	II	Pigs	Male		15–18 Kg	50%	3	Collagen
Sharma et al[29]	II	Monkeys (baboon)	Female		18–20 Kg	40%–50%	2.5	SIS + mesenchymal stem cells
Chen et al[30]	III	Rats (Sprague Dawley)	Male		300 Gm	50%	3	Collagen + basic fibroblast growth factor
Kajbafzadeh et al[31]	III	Rats (Sprague Dawley)	Male		250–270 Gm	50%	3	Bladder acellular matrix
Yu et al[32]	III	Rats (Sprague Dawley)	Male		400–450 Gm	50%	2	Collagen-coated poly (epsilon-caprolactone)
Mimura et al[33]	IV	Rats (Sprague Dawley)	Female		337.9 ± 30.2 Gm	50%	2	Pericardium
Piechota et al[34]	IV	Rats (Sprague Dawley)	Male + female			50%	4	Bladder acellular matrix
Piechota et al[35]	IV	Rats (Sprague Dawley)	Male + female	3 Mos		50%	4	Bladder acellular matrix
Koiso et al[36]	IV	Rabbits	Female		2–2.5 Kg	50%	12	Poly(e-benzyloxycarbonyl-l-lysine)

The type of control group varied across studies, which were categorized into 4 types (table 1). The studies demonstrate a high degree of heterogeneity with respect to animal species, extent of cystectomy, followup, biomaterials, and use of cells and growth factors.

Tissue Engineering for Bladder Reconstruction

The quality of the included studies was sufficient (supplementary fig. 2), specifying the most important details on animal number, species, biomaterial, extent of cystectomy and length of followup. Pooling the effect sizes of all study types was not possible because the use of different control groups required different interpretation of the results (table 2, fig. 2). Nevertheless, heterogeneity (I^2) was still high for individual study types, suggesting that besides control groups, other factors including animal species, biomaterials and surgical techniques may have a role in causing study type heterogeneity.

Meta-analyses for types I and II studies did not reveal a significant difference in bladder volumes between controls, either healthy or preoperative, and experimental animals. In the type III studies the sham control group was undefined but no significant difference was observed. By comparison, for type IV studies a significant effect was found, in that experimental animals presented with a larger bladder volume than control animals in which partial cystectomy was performed without augmentation (fig. 2).

Subgroup Analyses

Bladder augmentation is performed to restore normal bladder volumes. In type II studies

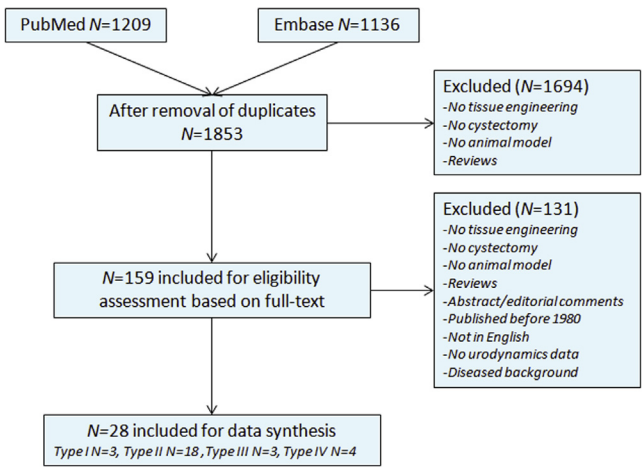

Figure 1. Flowchart of study inclusion criteria

Table 2. *Meta-analyses by study type*

Study Type	No. Studies	SMD (95% CI)	I^2 (%)
I	3	1.38 (−2.26, 5.03)	90
II	18	0.10 (−0.69, 0.89)	80
III	3	1.06 (−0.93, 3.04)	81
IV	4	5.54 (0.33, 10.74)	88

Study types I, II and III showed nonsignificant difference between control and experimental groups. Study type IV showed significant difference between control and experimental groups.

preoperative values were compared to postoperative values, an approach also used clinically. Thus, this study type comes closest to the clinical situation, and, therefore, was used for subgroup analysis.

