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Urethral Reconstruction Using Buccal Mucosa or Penile Skin Grafts: Systematic Review and Meta-Analysis

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Abstract

Introduction: Different types of grafts have been described in urethral reconstruction (UR), with penile skin graft (PSG) and buccal mucosa graft (BMG) as the most frequently used ones. It still remains unclear whether one graft is superior in terms of success when compared to the other. ***Material and Methods:*** A systematic review of the literature was performed searching the MEDLINE database with the following search strategy: 'urethroplasty' AND 'penile skin'/ 'urethroplasty' AND 'buccal mucosa'. 266 and 144 records were retrieved for urethroplasty with PSG and BMG, respectively. These records were reviewed to identify papers where PSG and BMG were used in UR and where individualized data on success were available within the same series. ***Results:*** 18 papers were found eligible for further analysis. In total, 428 and 483 patients were respectively treated with PSG or BMG. If available, follow-up duration was 64.1 versus 42.1 months ($p < 0.0001$) and stricture length 6.2 versus 4.6 cm ($p < 0.0001$) for PSG and BMG, respectively. Success of UR with PSG was 81.8 versus 85.9% with BMG ($p = 0.01$). ***Conclusions:*** Success of UR using BMG is significantly better compared to PSG. Results might be seriously biased by a longer follow-up duration and stricture length for PSG compared to BMG.

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Introduction

Urethral reconstruction (UR) using a graft to substitute the urethral mucosa is an established treatment for strictures at the penile urethra and for bulbar strictures not amenable with anastomotic repair [1–3]. Local skin flaps might also be used to substitute the urethra. Although the results seem to be equal to those of grafts, flaps are associated with more complications and less preferred by the patient [4]. Moreover, harvesting a flap is technically more challenging [4]. Therefore, grafts are preferred in substitution UR whenever possible. In UR, a graft is a piece of skin or mucosa that is totally removed from its vascular bed (donor area) and sutured in the urethra (acceptor area). Numerous grafts have been described in UR: genital and extragenital skin, tunica vaginalis, bladder mucosa, colonic mucosa, buccal mucosa, lingual mucosa and tissue-engineered grafts (allo- or autografts) [5]. Extragenital skin is associated with subop-
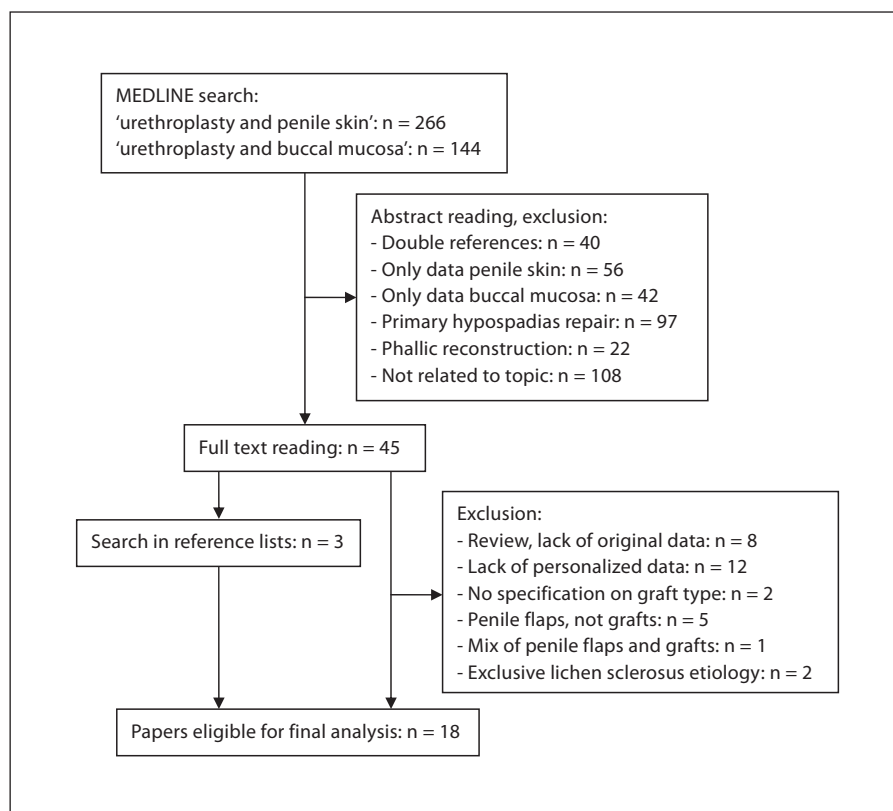
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Fig. 1. Flowchart on data collection.

