# Current Use of Injectable Agents for Female Stress Urinary Incontinence

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*Injectable materials of various types have been used for decades as an alternative to surgery for the treatment of stress urinary incontinence. Their success stems from their ability to improve intrinsic sphincter function, and patients with hypermobility may benefit as well. Nevertheless, the ideal agent has yet to be discovered, and surgery still may be necessary after treatment in some patients. Results vary among the different materials used, and safety, durability, and cost-effectiveness are important areas of concern in which more research is needed.*
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In 1938, Murless[1] first reported on the injection of sodium morrhuate around the urethra for urinary incontinence, and since then various materials have been injected as an alternative to surgery. Quackels[2] reported the use of paraffin wax in 1955, and Sachse[3] used sclerosing agents in 1963. The initial results were poor, and significant complications such as pulmonary emboli and urethral sloughing were seen. Polytetrafluoroethylene (Teflon®) paste was first introduced by Berg[4] and then popularized by Politano and associates[5] in the 1970s. Shortliffe

and coworkers[6] published the first report on glutaraldehyde cross-linked collagen, and more recently, autologous fat injection was described.[7] Newer agents, such as silicone microparticles[8] and carbon beads,[9] have also been reported.

This article will summarize the techniques of administration, properties, published results, and complications of the various injectable agents as well as outline some of the controversies. Some of the unmet needs associated with injectable agents will also be discussed.

## Mechanism of Action of Injectables

It is generally agreed that these agents improve intrinsic sphincter function. Collagen injections have been reported to augment urethral mucosa[10,11] and improve coaptation and intrinsic sphincter function, as evidenced by an increase in post-treatment abdominal leak pressure.[12-14] Initial investigators using collagen postulated obstruction as a mechanism of action,[15,16] but Monga and associates[11] showed that successfully treated patients have an increased area and pressure transmission ratio in the first quarter of the urethra. They suggested that placement of the injectable agent at the bladder neck or proximal urethra prevents bladder neck opening under stress. Proper placement of the injectable, possibly just below the bladder neck, rather than the actual quantity of the agent, improves intrinsic sphincter deficiency (ISD).[17]

The ideal injectable agent should be easily injectable and conserve its volume over time. If unsuccessful, it should not interfere with subsequent surgical intervention. It should also be biocompatible, nonantigenic, noncarcinogenic, and nonmigratory.[18] To date, no substance has met all of these requirements.

## Patient Selection

Patients with ISD and normal detrusor function are candidates for injectable agents.[19] McGuire and coworkers[20] identified these patients with the use of abdominal leak pressures to measure the strength of the intrinsic sphincter. Low leak pressures ($< 65$ cm water) correlate well with type 3 videourodynamic findings, that is, a poorly functioning bladder neck and proximal urethra (ISD), and higher leak pressures correlated with type 1 or 2 hypermobility.

The presence of ISD is the primary indication for the use of injectable agents in patients with stress urinary incontinence.[10] Because ISD can coexist with hypermobility,[21] injectables have been administered to patients with hypermobility, to improve the ISD component of their incontinence. Furthermore, elderly women with hypermobility, who are poor operative risks, have also received injectable agents.[22]

## Injection Techniques

The materials can be administered under local anesthesia with cystoscopic control as an outpatient procedure. Both the periurethral and transurethral methods are done to implant the agent within the urethral wall, preferably into the submucosa or lamina propria. It is thought that the implant should be positioned at the bladder neck or proximal urethra. Different sites can be chosen, such as 3 and 9 o'clock or 4 and 8 o'clock positions, although Defreitas and colleagues[23] recently demonstrated that patients with circumferentially distributed implants had better results than those with random deposits. The actual needle size required depends on the viscosity of the injectable. Pre- and postoperative antibiotics are usually administered.