Subgroup analyses were performed for different animal models (fig. 3) and construct types (cellular and acellular, fig. 4). Subgroup analysis showed that bladder reconstruction in rats resulted in a significantly larger bladder volume, in contrast to the overall effect found for all type II studies (fig. 3, *A*). This effect was not restricted to type II studies. In all of the rat studies bladder volumes increased regardless of type of control (2.77, 95% CI 0.78−4.77). In the 3 rabbit studies the bladder volume was negatively affected and included a large 95% CI. This result was mainly due to findings of Zhu et al (fig. 3, *B*).[16,17] Large animal models were limited to pigs and dogs, both of which correctly approximate the desired effect, as observed in the combined type II studies (fig. 3, *C* and *D*). Use of either species results in an I^2 of less than 75%, which is less than in the combined type II studies. Dogs demonstrated a narrower 95% CI, with an effect closer to the desired type II effect than was observed in pigs.

We also investigated the effect of (pre-)seeding biomaterials on bladder volume and compared cellular constructs with acellular constructs (fig. 4). No significant difference was observed between the 2 subgroups (large overlap in 95% CI). A slight shift toward a smaller bladder volume was observed for the cellular constructs.

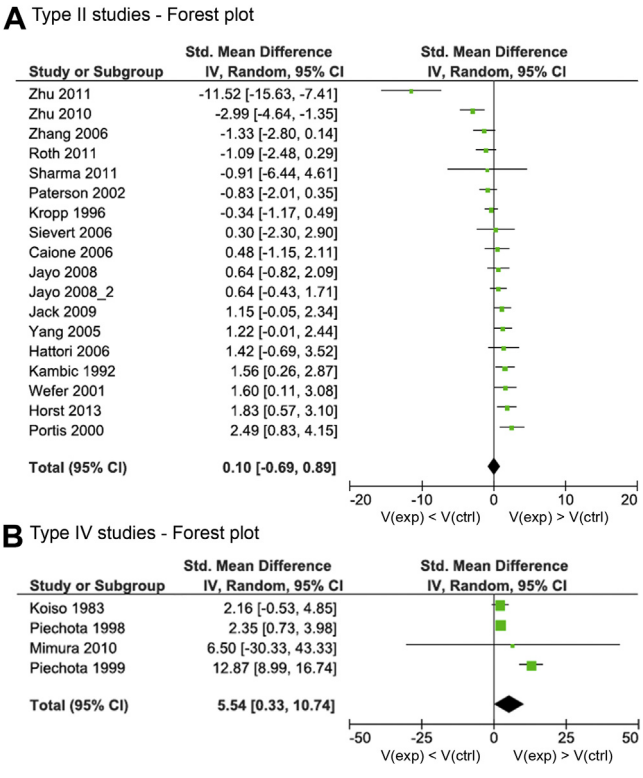

Figure 2. *A*, forest plot for type II studies. *B*, forest plot for type IV studies. *ctrl*, control. *exp*, experimental model. *V*, volume.

DISCUSSION

Bladder Tissue Engineering

Developments in preclinical research for bladder reconstruction have resulted in 2 clinical trials in the last decade.[3,40] We systematically searched the current literature to identify all preclinical research regarding tissue engineering for bladder reconstruction to investigate the feasibility of a tissue engineered bladder as a potential new therapy. Using predefined criteria, including cystometric bladder capacity outcome, 28 studies were included. Bladder augmentation aims to restore bladder volume and thereby protect the upper urinary tract. Thus, this parameter has the highest clinical significance, and, therefore, was chosen to be evaluated. The heterogeneity between these 28 studies was high, in that different species and biomaterials were used.

Based on control groups, the 28 studies were divided into 4 categories, ie healthy controls (type I), preoperative status as control (II), undefined sham operation (III) and partial cystectomy with primary closure (IV). Every type of control has specific advantages and disadvantages. In type II studies the approach is analogous to the clinical case, where increased bladder capacity is the primary goal of surgery. Therefore, type II studies were used for further subgroup analysis.

