Chapter 14
Urethral Bulking Agents

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Introduction

Urethral bulking agents (UBAs) are a minimally invasive treatment for either primary or recurrent SUI after other anti-incontinence procedures. First introduced in the early twentieth century, UBAs continue to evolve in composition, mechanism of action, and delivery method. Here we discuss indications for UBA usage, procedural aspects of injection, and historical and contemporary UBAs.

Method of Action

UBAs are used to treat stress urinary incontinence (SUI) in patients with intrinsic sphincter deficiency (ISD), a very weakened urethral closure mechanism [1]. UBAs can be injected transurethrally or through the periurethral tissue, thereby focally expanding urethral surface area and increasing pressure transmitted to the proximal urethra [2]. The bulking of the urethra improves urethral coaptation and urethral outlet resistance, preventing the leakage of urine. Injection of UBAs may also increase functional urethral length [3].

UBAs may be synthesized from biologic or synthetic materials. Biologic UBAs are comprised of decellularized membranes from either autologous, allogenic, or

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A. P. Cameron (ed.), *Female Urinary Incontinence*,
https://doi.org/10.1007/978-3-030-84352-6_14

xenogenic tissues [4]. Synthetic UBAs are categorized as either particulate or non-particulate. Particulate UBAs are composed of microspheres suspended in an absorbable gel carrier. As the gel is reabsorbed over time, the surrounding host tissue integrates with the remaining particles to create a bulky fibrotic capsule. Particles must be at least 80 μm in diameter to prevent migration from the original site of injection [5, 6]. Non-particulate UBAs are created from homogenous, non-absorbable gels; for these agents, the bulk is created by the thin fibrous networks that form to anchor the injected gel to the host tissue [5].

Although there are key differences in their mechanisms of action based on their composition, ideal UBAs share similar key characteristics. For a UBA to successfully support reconstruction of and augment periurethral tissue, it should be easily injectable, non-absorbable, nontoxic, and non-immunogenic. UBAs should also be acellular, nonmigratory, and induce minimal fibrosis and calcification [7, 8].

Patient Selection and Indications

UBAs are classically used in patients with SUI secondary to ISD, defined as an abdominal leak point pressure less than 60 cm H_2O on urodynamics. Ideal candidates should also lack urethral hypermobility and idiopathic detrusor contractions [9]. UBAs have been shown to be most efficacious in women with less than 2.5 episodes of SUI per day and those aged 60 years and older. The efficacy of UBAs in older women may be attributed to lower baseline activity levels as well as improvement in sphincter function through an increase in sphincter sarcomere length [10].

Although UBAs are less efficacious than the gold standard mid-urethral sling (MUS) for treating SUI with urethral hypermobility, they boast a more favorable side effect profile and have many indications [11]. UBAs can be considered in patients who are poor surgical candidates secondary to comorbidities, age, severe obesity, or inability to stop anticoagulation. UBAs can be offered to women of childbearing age who desire future pregnancies and those who want to avoid a surgery requiring general anesthesia but accept a lower rate of cure [12]. UBAs may also be utilized in cases of mild SUI, SUI with poor bladder emptying, or as an adjunct to other anti-incontinence procedures if SUI still persists [9, 12]. Contraindications to UBA injection include active urinary tract infection (UTI) or history of allergic reaction to the bulking agent of choice [12].

Procedural Aspects and Injection Techniques

UBAs can be injected under sedation or local or general anesthesia either in an office setting or the operating room [13]. To perform injections, the patient is traditionally placed in the dorsal lithotomy position. The genitals are prepped and draped in a sterile fashion. Topical anesthetics or lidocaine can be deposited transurethrally or injected within the urethral submucosa. It is recommended that practitioners

administer a single dose of prophylactic antibiotics in accordance with local antibiograms and prior patient urine cultures [14]. UBAs should be deposited into the proximal urethral mucosa near the bladder neck [15–17]. Three major methods of injection have been described.

Transurethral Injection

Transurethral injection involves the implantation of UBAs through the working channel of a cystoscope (Fig. 14.1a). The transurethral method allows the clinician to perform the injection under direct vision and select the precise location for implantation. The practitioner can also visualize urethral coaptation, potentially reducing the amount of bulking agent required. For optimal coaptation, injections should be performed at either 3 and 9 o'clock or 6 o'clock through a cystoscope [18]. Circumferential periurethral distribution and proximal urethral injection have been associated with optimal short-term success rates [19].