With the periurethral approach, perimeatal blebs are raised with 1% or 2% lidocaine at the 3 and 9 o'clock or 4 and 8 o'clock positions approximately 3 to 4 mm lateral to the urethral meatus. A 20F urethroscope with a 30° telescope is inserted into the urethra after instillation of topical urethral lidocaine. The periurethral needle is introduced and advanced parallel to the endoscope sheath until its position can be seen cystoscopically just below the bladder neck within the mucosa. Care must be taken to prevent the needle from getting too close to or entering the urethral lumen to avoid rupture of the mucosa and extravasation. Rocking the needle will confirm the position of the tip. If penetration of the mucosa occurs, the needle should be removed and repositioned. The substance is injected either unilaterally or bilaterally to create the appearance of "prostatic" lobes. The patient is asked to cough or strain in the supine and then the upright position. If leakage still occurs, more agent may be given. If no leakage is seen, the procedure may be ended. The patient then voids and can be discharged. Acute retention can be treated by insertion of a fine 8F catheter.

The implant can also be injected transurethrally through the cystoscope with flexible needle-tipped catheters or with specially designed injection scopes with rigid needles. Silicone microparticles, Teflon, and fat, because of their high viscosity, may require the use of injection guns. A recent modification of the transurethral technique has been reported by Tamanini and coworkers.[24] They used a device that fits into the urethra, and through needle-guiding channels, injected Macroplastique® (Uroplasty BV, Geleen, The Netherlands) into the 2, 6, and 10 o'clock positions.

## Collagen

Glutaraldehyde cross-linked collagen, or GAX collagen, is a highly purified suspension of bovine collagen in normal saline containing at least 95% type I collagen and 1% to 5% type III

collagen.[25] This cross-linking makes the GAX collagen resistant to the fibroblast-secreted collagenase. As a result, the GAX collagen is only very slightly resorbed. The implant causes no inflammatory reaction or granuloma formation and is colonized by host fibroblasts and blood vessels. It is not known to migrate. However, it does degrade over time and is replaced by host collagen, which explains its persistence.[25]

Because 2% to 5% of patients[26] are sensitized to collagen through dietary exposure, all patients must undergo a skin test at the volar aspect of the forearm 30 days before treatment. Those who show a positive response should not undergo the procedure.

*Collagen Results*

Numerous reports of its efficacy, safety, ease of administration, and relative lack of associated morbidity have appeared since the first description of collagen injection for urinary incontinence. Table 1 lists various reported series.

Persistence of the implant itself has been demonstrated with magnetic resonance imaging (MRI) of the urethra at intervals of up to 22 months after injection, although the measured volume was less than that injected.[27] Early results are generally good, with success rates of 72% to 100% (Table 1). Maintenance of good results in the long term may occur with durability of the initial procedure itself or with reinjections with additional collagen. It is important for authors to differentiate the durability of the original procedure(s) from that resulting from reinjections or top-ups by reporting the follow-up period starting from after the last injection.

Longer-term (more than 1 to 2 years) cure and improvement[17] varies from 57% to 94%.[28] Most patients need 1 or 2 treatment sessions with means of 5.6 to 15 cc of collagen used. Because patients are treated at different times and because durations of follow-up vary, the Kaplan-Meier curve can be useful to display the persistence of a good result. In our series, the probability of a patient remaining dry was 72% at 1 year, 57% at 2 years, and 45% at 3 years (Figure 1).[29] Winters and Appell[13] also reported a similar rate of complete continence (50%) in their multicenter trial after 2 years. Additional administration of collagen has usually resulted in restoration of continence, and this has to be factored into the reporting.

Berman and Kreder[30] analyzed the cost-effectiveness of collagen versus sling cystourethropexy for type 3 incontinence. They concluded that surgery was more cost effective than collagen injection.

The use of collagen in patients with hypermobility has been reported. Moore and associates[31] included patients with both type 1 and type 3 abnormalities. Faerber[22] treated elderly patients with type 1 abnormality. In the report by McGuire and Appell,[10] the results at more than 1 year in women with ISD were similar to those in women with hypermobility, although there were far more women with ISD. However, Appell[19] subsequently reported that these patients with hypermobility all required bladder neck surgery within 2 years. Monga and associates[11] included patients with hypermobility and found that cure rates were not reduced for women with up to 2.5 cm of movement. In our series of 181 patients, there was no significant difference in outcome with or without hypermobility.[32] Furthermore, in a prospective trial of patients with hypermobility, Bent and colleagues[33] reported a good outcome after 1 year.