Bladder capacity was used to compare the outcomes of the different studies and predict the success of a clinical tissue engineering approach. In animal models bladder volume should ultimately return to normal values after partial cystectomy and augmentation, resulting in a nonsignificant difference between healthy and experimental groups. The latter was true for type II studies, where animals served as their own controls. This finding suggests that the same bladder capacity can be achieved after partial cystectomy followed by

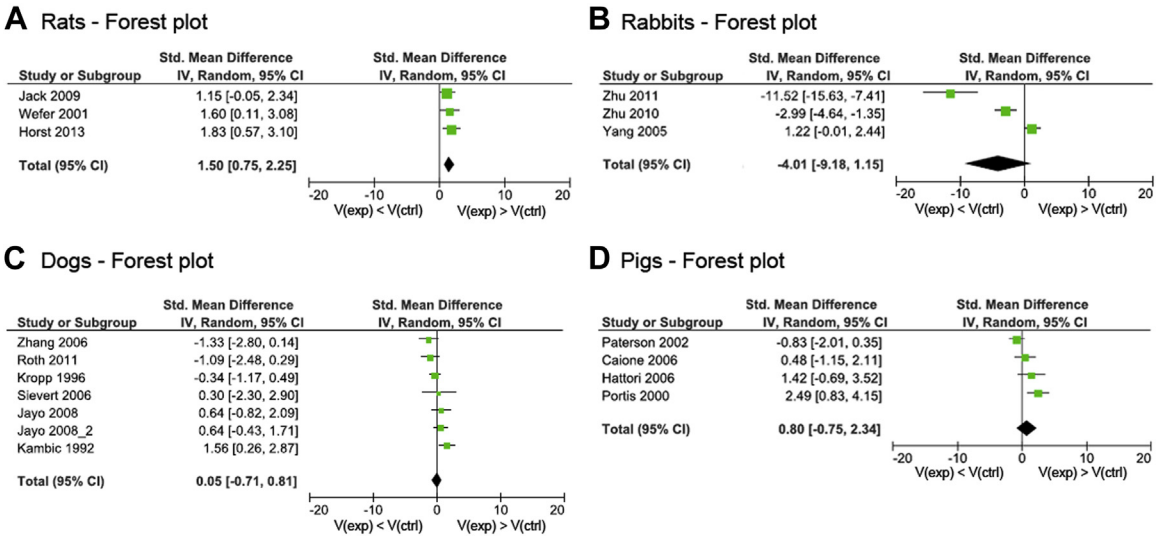

Figure 3. Forest plots for type II studies. *A*, rat studies (I^2 0%). *B*, rabbit studies (I^2 95%). *C*, dog studies (I^2 57%). *D*, pig studies (I^2 73%). *ctrl*, control. *exp*, experimental model. *V*, volume.

repair with a biomaterial, indicating the feasibility of tissue engineering for bladder augmentation. However, the variation within this study type was quite high (I^2), with deviations in positive and negative directions. Most likely this result is the corollary of inclusion of different animal species and biomaterials. In type IV studies the bladder volume was not restored to the original volume after partial cystectomy and primary closure of the defect. Comparison of type II and type IV studies indicates that the restoration of bladder capacity is indeed the consequence of the tissue engineering approach.