The flowchart contains the following boxes:

- MEDLINE search:
  'urethroplasty and penile skin': n = 266
  'urethroplasty and buccal mucosa': n = 144

- Abstract reading, exclusion:
  - Double references: n = 40
  - Only data penile skin: n = 56
  - Only data buccal mucosa: n = 42
  - Primary hypospadias repair: n = 97
  - Phallic reconstruction: n = 22
  - Not related to topic: n = 108

- Full text reading: n = 45

- Search in reference lists: n = 3

- Exclusion:
  - Review, lack of original data: n = 8
  - Lack of personalized data: n = 12
  - No specification on graft type: n = 2
  - Penile flaps, not grafts: n = 5
  - Mix of penile flaps and grafts: n = 1
  - Exclusive lichen sclerosus etiology: n = 2

- Papers eligible for final analysis: n = 18

timal results [6]. Harvesting a bladder [7] or colonic mucosal [8] graft substantially increases surgical morbidity without any evidence of superiority of these grafts. Tunica vaginalis is promising but experience and follow-up is limited [9]. Although having the advantage of off-the-shelf availability, results of tissue-engineered grafts are conflicting and experience is to date rather limited [10–12]. Lingual mucosa has comparable histological characteristics as buccal mucosa. Seen the encouraging preliminary results, lingual mucosa has recently been suggested as an alternative to buccal mucosa, but long-term results are lacking [13]. To date, penile skin graft (PSG) and buccal mucosa graft (BMG) are the most popular substitutes in UR [5, 14]. PSG was popularized in the USA by Devine et al. [15] and in Europe by De Sy and Oosterlinck [16]. PSG can be harvested at the inner surface of the prepuce and/or at the dorsal penile shaft. BMG was rediscovered and popularized in 1992 by Burger et al. [17]. BMG is harvested at the inner cheek and if necessary, can extend onto the lower lip. Several experts have stated that BMG is superior to PSG in UR [18, 19]. Because of the lack of well-conducted clinical trials comparing PSG with BMG, this statement can only be considered expert opinion.

The aim of this paper is to review the currently available literature on UR with PSG and BMG, and to assess whether one graft is superior to the other. To our knowledge, this is the first meta-analysis on outcome of PSG compared to BMG.

Materials and Methods

Evidence Acquisition
A systematic search was performed in the MEDLINE (PubMed) database with the last systematic search dated 17 March 2012. The following search strategy was used: 'urethroplasty' [Mesh] AND 'penile skin' [Mesh], followed by 'urethroplasty' [Mesh] AND 'buccal mucosa' [Mesh]. The following limits were activated: humans, gender [male] and language [English]. The reference list of reviews and relevant papers were also viewed to identify eventually missed but eligible papers on the topic. Only papers on UR containing individualized data on success of PSG versus BMG within the same paper were included in this review. Papers reporting on success of either PSG or BMG were not included. Papers reporting on penile skin flaps or a mixture of PSGs with penile skin flaps versus BMG were also excluded, as well as papers reporting on primary hypospadias repair. Since the use of genital skin is generally considered to be obsolete in UR for lichen
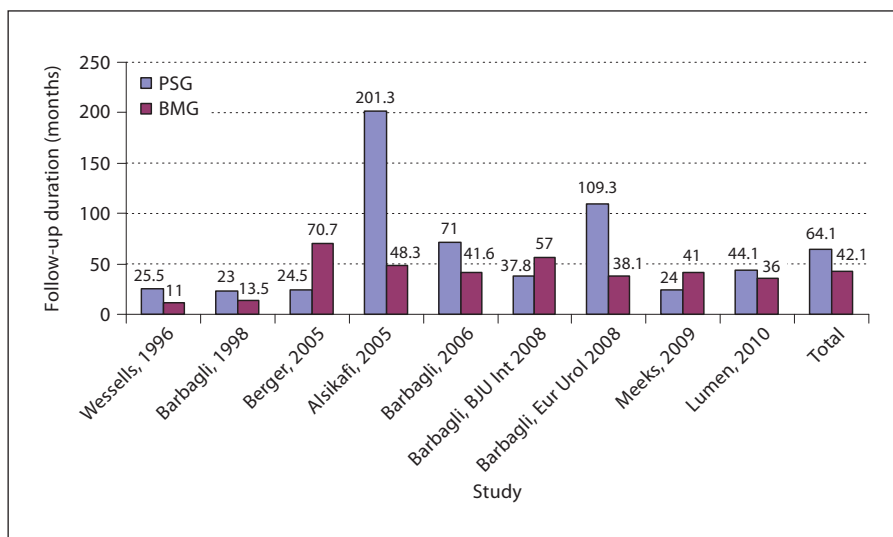
Fig. 2. Comparison of follow-up duration (if available) between UR with PSG and BMG.