*Collagen Complications*

Treatment-related morbidity has been minimal. Urinary retention ranges from 1% to 21%[12,13,19] and can be managed with intermittent catheterization or short-term Foley catheterization. Urinary tract infection occurs in 1% to 25%.[12,13,19] Extravasation

Figure 1. *Kaplan-Meier curve showing durability of cure of incontinence after the last collagen injection in 78 patients. (Reproduced with permission from Herschorn and Radomski.[29])*

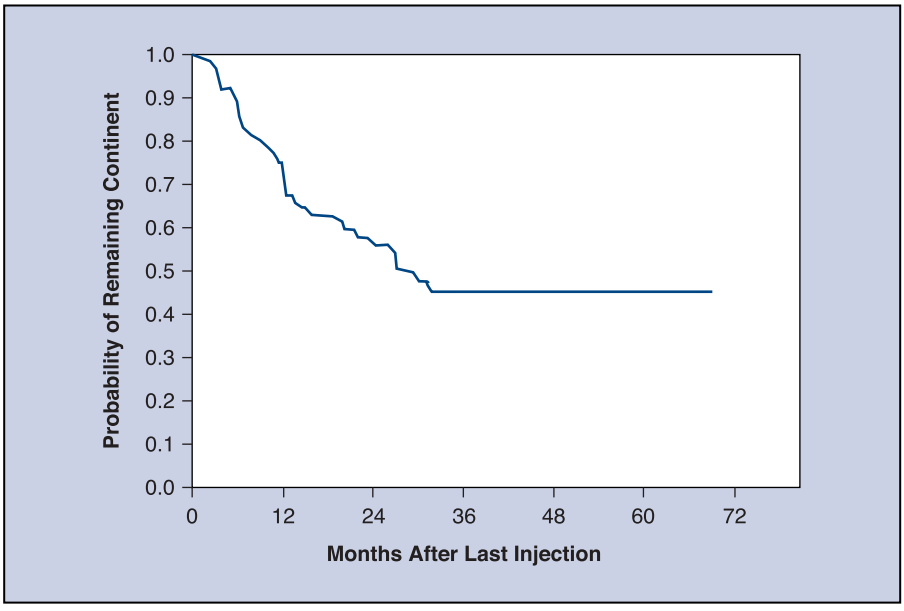

Table 1
Comparison of Collagen Parameters and Results

| Study | Patients | Type of Incontinence | Follow-up (mo) | Patients Dry (%) | Patients Improved (%) | Patients Failed (%) |
|---|---|---|---|---|---|---|
| Stricker and Haylen[70] | 50 | ISD | Mean: 11 (range, 1–21) | 21 (42) | 20 (40) | 7 (14) |
| Kieswetter et al[71] | 16 | Not specified | 9 | 7 (44) | 7 (44) | 2 (12) |
| Eckford and Abrams[15] | 25 | Not specified | 3 | 16 (64) | 4 (16) | 5 (20) |
| O'Connell et al[32] | 44 | 42 with ISD<br>2 hypermobile | 1–2<br>(longest, 7) | 20 (45) | 8 (18) | 16 (37) |
| Moore et al[31] | 11 | Types 1 and 3 | 2 | 1 (9) | 7 (63) | 2 (18) |
| Winters and Appell[13] | 50 | ISD | >12 | 48 (96) dry or socially continent | | 2 (4) |
| McGuire and Appell[10] | 17<br>137 | Mobile<br>ISD | >12<br>>12 | 8 (47)<br>63 (46) | 3 (17)<br>47 (34) | 6 (35)<br>29 (19) |
| Faerber[22] | 12 | Type 1 | 10.3 (range, 3–24) | 10 (83) | 2 (17) | 0 |
| Monga et al[11] | 60 | Some hypermobile | 3 (N = 59)<br>12 (N = 54)<br>24 (N = 29) | 27 (46)<br>22 (40)<br>14 (48) | 24 (40)<br>20 (37)<br>6 (20) | |
| Richardson et al[14] | 42 | ISD | 46 (10–66 after first injection) | 17 (40) | 18 (43) | 7 (17) |
| Herschorn and Radomski[29] | 181 | Type 1: 54<br>Type 2: 67<br>Type 3: 60 | Mean: 22 (range, 4–69)<br>≥24 (N = 62)<br>≥36 (N = 25) | 42 (23)<br>27 (43.5)<br>13 (52) | 94 (52)<br>29 (46.8)<br>8 (32) | 45 (25)<br>6 (9.7)<br>4 (16) |
| Smith et al[72] | 94 | Type 3 | Median: 14 | 36 (38.3) | 27 (28.7) | 31 (33) |
| Khullar et al[17] | 21 | Not specified | 24 (minimum) | 10 (48) | 2 (9) | 9 (43) |
| Swami et al[73] | 107 | Some hypermobile | 24 (minimum) | 27 (25) | 43 (40) | 37 (35) |