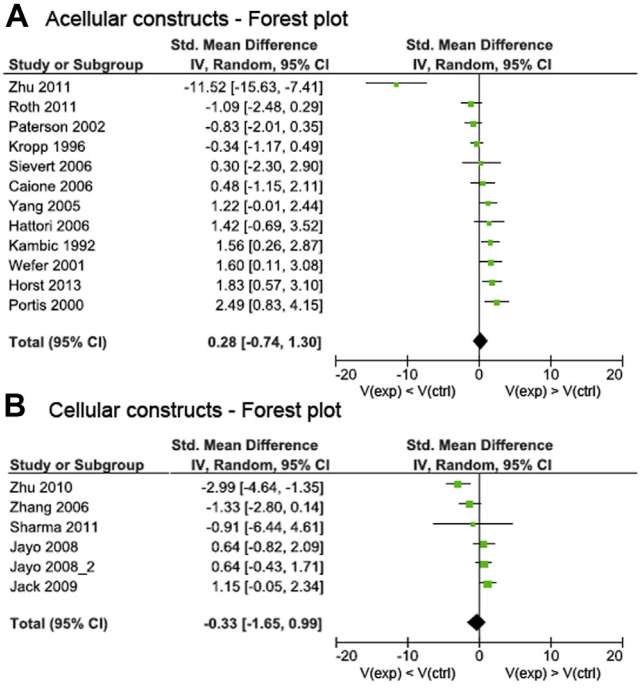

Figure 4. Forest plots for type II studies. *A*, acellular constructs (I^2 83%). *B*, cellular constructs (I^2 77%). *ctrl*, control. *exp*, experimental model. *V*, volume.

Cells and Bladder Volume

The effect of seeding/preseeding tissue engineered constructs in bladder reconstruction remains a subject of discussion within the field of tissue engineering. Although different groups have reported the advantageous effect of a cellular component, we found that in the evaluated animal models a cellular component does not result in a better bladder volume than acellular constructs.[16,41] Acellular and cellular constructs resulted in similar final bladder volumes after augmentation. In fact, a slight decrease in bladder volume was observed in the group with cellular constructs.

In this review we focused on bladder volume as the most important parameter. Although cells do not seem to aid in the preservation of bladder capacity, they might be necessary for long-term tissue regeneration. Whether cell seeding has a favorable effect on other essential parameters such as voiding patterns, bladder compliance and bladder histology is unclear, and is beyond the scope of this review as these parameters were not included. Only healthy animals were included in this review, and, therefore, only healthy cells were used for cell seeding. Other cell sources might be considered to achieve a clinically satisfactory outcome when cell seeded scaffolds are used. Alternatively a smart acellular scaffold might be considered.

Animal Models

Besides indicating the effectiveness of a tissue engineering approach, we aimed to identify an animal model that would adequately predict the behavior of tissue engineered constructs for bladder augmentation. Small animal species (such as rats and rabbits) do not appear to approximate the desired effect (type II). In rats bladder tissue engineering leads to a larger bladder volume after treatment regardless of study type (I to IV). This finding may be explained by the high regenerative capacity of the rat bladder, in that even after subtotal cystectomy without augmentation the bladder volume recovers completely.[42] The rabbit model exhibits a heterogeneous pattern of outcomes regarding bladder volume (fig. 3, *B*). Formation of calcifications, a known drawback of this model,[43] may explain the variation but was reported in only 1 of 3 studies (Zhu et al,[17] supplementary fig. 2). Type II studies in large animals are limited to dogs and pigs, and both appear to be representative for studying bladder tissue engineering since normal bladder capacities are reached after augmentation. However, the use of dogs in experimental research remains subject to ethical discussion.

Clinical Trials

In the first clinical study concerning bladder tissue engineering a seeded collagen or composite collagen-polyglycolic acid scaffold was used for augmentation cystoplasty in young patients with myelomeningocele.[3] This phase I study was based on preclinical experience in dogs.[37] The outcomes did not reveal any cytotoxicity and indicated the safety of this approach, suggesting a promising future for this technique. Further research in 2 dog studies supported these findings, with bladder capacity being regained at 3 to 6 months after implantation of the construct.[20,21]

From the clinical and preclinical data it appears that omental wrapping and bladder cycling are crucial to success as they result in larger postoperative bladder capacities. No major complications were reported in the preclinical studies. Unfortunately the results were disappointing in a phase II clinical trial that included 10 patients with neuropathic bladder due to spina bifida. A seeded PLGA copolymer scaffold adapted to the individual size was implanted onto the bladder. Many patients experienced multiple adverse events, and most had undergone conversion to a traditional ileocystoplasty at publication of the study.[40] Although the phase I and phase II trials were comparable in design, using the same clinical background, cell types, omental wrapping and bladder cycling techniques, the promising efficacy of the phase I study could not be substantiated in the phase II study.