sclerosus (LS)-related strictures [20], papers reporting on the outcome of UR for (exclusively) LS-related strictures were also excluded. Success of UR was defined as a patent urethra without the need for any additional instrumentation (including dilation) or reoperation. Spontaneous closure of a postoperative urethrocutaneous fistula was not considered a failure. Other data (if available) extracted were: stricture etiology, follow-up duration, stricture length, stricture location and type of UR. Data on previous interventions and donor site-related complications were not or only poorly described and were not subject for further analysis. Literature search and data extraction were performed by two authors (N.L. and P.H.) and in case of disagreement, arbitration by a third author (W.O.) was carried out.

Statistical Analysis

To compare the success of UR using PSG versus BMG, meta-analysis was performed using RevMan 5.1™ software. Statistical heterogeneity was tested using χ^2 and I^2. A p value <0.10 was used to indicate heterogeneity and in the absence of statistical heterogeneity the fixed-effects model (Mantel-Haenszel method) was used. Other data (continuous variables) were evaluated with Student's t test. A p value <0.05 indicates statistical significance.

Results

Literature Search (fig. 1)

The MEDLINE search yielded 266 and 144 records for UR with PSG and BMG respectively. After the removal of double references and after reading the abstracts, 45 articles were retrieved in full text for further evaluation. A search in the reference lists yielded 3 additional relevant articles. Reasons for exclusion were: review with lack of original data (n = 8), lack of personalized data (n = 12),

no specification on graft type (n = 2), use of penile flaps instead of grafts (n = 5), mix of penile grafts with flaps (n = 1) and exclusively LS etiology (n = 2). Finally, 18 papers [21–38] were included for evaluation and meta-analysis.

Study Characteristics (table 1) *and Outcomes*

These 18 papers enrolled a total of 911 patients. In 428 and 483 patients, UR was performed with PSG and BMG respectively. None of the papers were prospective randomized trials comparing PSG with BMG (level of evidence 1b). Data collection was prospective in 6 and retrospective in 12 papers. Etiology was diverse in 13 papers with 5 of them containing a small subgroup (≤13.5%) of patients with LS etiology. The remaining 5 papers dealt with urethral pathology related to a specific topic. In 9 papers, individualized data on follow-up duration were available (300 and 372 patients with respectively PSG and BMG). Among these papers, follow-up duration was significantly longer when PSG was used compared to when BMG was used (64.1 vs. 42.1 months, p < 0.0001; fig. 2). In 6 papers, individualized data on stricture length were available (181 and 131 patients with respectively PSG and BMG). Among these papers, stricture length was significantly longer for UR with PSG compared to BMG (6.2 vs. 4.6 cm, p < 0.0001; fig. 3). Stricture location was exclusively at the penile urethra in 3 papers, and exclusively at the bulbar urethra in 7 papers. One paper dealt with treatment of panurethral strictures, the remaining 7 papers included strictures at diverse segments of the urethra. Diverse types of UR were used among the different papers (dorsal onlay, ventral on-