Periurethral Injection

Periurethral injection involves the direct placement of the UBA in the urethral mucosa in the perimeatal region (Fig. 14.1b). In comparison with the transurethral method, periurethral injection offers certain benefits including less mucosal leakage and bleeding [20]. However, periurethral injections are associated with a higher

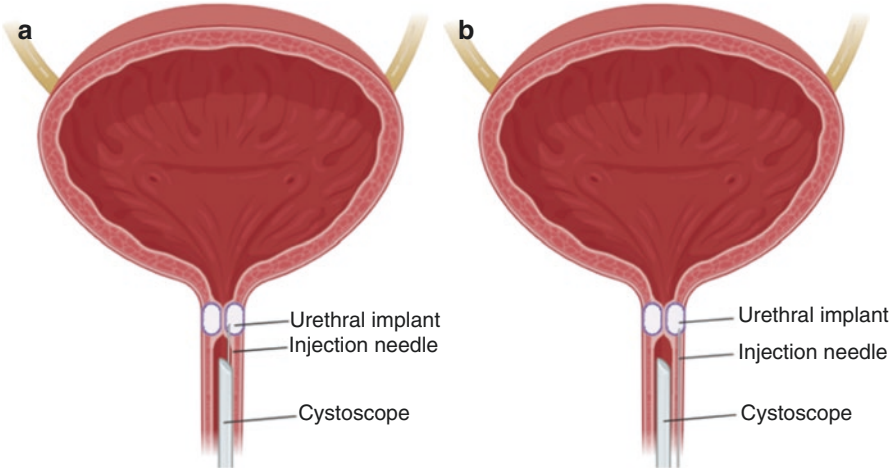

Fig. 14.1 (**a**) Technique for transurethral injection where the needle for urethral bulking agent delivery is advanced through the working channel of a cystoscope. (**b**) Technique for periurethral injection of urethral bulking agent by direct placement of the injection needle in the perimeatal region. (Created with BioRender.com)

risk of acute urinary retention, which is hypothesized to be caused by the use of higher volumes of the bulking agent, since direct visualization may not be utilized [20, 21].

Device-Guided Injection

Some UBAs are deposited through specially made dispensers. The Macroplastique™ Implantation System contains an injection device placed in the urethra to the level of the bladder neck, which is identified when urine flows through the device's central channel (Fig. 14.2a). The clinician withdraws the device 1 centimeter distally. Needles are then placed through the implantation device into the urethral mucosa at the 2, 6, and 10 o'clock positions [17].

Bulkamid™ is injected through a urethroscope containing a zero-degree lens and light cord for visualization (Fig. 14.2b). A specialized needle is inserted 1 cm into the submucosa at the 6 o'clock position. Additional injections are placed at either 2 and 10 o'clock or 3, 9, and 12 o'clock. The practitioner should visualize the formation of blebs after each submucosal injection [15].

Similarly, Urolastic™ is administered through a dispenser gun containing an applicator which is placed in the mid-urethra. Injections are then performed at the 2, 5, 7, and 10 o'clock positions for optimal urethral coaptation. If persistent leakage occurs after a cough test, additional deposits can be placed in the 3 or 9 o'clock regions [16].

Postoperative Recommendations and Findings

Practitioners should measure a PVR for all patients postoperatively [14]. Patients with PVRs greater than 100–150 ml may require a single catheterization with a 10–12 French Foley catheter. A smaller catheter is recommended as to not displace the

Fig. 14.2 Device-guided injection dispensers. (**a**) Macroplastique™ Implantation System contains an injection device which is placed in the urethra to the level of the bladder neck in order to optimally position the injection sites [90]. (**b**) Bulkamid™ rotatable sheath is advanced through the urethra under direct visualization, after which the clinician may perform injections [15]

recently injected bulking agent. If urinary retention persists, patients should be taught to perform clean intermittent catheterization. Patients may return to work after 24 hours if performed under general anesthesia [15, 16] or same day if done under local anesthesia. Minimal, if any, pain medication is usually required following the procedure.

Of note, bulking agents can be seen on computed tomography (CT) or magnetic resonance imaging (MRI) and can be confused with urethral masses. Some are also radiopaque (Coaptite, Durasphere) and can be mistaken for bladder stones on kidney, ureter, and bladder x-ray (KUB) (Fig. 14.3). A recent retrospective study revealed occasional misdiagnosis of periurethral bulking agents in patients with SUI [22]. In this study, urethral findings were rarely mentioned on abdominal or pelvic imaging interpretation. In the infrequent cases in which they were mentioned, greater than 60% misdiagnosed the bulking material as a genitourinary pathology such as pelvic mass or urethral diverticulum [22].