| Cross et al[28] | 103 | Type 3 | Median: 18 (range, 6–36) | Substantially improved 103 (74) | 29 (20) | 7 (6) |
| Groutz et al[74] | 63 | Type 3 | 6 | 8 (13) | 44 (70) | |
| Bent et al[33] | 90 | Types 1 and 2 | 12 | 19 (21) | 19 (21) | 11 (17) |
| Corcos and Fournier[75] | 40 | Type 1 (8)<br>Type 2 (20)<br>Type 3 (12) | 52 | 12 (30) | 16 (40) | 62 (58) |

ISD, intrinsic sphincter deficiency.

resolves quickly with flushing away of the dilute collagen suspension and sealing over of the small needle insertion site. Hematuria occurs in 2% of patients.[19] Other rare complications include periurethral abscess formation.[34]

Other reported complications include de novo detrusor overactivity (instability), which was seen in 11 (39%) of 28 elderly women treated by Khullar and colleagues.[17] Stothers and coworkers[35] reported de novo urgency with urgency incontinence in 43 (12.9%) of 337 patients, 21% of whom did not have response to anticholinergics.

Another rare complication is a reaction at the previously negative skin test site following a urethral collagen injection. In one study, this occurred in 3 patients (1.9%) and was associated with arthralgias in 2.[26] This reaction has been reported before in the dermatologic literature,[36] and 2 negative pretreatment skin tests have been suggested to prevent it. The potential for hypersensitivity reactions is present because antibody production is stimulated by collagen injection.[37]

## Silicone Microparticles

Silicone microparticles are solid polydimethylsiloxane (silicone rubber) particles suspended in a nonsilicone carrier gel that is absorbed by the reticuloendothelial system and excreted unchanged in the urine.[8] Because 99% of the particles are between 100 μm and 450 μm in diameter, the likelihood of migration is low. Henly and associates[38] demonstrated distant migration of small particles less than 70 μm in diameter but no migration of particles greater than 100 μm in diameter. Although there was a typical histiocytic and giant-cell reaction within the injection site, there was no granuloma formation in response to the larger particles. Because the substance is quite viscous, it must be injected with an injection gun and a transurethral needle with 16-gauge tip.