Table 1. Study characteristics

Study	Data collection	Etiology	Follow-up PSG months	Follow-up BMG months	Stricture length PSG cm	Stricture length BMG cm	Stricture location PSG	Stricture location BMG	Type of technique PSG	Type of technique BMG
Wessells, J Urol 1996 [21]	R	diverse (LS 7.5%)	25.5	11	NID	NID	anterior urethra	anterior urethra	VO	VO
Wessels, J Urol 1997 [22]	R	diverse (LS 8%)	NID	NID	NA	NA	panurethral	panurethral	CU	CU
Barbagli, J Urol 1998 [23]	R	diverse (LS 13.5%)	23	13.5	4.7	4	bulbar	bulbar	DO	DO
Guralnick, J Urol 2001 [24]	R	diverse	NID	NID	NID	NID	bulbar	bulbar	AAR	AAR
Wessells, Urol Clin N Am 2002 [25]	R	diverse	NA	NA	NA	NA	bulbar	bulbar	VO	VO
Raber, Eur Urol 2005 [26]	P	diverse	NID	NID	4.3	3.2	bulbar	bulbar	DO	DO
Berger, BJU Int 2005 [27]	R	posttraumatic	24.5	70.7	6.5	3	all urethral segments	all urethral segments	DO	VO
Alsikafi, 2005 [28]	R	diverse	201.3	48.3	5.7	4.7	anterior urethra	anterior urethra	OSU, not specified	OSU, not specified
Barbagli, J Urol 2006 [29]	R	diverse (LS and FHR excluded)	71	41.6	NA	NA	bulbar	bulbar	DO	VO (17); DO (27); LO (6); AAR (12)
Lumen, Curr Urol 2007 [30]	R	diverse (LS 2.4%)	NID	NID	NID	NID	bulbar	bulbar	VO	VO
Barbagli, BJU Int 2008 [31]	R	diverse (LS and FHR excluded)	37.8	57	NA	NA	penile	penile	Asopa	Asopa
Meeks, J Urol 2008 [32]	P	prior kidney-pancreas transplant	NID	NID	NA	NA	penile	anterior urethra	OSU, not specified	OSU, not specified
Barbagli, Eur Urol 2008 [33]	R	diverse (LS and FHR excluded)	109.3	38.1	NA	NA	bulbar	bulbar	AAR (9); DO (38)	AAR (31); OSU, not specified (132)
Casey, J Urol 2008 [34]	P	neurogenic bladder dysfunction-related urethral pathology	NID	NID	NID	NID	anterior urethra	anterior urethra	OSU (3); TSU (1)	OSU (5)
Meeks, BJU Int 2009 [35]	P	indwelling urethral catheter-induced erosion	24	41	7.3	10	penile	penile	DO	DO
Meeks, J Urol 2009 [36]	P	FHR	NID	NID	NID	NID	penile	penile	TSU	TSU
Lumen, Int J Urol 2010 [37]	P	diverse (LS 4.76%)	44.1	36	7.3	6.4	anterior urethra	anterior urethra	OSU, not specified	OSU, not specified
Mathur, Updates Surg 2011 [38]	R	diverse	NID	NID	NID	NID	all urethral segments	all urethral segments	OSU, not specified	DO

AAR = Augmented anastomotic repair; CU = combined urethroplasty; DO = dorsal onlay; FHR = failed hypospadias repair; LO = lateral onlay; LS = lichen sclerosus; NA = not available; NID = no individual data; OSU = one-stage urethroplasty; P = prospective; R = retrospective; TSU = two-stage urethroplasty; VO = ventral onlay.
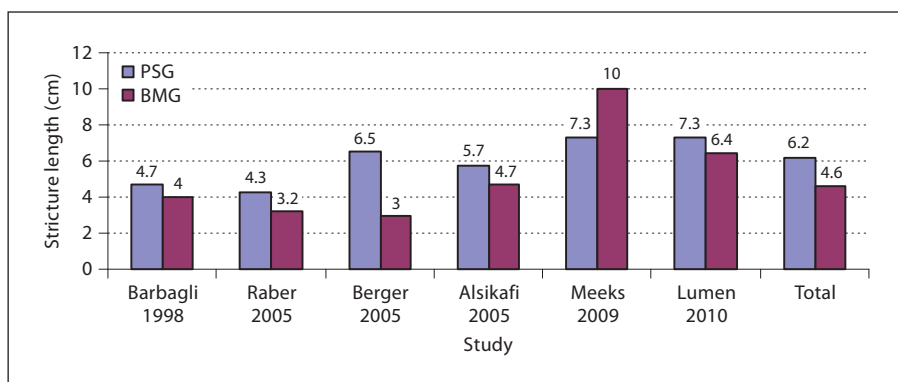
Fig. 3. Comparison of stricture length between UR with PSG or BMG.