Comparison of Injection Methods

Benefits and disadvantages associated with each injection method have been described, but there is no evidence favoring one method over another in terms of clinical success rates. One study comparing transurethral (n = 24) to periurethral

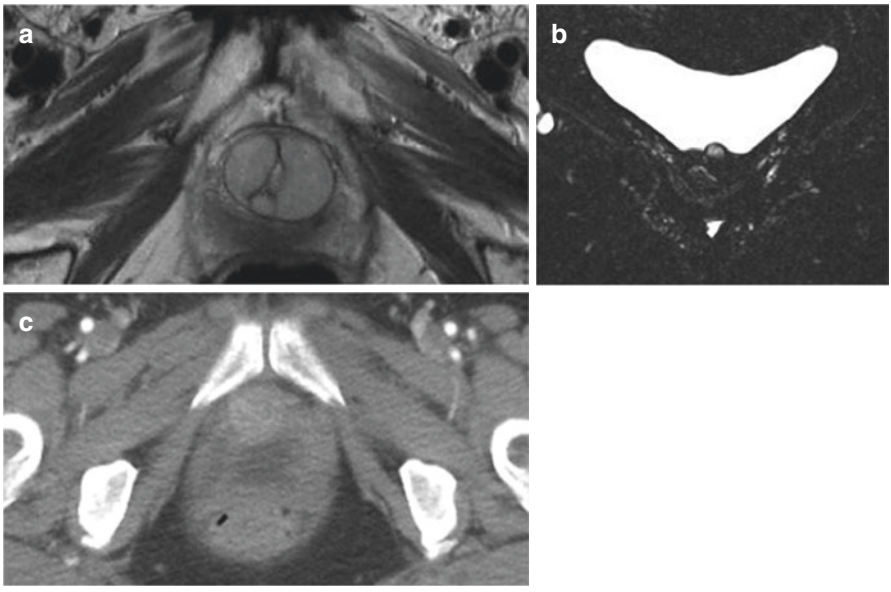

Fig. 14.3 UBAs identified on various imaging modalities can be easily misinterpreted. (**a**) Axial magnetic resonance imaging of collagen bulking agent which was correctly interpreted on radiographic read. (**b**) Coronal magnetic resonance imaging of collagen bulking agent which was radiographically interpreted as "possible urethral diverticulum." (**c**) Axial computerized tomography imaging of Macroplastique™ bulking agent which was radiographically interpreted as "increased attenuation of soft tissue". (Images **a**-**c** courtesy of Anne Cameron MD)

(n = 21) collagen injection demonstrated no statistically significant difference in cure, symptomatic improvement, or complication rates after six months. However, the amount of collagen injected was lower (4.7 vs 10.1 ml) for the transurethral compared to the periurethral group, respectively [21].

These results were corroborated by an analysis of 40 women with SUI or mixed urinary incontinence (MUI) randomized to receive either periurethral or transurethral injection of dextran copolymer. There was no significant difference in dry rates or subjective mean symptomatic improvement at one, three, six, or 12 months. Primary reason for SUI (ISD vs urethral hypermobility) had no significant relationship with clinical results. Importantly, there was a significantly higher incidence of urinary retention in the periurethral group compared to the transurethral group (30% vs 5%, respectively). While there were no differences in the volume of UBA injected overall, patients in the periurethral group who experienced urinary retention had a significantly larger quantity of bulking agent deposited than those in the transurethral group (5.1 vs 3.4 ml) [20].

Summary of Urethral Bulking Agents in Women: Safety and Efficacy

Historical Agents

Historical UBAs are summarized in Table 14.1.

Table 14.1 Historical urethral bulking agents

Urethral bulking agent	Trade name(s)	Agent class	Associated complications
Sodium morrhuate	N/A	Sclerosing agent	Pulmonary embolus, cardiac arrest
Granugenol oil/Dondren	N/A	Sclerosing agent	Pulmonary embolus, urethral sloughing
Polytetrafluoroethylene	Teflon™	Microsphere particulate UBA	Particle migration, particle extrusion, periurethral abscess,urethral diverticula, granuloma formation, possible carcinogen
Autologous fat	N/A	autologous fat	Pulmonary fat embolism
Glutaraldehyde Cross-Linked (GAX) Collagen	Contigen™	Bovine collagen	Allergic reactions, pulmonary emboli, sterile abscess formation
Ethylene vinyl alcohol	Uryx™, Tegress™	Copolymer non-particulate UBA	Urethral erosions
Dextranomer with hyaluronic acid	Zuidex™, Deflux™	Microsphere particulate UBA	Sterile abscess, injection site mass, and pseudocyst formation

Sclerosing Agents

Sodium morrhuate, a sclerosing agent, was the first documented UBA. First described in 1938, Murless injected sodium morrhuate into the anterior vaginal wall to stimulate scarring of the periurethral tissue in order to prevent urethral hypermobility. While somewhat successful, some severe adverse effects ensued including pulmonary embolus and cardiac arrest [23, 24]. In 1963, Sachse injected granugenol oil, or Dondren, another sclerosing agent, into both female and male urethras. Although patients did experience some symptomatic improvement, several developed pulmonary emboli and urethral sloughing [25].

Polytetrafluoroethylene (Teflon™)

Polytetrafluoroethylene, or Teflon™, contains microparticles ranging in size from less than 50 μm to 300 μm [26]. It was used in the 1970s and 1980s with success rates as high as 75% [27] but was never approved for use in the United States due to significant complications related to particle migration to distant sites and its carcinogenic potential [23, 28]. Furthermore, there were several reports of extrusion, periurethral abscess, urethral diverticula, and granuloma formation [23, 29].