Table 2
Results of Macroplastique Injections

| Study | Patients | Follow-up (y) | Patients Dry (%) | Patients Improved (%) | Patients Failed (%) |
|---|---|---|---|---|---|
| Harriss et al.[8] | 40 | 3 | 16 (40) | 7 (18) | 17 (42) |
| Sheriff et al[39] | 34 | 2 | 16 (48) | | 18 (52) |
| Koelbl et al[40] | 32 | 1 | 19 (60) | | 13 (40) |
| Radley et al[41] | 60 | 1.5 | 12 (20) | 25 (41) | 23 (39) |
| Barranger et al[42] | 21 | 2.5 | 4 (19) | 6 (29) | 11 (52) |
| Tamanini et al[24] | 21 | 1 | 12 (57) | 4 (19) | 5 (24) |

*Silicone Microparticles Results*

The results from reported series using this injectable are shown in Table 2. Harriss and coworkers[8] reported on 40 patients who were followed for a minimum of 3 years, at which time 16 (40%) were dry, 7 (18%) were improved, and 17 (42%) had failure. Twelve of the 16 required 1 injection and 4 needed 2 injections to achieve dryness.

Sheriff and colleagues[39] reported an overall success rate of 48% in 34 patients after unsuccessful stress incontinence surgery, and Koelbl and colleagues[40] reported a 60% success rate in 32 women after 12 months but noted a time-dependent decrease in success. Radley and coworkers[41] reported a success rate of 61% (19.6% cured and 41.1% improved) in 60 women after a mean of 19 months. Barranger and associates[42] reported a dryness rate of 19%, improvement rate of 29%, and failure rate of 52% in a group of 21 patients at a median follow-up of 31 months. Interestingly, they did not observe a time-dependent decrease in results.

Similar success was shown by Tamanini and coworkers[24] using an implant system that allows a transurethral injection without cystoscopy.

*Silicone Microparticles Complications*

Self-limited side effects of hematuria, dysuria, frequency, and retention have been reported in a minority of patients. The lack of a granulomatous reaction and migration of the large silicone particles may provide some benefit over Teflon, although long-term data are not yet available. Despite the laboratory and clinical evidence of safety with the large particles, concerns still exist about small silicone particle migration and long-term tissue response to the injections.[43]

## Carbon Beads (Durasphere)

A newer injectable bulking agent designed to be biocompatible, which is composed of nonmigratory and nonabsorbable pyrolytic carbon-coated zirconium oxide beads suspended in a carrier gel (Durasphere®; Boston Scientific, Natick, MA), was reported by Lightner and colleagues.[9] The bead size ranges from 251 to 300 μm, more than 3 times larger than the 80-μm threshold for particle size associated with migration in tissue.[44] The absorbable carrier gel is 2.8% glucan—a

polysaccharide used in wound healing. The agent is prepackaged in 1.0-mL syringes and administered transurethrally through an 18-gauge needle.

In a multicenter, prospective, randomized, double-blind trial with collagen as control, at 1 year after the last treatment, 49 (80.3%) of 61 women treated with Durasphere showed improvement of 1 continence grade or more, compared with 47 (69.1%) of 68 women treated with collagen ($P = .162$).[9] The difference was not statistically significant. There was also no difference in number of injections or pad weight test. However, the initial and repeated injection volumes of Durasphere were significantly less than those of collagen. The adverse events were similar in both groups, but the Durasphere group had an increased short-term risk of urgency and urinary retention. Pelvic x-rays obtained at 1 and 2 years after injection showed stability of the bulking agents at the injection site. This suggests potential durability.

In another small series of 13 women and 7 men treated with Durasphere injections, Pannek and coworkers[45] reported an overall 12-month success rate of 33%. Furthermore, they demonstrated bead migration on plain radiographs in 2 asymptomatic patients.

Long-term results with particular attention to migration risk are required to assess the benefit of this injectable agent.

## Polytetrafluoroethylene Paste (PTFE, Teflon, Urethrin)

Polytetrafluoroethylene paste (Teflon) is composed of equal parts Teflon paste and glycerine with polysorbate 20.[46] Teflon is a resin polymer with a very high molecular weight and high viscosity that is composed of small particles (40 μm in diameter). It is inert, stable, and does not induce an allergic response. However, it does cause a local inflammatory response, with histiocytes phagocytizing the particles and coalescing to form foreign-body giant cells and a granuloma. There is also fibrous tissue ingrowth that adds to the bulk formed by the Teflon. Malizia and colleagues[44] also showed distant migration of Teflon particles to pelvic nodes, lung, brain, and kidneys of experimental animals, due to the small particle size.