Study or subcategory	Penile skin		Buccal mucosa		Weight %	Risk ratio M-H, fixed (95% CI)	Year	Risk ratio M-H, fixed, 95% CI
	events	total	events	total				
Wessels, J Urol	16	21	7	7	3.8	0.80 (0.59, 1.08)	1996	
Wessels, J Urol	5	6	8	8	2.5	0.83 (0.55, 1.26)	1997	
Barbagli, J Urol	28	31	6	6	3.6	0.96 (0.76, 1.22)	1998	
Guralnick, J Urol	17	19	3	3	2.0	1.00 (0.67, 1.50)	2001	
Wessells, Urol Clin N Am	17	19	16	17	5.8	0.95 (0.78, 1.16)	2002	
Berger, BJU Int	38	40	3	7	1.7	2.22 (0.94, 5.23)	2005	
Raber, Eur Urol	13	17	11	13	4.3	0.90 (0.64, 1.28)	2005	
Alsikafi, J Urol	20	24	83	95	11.4	0.95 (0.79, 1.16)	2005	
Barbagli, J Urol	33	45	52	62	14.9	0.87 (0.71, 1.08)	2006	
Lumen, Curr Urol	31	33	7	8	3.9	1.07 (0.81, 1.41)	2007	
Barbagli, BJU Int	18	23	18	22	6.3	0.96 (0.71, 1.28)	2008	
Meeks, J Urol	1	1	5	5	0.9	1.00 (0.43, 2.31)	2008	
Barbagli, Eur Urol	28	47	135	163	20.6	0.72 (0.56, 0.92)	2008	
Casey, J Urol	2	4	4	5	1.2	0.63 (0.21, 1.83)	2008	
Meeks, J Urol	1	1	11	12	1.0	0.85 (0.37, 1.93)	2009	
Meeks, BJU Int	1	3	1	1	0.7	0.50 (0.11, 2.23)	2009	
Lumen, Int J Urol	55	66	8	9	4.8	0.94 (0.73, 1.21)	2010	
Mathur, Updates Surg	26	28	37	40	10.4	1.00 (0.88, 1.15)	2010	
Total (95% CI)		**428**		**483**	**100.0**	**0.91 (0.84, 0.98)**		
Total events:	350		415					

Test for heterogeneity: $\chi^2 = 14.39$, d.f. = 17 (p = 0.64), $I^2 = 0\%$
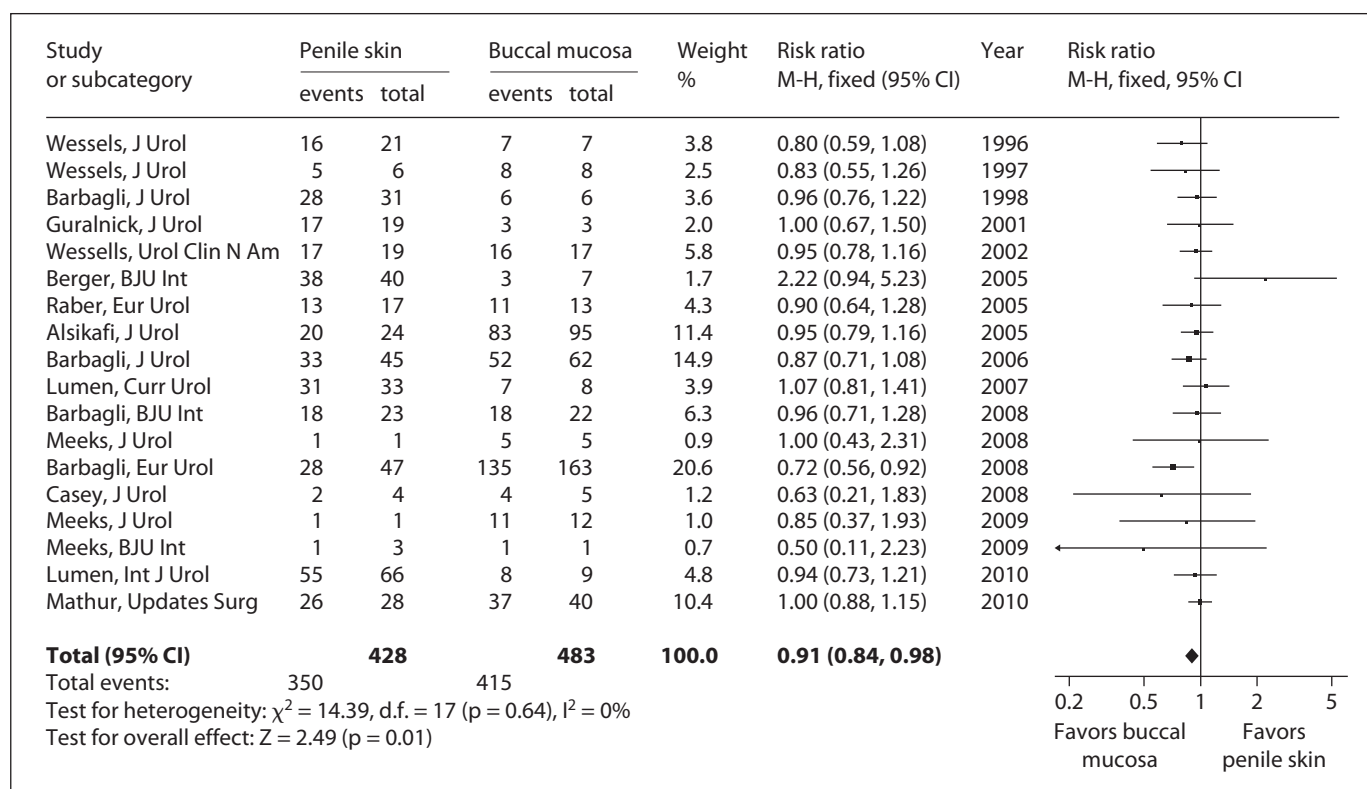Test for overall effect: Z = 2.49 (p = 0.01)