Autologous Fat

As early as 1989, several groups trialed periurethral injections of autologous fat harvested from the abdominal wall [30]. Thought to be a suitable material for a UBA for its ease of access and biocompatibility, a randomized double-blind trial comparing periurethral injections of autologous fat or saline placebo failed to demonstrate a significant difference in cure rates. One patient even experienced death secondary to pulmonary fat embolism [31], which further discouraged its usage as a UBA. The durability of autologous fat grafts is limited, as grafts lose up to 55% of volume by six months [32].

Glutaraldehyde Cross-Linked (GAX) Collagen (Contigen™)

In 1993, GAX bovine collagen in phosphate-buffered saline, marketed as Contigen™ (CR Bard, Murray Hill, New Jersey, USA), was approved by the US Food and Drug Administration (FDA) as a UBA. Initial symptomatic improvement rates ranged from 68 to 90%, usually after approximately three injections, but declined over time [33, 34]. Comprised of 95% type I collagen and 1–5% type III collagen, women undergoing Contigen injection required skin testing 30 days prior to their procedure, as it caused allergic reactions in 4% of patients due to its antigenic nature. Other adverse events included UTI, hematuria, de novo urgency, arthralgia, pulmonary emboli, and sterile abscess formation [35]. Contigen was discontinued by its manufacturer in 2011.

Ethylene Vinyl Alcohol (Uryx™, Tegress™)

Ethylene vinyl alcohol (EVA) is a copolymer suspended in dimethyl sulfoxide (DMSO), also known as Uryx™ (Genyx Medical, Inc., Aliso Viejo, CA/C.R. Bard, Murray Hill, NJ, USA) or Tegress™ (CR Bard, Murray Hill, NJ, USA). EVA was approved by the FDA in 2004 for use as a UBA. When injected and exposed to blood or extracellular fluid at body temperature, the DMSO dissolves, and the EVA forms a spongiform mass, creating the urethral bulk [36]. When compared to collagen injections, EVA injections had higher cure and symptomatic improvement rates [37]. However, it was ultimately withdrawn from the market in 2007 due to multiple adverse effects including severe urethral erosions and fistula formation [38].

Dextranomer with Hyaluronic Acid (Zuidex™, Deflux™)

Zuidex™ (Q-Med AB, Uppsala, Sweden) or Deflux™ (Oceana Therapeutics Inc., Edison, New Jersey, USA) are gels containing dextranomer microspheres suspended in hyaluronic acid. As the hyaluronic acid gel dissolves, the microspheres remain in place for four years, promoting connective tissue ingrowth. These agents are commonly used and approved for endoscopic treatment of vesicoureteral reflux in children.

A multicenter study with 142 patients with invasive-treatment naïve SUI who underwent Zuidex injections demonstrated a 77% positive response, defined as ≥50% reduction in provocation test leakage, after one year. Significant reductions were also noted for 24-hour pad-weight test and number of daily incontinence episodes. Most adverse events were transient and included urinary retention, UTI, injection site reaction, urinary urgency, vaginal discomfort, dysuria, pain, pseudocyst formation, and injection site infection [39].

A subsequent non-inferiority trial compared outcomes in patients with SUI, who were randomized to receive either midurethral injection of Zuidex (n = 227) or Contigen injection at the bladder neck (n = 117). Those who underwent Contigen injection had higher dry and positive response rates, also defined as ≥50% reduction in provocation test leakage. Although both groups had identical rates of urinary retention (28%), the Zuidex group experienced more complications, including sterile abscess, injection site mass, and pseudocyst formation [40], leading to its discontinuation as a UBA for SUI.

Contemporary UBAs

Contemporary UBAs are summarized in Table 14.2.

Table 14.2 Contemporary urethral bulking agents (Updated January 2021)

Urethral bulking agent	Trade name(s)	Composition	Mechanism of action	Particle size	Year of FDA approval
Particulate agents					
Carbon-coated zirconium	Durasphere™	Carbon-coated zirconium particles in 2.8% beta-glucan hydrogel carrier	Hydrogel degrades over times, leaving particles behind to create bulk	212 to 500 μm	1999
Calcium hydroxylapatite	Coaptite™	Calcium hydroxylapatite microspheres incarboxymethyl cellulose gel carrier		75 to 125 μm	2005
Cross-linked polydimethylsiloxane	Macroplastique™	Cross-linked polydimethylsiloxane elastomer particles in polyvinylpyrrolidone hydrogel carrier		110 μm	2006
Non-Particulate Agents					
Porcine collagen	Permacol™	Cross-linked porcine dermis	Injected collagen matrix integrates with host tissue and blood vessels	N/A	2004
Polyacrylamide hydrogel	Bulkamid™, Aquamid™	Hydrogel containing 97.5% nonpyrogenic water and 2.5% cross-linked polyacrylamide	Hydrogel invaded by macrophages and giant cells, allowing for integration with host tissue	N/A	2020
Polydimethylsiloxane	Urolastic™	Vinyl dimethyl terminated polydimethylsiloxane polymer, tetrapropoxysilane cross-linking material, and platinum divinyltetramethyl siloxane complex catalyst	Injected as a liquid which hardens and becomes encased in scar tissue	N/A	pending