Teflon paste has been used to treat urinary incontinence since 1964, but it was not reported until 1975, by Berg.[4] Since that time, numerous reports relating to its use in treating incontinence have appeared in the literature. It may be injected via the periurethral route; volumes of up to 10 to 20 cc are reported. The procedure is done under local or spinal anesthesia and repeated injections may be done after 6 months. Small amounts (2.5 cc) can be injected via the periurethral approach with local anesthesia.[46] Heating the Teflon reduces its viscosity and allows injection without a gun.

Table 3
Teflon Results for Female Stress Incontinence

| Study | Patients | Follow-up (mo) | Patients Dry (%) | Patients Improved (%) | Patients Failed (%) |
|---|---|---|---|---|---|
| Politano[83] | 51 | 6 | 26 (51) | 10 (20) | 15 (29) |
| Lim et al[49] | 28 | — | 6 (21) | 9 (33) | 13 (46) |
| Schulman et al[48] | 56 | 3 | 39 (70) | 9 (16) | 8 (14) |
| Deane et al[76] | 28 | 3–24 | 9 (32) | 8 (28) | 11 (40) |
| Beckingham et al[77] | 26 | 36 | 2 (7) | 7 (27) | 17 (66) |
| Harrison et al[78] | 36 | 61 | 4 (11) | 8 (22) | 24 (67) |
| Lotenfoe et al[79] | 21 | 11 | 8 (38) | 4 (19) | 9 (43) |
| Lopez et al[80] | 74 | 31 | 41 (56) | 15 (20) | 18 (24) |
| Vesey et al[81] | 36 | 9 (3–36) | 20 (56) | 4 (11) | 12 (33) |
| Herschorn and Glazer[46] | 46 | 12 | 14 (31) | 19 (41) | 13 (28) |

*Teflon Results*

Table 3 lists various series investigating the use of Teflon. The outcomes are wide ranging, with longer-term series showing poorer results (33%–76% cure and improved) than short-term series (57%–86%).

*Teflon Complications*

Because relatively large volumes of Teflon have been injected with the patient under general anesthesia, the incidence of urinary retention (25%)[47] is higher than that of collagen. Irritative voiding symptoms have also been seen transiently in 20%.[48] Urinary infection is rare at 2%.[49] Perineal discomfort may occur in 5%[47] and transient fever in 10% to 15% of patients. Perforation and extravasation can occur, and if this is recognized at the time of injection, the Teflon should be removed.

Although Teflon particles can migrate,[44] only 1 case of clinical significance has been reported in the literature in humans. Claes and coworkers[50] described a woman previously treated with large volumes

of periurethral Teflon for urinary incontinence who later presented with lymphocytic alveolitis and fever. Light microscopy showed Teflon particles in the lungs. She was treated successfully with corticosteroids. Mittleman and Marraccini[51] reported an incidental finding of postmortem interstitial pulmonary granulomas in a previously asymptomatic man who had received Teflon injections. Kiilholma and coworkers[52] reported 3 complications among 22 women: a sterile periurethral abscess, a urethral diverticulum, and a urethral granuloma that all required surgical intervention. In another case, the material migrated into the bulbar corpus spongiosum, causing perineal pain for 3 months and necessitating medication for pain relief.[53]

Although neoplastic transformation was hypothesized,[44] there has never been a clinical occurrence reported. Furthermore, in a long-term rat study, Dewan and associates[54] demonstrated no increase in tumor risk and no tumors found at the injection site.

Despite the potential for complications with Teflon, the actual rate of reported problems is low. However, Teflon is rarely used now as an injectable.