In contrast, repair of exstrophic bladders (a different disease status) with SIS alone in 5 patients 5 to 17 years old showed a more favorable outcome.[44] The authors demonstrated the development of a bladder wall covered with a multilayered urothelium fully covering the lamina propria, similar to normal urothelium. The smooth muscle wall was less developed compared to the native detrusor wall, and long-term continence was not achieved. Therefore, one might question the predictive value of preclinical experiments in healthy large animals.[27,40]

Diseased Animal Models

The different outcomes of the phase II studies of patients with neuropathic bladder may be explained by the disease status of the bladder. The harvested bladder material as a cell source or the regenerative capacity of the bladder itself might have influenced the regeneration process. These factors may have caused the unsatisfactory clinical outcome, whereas the preclinical studies suggested a favorable outcome. It is unclear whether the favorable outcome in the exstrophic bladder scenario was the result of the more potent regenerative capacity in young patients or the superior quality of the urothelium of exstrophic compared to neuropathic bladders.

Although the number of studies in diseased animals is low, the exclusion of these studies might have biased our extrapolation of the preclinical results. Three studies investigating tissue engineering of a diseased bladder were identified. The rat studies revealed a positive outcome for tissue engineered bladder augmentation in a disease model.[45,46] However, these results have to be viewed with caution given the inherent regenerative capacity of the rat bladder, which might have influenced the outcome positively. Bladder augmentation after outlet obstruction in a large animal model was less effective than in healthy animals, which might indicate the negative effect of disease status on bladder regeneration.[47] Furthermore, age might influence the regenerative capacity of the bladder. In newborn lambs with bladder exstrophy the regeneration pattern in diseased and normal bladders was similar.[48] However, the regenerative capacity in newborns is more potent than in adults, which may have obscured abnormalities that can occur when older animals are studied. This factor might explain why a slightly better outcome was observed in the clinical trial of patients with bladder exstrophy.

The evidence in diseased animal models, although limited, suggests that the disease status might influence the regenerative capacity of the subject. Indeed, in vitro analysis showed that the proliferation and differentiation capacity of isolated UCs and SMCs from diseased patients was

diminished and altered compared to healthy individuals.[49,50] The altered proliferation capacity observed in 2 patients in the phase II clinical study suggests that this factor may have had a role in the clinical outcome and may explain the disappointing results. Collectively the evidence appears to imply that disease status influences the outcome of bladder tissue engineering.

Study Limitations and Recommendations

A systematic review in combination with a meta-analysis is an adequate approach to objectively identify and analyze studies within a certain field of research. Using predefined selection criteria is objective but might result in the exclusion of indirectly relevant and high quality articles, which is a drawback of this approach. The key parameter of this systematic review was bladder capacity, although other parameters including bladder compliance, voiding patterns and tissue regeneration using histological and morphological analyses were of equal importance. Furthermore, variables including biomaterials, growth factors and extent of cystectomy may influence study outcomes. To further investigate the efficacy of this approach, these parameters need to be addressed to gain more insight into bladder tissue engineering. As indicated, a successful preclinical outcome does not necessarily translate into a successful clinical trial. Therefore, it is important to design a preclinical study using the best predictive model available with an adequate disease background to mimic the clinical situation. For bladder tissue engineering large animals with diseased bladders appear to represent the best possible study model.

CONCLUSIONS

The preclinical evidence suggests that tissue engineered bladder augmentation in healthy animals results in normal bladder capacity on followup. The advantageous effect of cell seeding with respect to bladder volume was not evident in animal studies from the evaluated literature. Large animals such as pigs and dogs appeared to be the best predictive models, although the translational value of healthy animal models appears to be questionable since the regenerative capacity might be overestimated compared to the clinical setting. Tissue engineering of the bladder might become a reality in the future. However, to correctly predict the effect of tissue engineering for bladder augmentation, animal models with dysfunctional bladders should also be evaluated.

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