Porcine Collagen (Permacol™)

Permacol™ (Covidien, Gosport, United Kingdom) is sourced from cross-linked porcine dermis. During processing, cells, DNA, and RNA are removed in such a way that allows the collagen matrix to retain its microscopic constitution [41]. The matrix resembles human dermis, allowing integration with host tissue and blood vessels. Unlike Contigen, it does not require allergy testing prior to implantation [42]. Data surrounding the efficacy of Permacol is mostly limited to one trial which randomized women with SUI to receive either injection with Permacol ($n = 25$) or Macroplastique ($n = 25$). Six weeks postinjection, Permacol patients had insignificantly higher dry rates (60% vs 41.6%). At six months, 62.5% of the Permacol patients remained dry compared with 37.5% of Macroplastique patients. Additionally, fewer Permacol patients experienced transient post-procedural urinary retention (8 vs 12%) [42].

Calcium Hydroxylapatite (Coaptite™)

Coaptite™ (Bioform Medical Inc., San Mateo, California, USA) is a synthetic UBA consisting of calcium hydroxylapatite microspheres suspended in a carboxymethyl cellulose gel carrier. Microsphere particles range in size from 75 to 125 μm [43]. The gel initially provides the bulking effect but degrades over time allowing native tissue to grow around the particles, which also eventually dissolve [43]. The volume of the Coaptite deposit decreases by approximately 40% after three months, and patients who retain more volume are more likely to have sustained symptomatic improvement [44].

The main data supporting the efficacy of Coaptite is derived from a multicenter prospective randomized control trial. In this non-inferiority study, women with SUI secondary to ISD without urethral hypermobility received injection with either Coaptite or Contigen, the gold standard at the time of publication. After one year, there was an insignificant improvement in patient success, defined as improvement of at least one Stamey grade, favoring the Coaptite group (63.4 vs 57.0%). There were also no differences in the one-year cure rate (39% vs 37%) and percentage of participants having at least 50% reduction in 24-hour pad weight (62% vs 54%) for the Coaptite and Contigen groups, respectively. Furthermore, more patients in the Coaptite group only required a single injection [43].

There were no differences between the groups in terms of most minor procedure-related adverse events, including dysuria or urinary retention, although there was a significantly lower risk of developing urge incontinence in the Coaptite group (5.7% vs 12%). Two major complications were reported in the Coaptite group, specifically vaginal wall erosion into the distal urethra and dissection of the material beneath the trigone. These serious events were attributed to injection technique and the large particle size causing pressure on host tissues [43]. Other rare side effects of Coaptite including urethral prolapse and granuloma formation requiring surgical correction have been reported [45, 46].

Carbon-Coated Zirconium (Durasphere™)

Durasphere™ (Carbon Medical Technologies, St. Paul, Minnesota, USA) contains nondegradable carbon-coated zirconium particles suspended in a dissolvable 2.8% beta-glucan hydrogel carrier. The relatively large particles range in size from 212 to 500 μm [47], which can make injection more difficult due to increased resistance [5]. It became FDA approved for use as a UBA in 1999 [48].

Durasphere was shown to have equivalent efficacy to collagen injections in a multicenter trial. The study randomized 355 women with SUI secondary to ISD to receive either Durasphere or bovine collagen. Clinicians used a significantly lower volume of Durasphere than collagen during injection (4.83 vs 6.23 ml, respectively). At one year after injection, there was no difference in pad weight or improvement in continence grade. After both one and two years, no evidence of particle migration was observed on pelvic radiographs [48]. However, after 24 months and beyond, Durasphere's objective benefits diminished [49]. With respect to adverse events, patients in the Durasphere group experienced significantly more urinary urgency and transient acute retention. Otherwise, complication profiles were similar [48]. While most adverse effects are self-limited, other serious complications including particle migration to lymph node tissue [50], periurethral abscess formation, and urethral prolapse [51] have been reported as well as visible staining/tattoo of vaginal mucosa since the product is black in color.

Durasphere has also been used in combination with Contigen. In a study comparing women who underwent combined Contigen/Durasphere injections ($n = 33$) with Contigen alone ($n = 33$), there was a significantly higher cure rate in the combined group after two weeks (72.7% vs. 39.2%). The benefits were not sustained, and dry rates after six months were equivalent between the combined and Contigen alone groups (33.3 vs 29.4%). There was no difference between groups in the need for subsequent anti-incontinence procedures [52].