Fig. 4. Forest plot on success of UR using PSG or BMG.

lay, Asopa's technique, augmented anastomotic repair, combined urethroplasty, two-stage urethroplasty). The technique used for UR was exactly the same for PSG and BMG in 10 papers, but was different or no further specified in 8 papers. A successful UR was reported in 350 of 428 patients (81.8%) treated with PSG versus 415 out of 483 patients (85.9%) treated with BMG. This difference in success (4.1%) was statistically significant in favor of BMG (risk ratio 0.91, p = 0.01; fig. 4).

Discussion

PSG and BMG are the most popular grafts in UR, with a steady increase in the use of BMG in the last two decades [3]. Several advantages and disadvantages must be taken into consideration when using BMG or PSG. BMG has the advantage of large availability and a concealed donor area. It has a thick epithelium with a thin but well-vascularized lamina propria and contains no hair. Moreover,

the graft is used to a wet environment and supposed to be more resistant against infection [2, 3]. Disadvantages are the need of an additional operation field and donor site-related complications: transient oral pain in the first postoperative days (83–100%), perioral numbness (16–26%), alterations in saliva production (11%), oral tightness (9–32%) and risk of retraction of the lower lip (if extension to the lower lip) [39, 40]. PSG harvesting is easy and lies within the operation field. PSG is very elastic and contains no hair. Disadvantages are an altered genital appearance and sometimes the unavailability (e.g. after circumcision or after hypospadias) [2].

This meta-analysis has shown a superior outcome when BMG was used compared to PSG, thus supporting the statement of several experts that BMG is superior in UR [1, 18, 19]. However, several remarks must be taken into consideration before discouraging the use of PSG based on our results:

(1) Quality of included studies: The quality of a meta-analysis largely depends on the quality of included studies. Ideally, a meta-analysis includes only prospective randomized clinical trials. After performing a systemic review of the literature, not one prospective randomized trial (level of evidence 1b) comparing PSG versus BMG in UR was found. As a consequence, only papers of lower quality and thus a lower level of evidence could be included. Only 6 out of 18 papers in this meta-analysis were based on prospective data collection of nonrandomized and nonmatched cohorts of PSG versus BMG (level of evidence 2b). The remaining 12 papers were even of lower quality with retrospective data collection (level of evidence 3). In the absence of prospective randomized trials it remains difficult to determine which graft is now really superior, despite of the findings of this meta-analysis in favor of BMG. Although conducting prospective randomized trials in the field of urethroplasty is difficult [41], any attempt to do so should be strongly encouraged.