Cross-Linked Polydimethylsiloxane (Macroplastique™)

Macroplastique™ (Cogentix Medical, Orangeburg, New York, USA) is a silicone polymer containing cross-linked polydimethylsiloxane elastomer particles suspended in a polyvinylpyrrolidone hydrogel carrier. After injection, the Macroplastique deposit is enveloped in a fibrin capsule, which is infiltrated with collagen. The hydrogel is absorbed and excreted by the kidneys [53]. The nondegradable particles, approximately 110 μm in size, remain in place after the gel carrier dissolves [5, 54].

The most compelling data demonstrating Macroplastique's efficacy was described in a trial of 247 women with SUI secondary to ISD who were randomized to receive transurethral injection of either Macroplastique or Contigen. At 12 months, the Macroplastique group demonstrated a significantly higher dry rate than the Contigen group (36.9% vs 24.8%). More patients in the Macroplastique cohort also improved by at least one Stamey grade (61.5% vs 48%). Both cohorts exhibited a reduction in urine loss from baseline, although there was no distinguishable

difference from each other. The number and volume of injections between groups were also equivalent. Both groups had similar rates of treatment-related adverse events. The most common side effects included UTI, lower urinary tract symptoms, urinary retention, and implantation site pain. Three patients experienced urethral erosion (two in the Macroplastique group and one in the Contigen group) [54]. After two years of follow-up, 84% of patients reported continued improvement from their treatment, 67% of whom were dry. Incontinence quality of life (I-QoL) scores and mean pad weight also remained significantly improved from baseline. There were no treatment-related adverse events during the follow-up period [53].

A subsequent systematic review combining data from 958 women with SUI who underwent Macroplastique injection demonstrated short-term, mid-term, and long-term dry rates of 43%, 37%, and 36% and improvement rates of 75%, 73%, and 64%, respectively. The median reinjection rate was 30%, with 63% of those patients reporting symptomatic improvement from SUI. Adverse events were all minor, such as transient urinary retention, urge incontinence, UTI, dysuria, and hematuria [55]. However, despite an overall favorable complication profile, a number of rare and serious complications were described including extrusion secondary to suspected immune reaction, bladder neck and urethral erosion, and suburethral, vaginal, and bladder mass formation [56–60]. Several other studies have demonstrated Macroplastique's durable response with cure rates ranging from 47 to 49% after two to three years. While many patients require more than one injection, most objective improvement rates remain stable after six months. There are also sustained decreases in daily pad weight after several years of follow-up [61–63].

Macroplastique may also be useful in patients with SUI after hysterectomy. In a study of 24 cervical cancer patients who underwent radical hysterectomy with resultant SUI, Macroplastique injection was associated with a 42% dry rate and 42% improvement rate after one year. Failure was correlated with presence of urethral hypermobility [64].

Polyacrylamide Hydrogel (Bulkamid™, Aquamid ™)

Bulkamid™ and Aquamid™ (Contura International A/S, Soeborg, Denmark) are derived from a nondegradable hydrogel containing 97.5% nonpyrogenic water and 2.5% cross-linked polyacrylamide [7]. The viscoelastic, hydrophilic nature of polyacrylamide hydrogel allows it to exchange water molecules, nutrients, and waste with the surrounding host tissue matrix [5]. Over several years, the hydrogel is invaded by macrophages and giant cells which are then replaced by a permanent network of thin fibers and vessels [65] to prevent migration [66].

The effects of Bulkamid have been investigated in a number of settings including SUI, mixed incontinence, and vulnerable patients. With respect to treatment for SUI and MUI, a systematic review of mostly observational studies revealed improvements in the number of incontinence episodes, quantity of urine leakage, and quality of life after Bulkamid injection. The overall reinjection was calculated to be 24.3%. Complications were mostly minor including pain at injection site, UTI, hematuria,

and transient acute urinary retention [67]. Rare serious adverse events included abscess formation and urethral mucous membrane rupture at injection site [67–69]. The only randomized double-arm study included was a multicenter trial demonstrating the non-inferiority of polyacrylamide hydrogel to Contigen for treatment of SUI or stress-predominant MUI. After one-year postinjection, cure/improvement rates were 77.1% and 70% for the polyacrylamide hydrogel and Contigen groups, respectively. There was no difference in complication rates between cohorts, which were mostly limited to minor, transient lower urinary tract symptoms, urinary retention, and de novo incontinence. Only one serious treatment-related adverse effect, transient hematuria, was reported in the polyacrylamide hydrogel group [8]. On post hoc analysis, a 90% treatment effect rate and 38% cure rate were seen in women over age 60, compared to just a 13% cure rate for younger women [10].

In addition to improving incontinence, Bulkamid has been shown to have a positive effect on sexual activity. Leone Roberti Maggiore et al. described the effects Bulkamid injection on sexual function in 29 women with SUI. After one year of follow-up, 100% of the 23 previously sexually active patients were able to resume sexual activity after injection. These women reported less incontinence or fear of incontinence during intercourse, improvement in desire, climax, and satisfaction with their sex lives. The remaining six nonsexually active women were able to reestablish sexual activity as well [70].

Bulkamid has also been successfully utilized in a number of special populations including octogenarians and postradiation patients [71, 72]. In a group of 20 octogenarians with a mean age of 84.5 years old, Vecchioli-Scaldazza et al. found a significant reduction in urine lost with a cough stress test and number of pads needed after two years after Bulkamid injection. Quality of life scores and urodynamic parameters, including abdominal leak point pressure, mean urethral closure pressure, and urethral length also improved [72]. Krhut et al. administered Bulkamid to 46 women with a history of a gynecologic cancer with resultant SUI treated with and without pelvic radiotherapy. After injection, cure rates for the radiation group and non-radiation group were 25% and 36.4%, respectively, and no severe adverse events were reported [71]. Taken together, these findings highlight how polyacrylamide hydrogel can be a useful tool with minimal risk in vulnerable patients with incontinence.

Polydimethylsiloxane (Urolastic™)

Urolastic (Urogyn BV, Nijmegen, The Netherlands) is a synthetic compound containing vinyl dimethyl terminated polydimethylsiloxane polymer, a tetrapropoxysilane cross-linking material, and a platinum divinyltetramethyl siloxane complex catalyst. The addition of titanium dioxide radio-opacifies this bulking agent [73]. Unlike Macroplastique, the Urolastic deposit does not contain any particles and is injected as a liquid. Once the liquid hardens, it is encircled in scar tissue and does not degrade, lose volume, or migrate over time [74]. Currently, Urolastic is only approved for usage in Europe.

The efficacy and complication profile of Urolastic for treating SUI has been described in a few small series [73–77]. Zajda et al. reported on 20 women with SUI who underwent Urolastic injection, 35% of whom required a second injection. After 12 and 24 months of follow-up, 68% and 45% of patients remained dry, respectively. Eighty-nine percent of patients reported improved continence after 12 months which was reduced to 66% at two years [74, 77]. Minor complications occurred in 30% of patients, which included hematoma formation, urinary retention, and dyspareunia or vaginal pain requiring removal of the deposit [74]. At 24 months, four out of 18 patients included in the follow-up analysis underwent implant removal because of dyspareunia and suboptimal dryness [77]. Likewise, Futyma et al. performed Urolastic injection on 105 women with either primary or recurrent SUI. After 12 months, objective success rates, defined as negative pad and cough stress tests, were 71.4% and 59.3% in the primary and recurrent groups, respectively. The overall reinjection rate was 17%. Four out of 10 patients with urinary retention required implant excision [75]. After 24 months, those with recurrent SUI had a 22.4% cure rate, with 32.7% reporting objective success (either cure or improvement) [76].

Urolastic has also been trialed in women who are medically unfit for surgery. Kowalik et al. evaluated the effects of Urolastic periurethral injection in 20 women deemed unfit for a MUS. Five patients required a second injection due to persistent incontinence, three of which required removal of the bulking agent from the first injection. Six months postinjection, 90% of patients reported subjective symptomatic improvement, and 65% of patients had a negative cough stress test. Health-related quality of life scores improved significantly in all domains, as measured by the Urogenital Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7). Peri-procedural complications included hematoma formation, pain, and injection of the UBA at epithelial surface requiring excision. Reported adverse events were all managed in the outpatient setting and included urinary retention immediately after injection, bulking material exposure, and spontaneous loss of bulking material [73].

Long-term success of Urolastic appears comparable to other bulking agents. In a systematic review with follow-up between six and 24 months, objective cure rates ranged between 32.7% and 67% with a pooled rate of 57%. The pooled subjective improvement rate was 84%. A second injection was required in 16.7%–35% of study cohorts. The pooled complication rate was 36%, the most common of which was urgency, post-void residual greater than 150 ml, and exposure or erosion [78]. Ultimately up to 18% of patients may require excision of Urolastic for persistent pain, exposure, or erosion [79].

The Use of UBAs Compared with Other Anti-Incontinence Procedures

Practices for managing SUI widely vary among clinicians, as there is no accepted standardized algorithm. The 2017 American Urological Association/Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (AUA/

SUFU) Guidelines for SUI state that in index patients with SUI considering surgical treatment, clinicians may offer UBAs as well as synthetic MUS, autologous fascial pubovaginal sling, or a Burch colposuspension. The Guidelines also state that UBAs may be offered to non-index patients with ISD in addition to retropubic MUS and pubovaginal slings. No recommendations are given with respect to the order in which these treatment options should be trialed, although the discussion statement does express that UBAs should be offered to patients who want a minimally invasive procedure and acknowledges that repeat injections are common [80]. Similarly, the European Association of Urology (EAU) 2018 Guidelines on urinary incontinence state that bulking agents should be offered to women with SUI who desire a low-risk procedure and understand that they will likely require repeat injections [81].