(2) Etiology: The relationship between etiology and the success of UR has been recently studied by Mathur et al. [42]. They came to the conclusion that etiology may play an important role in the outcome of UR, with the best results for posttraumatic strictures and the poorest results for postinflammatory strictures. Lumen et al. [43] have reported a poorer outcome of UR when strictures were related to failed hypospadias repair (FHR) compared to a matched cohort of non-FHR related strictures. The etiology of urethral pathology was diverse in the majority of the studies without knowledge of the individual distribution of stricture etiology in the cohorts of PSG versus BMG. If in the cohorts of PSG more inflammatory and FHR-related strictures were present, this could have led to a possible poorer outcome. It is however unclear and not determinable whether this is the case in this meta-analysis. LS is a chronic inflammatory disease of unknown origin affecting genital skin, the glans, the meatal orifice and even extending into the urethra [44]. The use of penile skin in UR is obsolete seen the fact that LS has a high chance to recur in the PSG, finally leading the failure of UR [45, 46]. Trivedi et al. [47] evaluated the success of UR in LS-related strictures and found a very favorable success rate with BMG (92.2%) compared to a very poor success rate with PSG (4%). In case of LS, BMG is thus certainly the graft of choice and PSG is not advised [19, 47]. Exclusively LS etiology was a reason for exclusion, and for this reason, the study of Trivedi et al. [47] was not included in the meta-analysis. However, in some studies of this meta-analysis, a small subgroup of patients did have LS etiology [21–23, 30, 37]. If these patients were treated with PSG, this could have led to a poorer outcome of PSG.

(3) Follow-up duration: Grafts have the tendency to shrink over time and thus the results of UR using grafts tend to deteriorate over time [48]. The longer the follow-up, the poorer the success of UR to be expected. Because BMG is a more recent development in UR compared to PSG, it is more likely that the follow-up with BMG is not that extensive compared to PSG. This is supported by the results of this meta-analysis derived from 9 papers where individual data on follow-up duration were available. In 6 studies, follow-up was longer with PSG and overall, follow-up with PSG was on average 22 months longer compared to BMG. The largest study (greatest weight into this meta-analysis) and the only study showing individually a significant advantage for BMG [33] has also a significant longer follow-up with PSG. This longer follow-up might be an explanation of the poorer outcome with PSG.

(4) Stricture length: The longer the stricture and thus the graft length needed for UR, the higher the chance that at a certain place graft take can go wrong with failure as a consequence. In a recent analysis of Breyer et al. [49], assessing risk factors for failure of UR, a longer stricture length was found to be a negative prognostic factor. Based on available individualized data in 6 studies, stricture length was on average 1.6 cm longer when PSG was used. This longer stricture length might also have influenced outcome of PSG compared to BMG.

(5) Stricture location and type of technique: Stricture location was comparable in most studies and it is thus unlikely that this would have an influence on the outcome. Numerous techniques have been described in UR

[1–3, 37], but not every technique is suitable for a specific type of stricture [1, 3, 37]. In order to achieve a successful UR, a graft must survive. Graft survival occurs thanks to imbibition and inosculation and the quality of the graft bed is thus of utmost importance [50]. A graft is only as good as the bed where it is sutured on. In 8 papers, the technique was not specified or different among the cohort of PSG versus BMG. A different selection of techniques for PSG compared to BMG might influence the outcome, however this meta-analysis is unable to assess this.

Although UR with BMG has a significantly better outcome, the absolute difference in success compared to PSG is only 4.1%. In some conditions (e.g. oral leukoplakia, poor oral hygiene with heavy tobacco smoking/chewing, previous irradiation, previous BMG), BMG harvesting is not possible or not advised. In these cases (except LS), PSG remains a possible option in UR. BMG and PSG should be considered as complementary in UR, and a urologist who is able to harvest different types of grafts has certainly an advantage in the field of UR. Therefore, the technique of PSG harvesting in UR should not be forgotten.

The major shortcoming of this meta-analysis, as mentioned above, is the poor quality of included studies and the substantial heterogeneity in follow-up, stricture length, etiology and type of technique among the cohorts of PSG versus BMG.

Conclusions

The level of evidence of papers reporting on outcome of UR with PSG and BMG is low. Success of UR using BMG is significantly better compared to PSG, supporting the use of BMG as graft of first choice. The result might be seriously biased by a significant longer follow-up duration and stricture length for PSG compared to when BMG was used. Prospective randomized trials in a homogenous population are needed to finally answer the question which graft is best in UR.

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