The precise location in which UBAs should fall on the SUI surgical management decision tree is unknown. This ambiguity is likely due to a paucity of randomized prospective studies comparing UBAs to other anti-incontinence procedures [82].

In a 2015 systematic review and meta-analysis, the authors identified just three studies comparing UBAs to other anti-incontinence procedures, only two of which were randomized control trials. The analysis concluded that UBAs are associated with significantly higher objective recurrence rates for both primary and recurrent SUI when compared with other anti-incontinence procedures, which included pubovaginal slings, MUS, bladder neck suspensions, and Burch colposuspensions. UBAs were associated with less voiding dysfunction. However, the small size of this meta-analysis and numerous other limitations highlight the need for additional comparative data [82].

More recently, a trial randomized 224 women with primary SUI to receive either tension-free vaginal tape ($n = 111$) or polyacrylamide hydrogel injection ($n = 113$). After one year of follow-up, patients who underwent MUS reported higher patient satisfaction scores and higher rates of dryness as measured by a negative cough stress test compared with those who underwent polyacrylamide hydrogel injection (95% vs 66.4%, respectively). Women in both groups exhibited improved sexual function and health-related quality of life, particularly in the domains of physical and social functioning. However, MUS was associated with a higher rate of perioperative complications and reoperations [11, 83]. Therefore, it is important to counsel patients with SUI on both options, as some patients may be willing to accept the trade-off between lower cure rates with UBAs and higher complication rates associated with MUS [84]. Ultimately, more prospective data comparing UBAs to other anti-incontinence procedures evaluated in diverse patient settings are needed to clearly define the role of UBAs in managing primary and recurrent SUI.

UBAs as a Salvage Procedure After Failed MUS

There is currently no established gold standard or consensus for the ideal salvage technique after a failed MUS [66]. In a survey of the members of the International Urogynecological Association, UBAs were reported as the preferred salvage procedure in patients without urethral hypermobility [85]. Despite the proclivity of some surgeons to trial UBAs for recurrent SUI after a sling, the evidence regarding the

efficacy and durability of UBAs as a salvage procedure for recurrent SUI after a failed MUS is limited to small retrospective reports and lacks high-quality evidence.

A study including 23 women who underwent salvage injection with either Macroplastique or Durasphere after a failed MUS demonstrated a cure rate of 34.8% after just 10 months, despite improved I-QoL scores and 92% perceived benefit of treatment [86]. Similarly, Dray et al. examined 73 patients with recurrent SUI after MUS placement who underwent salvage injection with either Macroplastique or collagen. After an average of 2.6 injections, 71% of patients reported symptomatic improvement, 24.7% of whom had complete resolution of SUI. Just two of 40 women with long-term follow-up information after a mean of 39.5 months reported complete resolution of SUI, although there was a significant improvement in most domains on the Michigan Incontinence Symptom Index (M-ISI) [18]. In an analysis of 17 women who underwent injection with 2 ml of Bulkamid after failed MUS, Clark et al. reported a 42% reinjection rate (occurring between 10 and 46 months after the initial injection) but a 71% perceived rate of benefit [87]. Zivanovic et al. performed a retrospective observational analysis looking at 60 patients with refractory SUI or MUI after a failed MUS who underwent injection with 1 to 3 ml of Bulkamid. After one month, 93.3% of patients were either cured or had symptomatic improvement, which slightly dropped to 88.3% and 83.6% at six and 12 months, respectively. The most common adverse event was persistent urge urinary incontinence in 20%, 16.7%, and 20% of patients after one, six, and 12 months, respectively. Other adverse events were seen in a small minority of patients and included voiding dysfunction, UTI, de novo urgency, hematuria, injection site laceration, and hematoma [66].

Only one analysis has directly compared repeat MUS ($n = 98$) with UBA using either Contigen, Coaptite, or Macroplastique ($n = 67$) as a salvage technique after failed MUS. Those who underwent UBA injection experienced a significantly higher risk of failure after one year of follow-up compared to repeat MUS patients (38.8% vs 11.2%, respectively), although there was no difference in complication rates [88].

UBAs have also been utilized as a salvage technique after MUS removal. Rodriguez et al. evaluated 70 women who underwent UBA injection with Macroplastique after excision of failed MUS. They demonstrated a 69% overall success rate, with an 83% subjective improvement rate and 78% reduction in pad usage [89]. While these studies are small, it does appear that multiple types of UBAs offer both subjective and objective symptomatic benefit to many women when used as an adjunctive salvage procedure or after MUS removal, although the benefit diminishes over time and may require reinjection.

Conclusion

UBAs are an important tool in a urologist's armamentarium for managing SUI. They are particularly useful in women who are not surgical candidates or who wish to avoid general anesthesia. Although associated with lower rates of cure than other

anti-incontinence procedures, UBAs demonstrate more favorable complication profiles. More prospective randomized data is necessary to elucidate the optimal composition and long-term outcomes of UBAs.

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