## Autologous Fat

Autologous fat has been used for aesthetic and defect reconstruction since the 1980s.[55] Although fat is biocompatible and readily available, 50% to 90% of the transferred adipose tissue graft may not survive.[43] Graft survival depends on minimal handling, low suction pressure during liposuction, and the use of large-bore needles. Smaller grafts survive better than larger ones.[56]

The procedure involves harvesting abdominal wall fat by liposuction either under local[57] or general anesthesia.[58] The injection is usually carried out via the periurethral route with a 16- or 18-gauge needle. Postprocedure care may involve intermittent catheterization or even a suprapubic tube.[58]

### *Autologous Fat Results*

A number of reports of urethral fat injections have been published and appear in Table 4. Most of the series report short-term results with success apparently lower than that of other injectables, apart from the study of Su and associates,[58] which had a follow-up of more than 12 months. Palma and colleagues[59] showed that repeated injections improved the cure rate from 31% to 64%. Haab and associates[60] reported a comparative study with collagen: after a mean of 7 months, 13% of the women with fat injection experienced cure, versus 24% of the women who received collagen injections. The subjective improvement rate was also higher with the collagen.

Lee and colleagues[61] reported a randomized double-blind study of autologous fat versus saline injection. At 3 months, 6 (22.2%) of 27 and 6 (20.7%) of 29 women had cure or improvement in the fat and saline groups, respectively. In this study, periurethral fat injection did not appear to be more efficacious than placebo in treating stress urinary incontinence.

### *Autologous Fat Complications*

Reported complications are similar to those with other injectables, with urinary infection, retention, hematuria, and extravasation reported. Additional problems at the donor site (the abdominal wall), such as pain, hematomas, and infection, may also be seen. Other noteworthy complications are urethral pseudolipoma[62] and fat embolism,[34] 1 of which was fatal.[63]

## Autologous Chondrocytes

A bulking agent composed of autologous chondrocytes has been used to treat children with vesicoureteral reflux.[64] Animal studies of the implant demonstrated stability and lack of migration over time.[65,66] The injectable

Table 4
Results of Autologous Fat Injection

| Study | Patients | Follow-up (mo) | Patients Dry (%) | Patients Improved (%) | Patients Failed (%) |
|---|---|---|---|---|---|
| Cervigni and Panei[7] | 14 | 9.7 | 8 (57) | 4 (29) | 2 (14) |
| Santarosa and Blaivas[82] | 12 | 11 | 7 (58) | | 5 (42) |
| Trockman and Leach[57] | 32 | 6 | 4 (12) | 14 (44) | 14 (44) |
| Haab et al[60] | 45 | 7 | 6 (13) | 13 (29) | 26 (58) |
| Su et al[58] | 26 | Mean: 17.4 (range, 12–30) | 13 (50) | 4 (15) | 9 (35) |
| Palma et al[59] | 30 | 12 | 1 injection: 4/13 (31)<br>2 injections: 11/17 (64) | | |

material consists of autologous chondrocytes in a calcium alginate gel administered endoscopically through a 22-gauge needle. The chondrocytes, obtained from biopsy of the external pinna of the patient's ear, are expanded in tissue culture and combined with a carrier gel that degrades after injection.

Bent and coworkers[67] reported 12-month results in 32 women after a single outpatient injection in a multicenter trial. Incontinence grading indicated 16 patients were dry and 10 improved, for a total of 26 (81.3%). Side effects were minimal.

### Calcium Hydroxyl Apatite

This normal constituent of bone can be synthesized and formulated in a size to resist migration. It can be used for soft tissue augmentation and does not form heterotopic bone.[68]

Mayer and colleagues[69] reported results in 10 women at 1 year. The substance used had a mean particle size of 100 μm and was injected transurethrally through a 7F catheter with a 21-gauge needle tip. Seven women were substantially improved, 2 used fewer pads, and 1 had no change. No significant complications were seen.

### Current Unmet Needs

The unmet needs surrounding injectable agents for stress incontinence can be grouped into those regarding agent, technique, and scientific characteristics.

The ideal agent has been described and mentioned above.[18] We still require an agent that is biocompatible, that causes little or no inflammation, and that is nonantigenic. It should retain its bulk and not be molded by the movement of the urethra and pelvic muscles. It should not interfere with the closure mechanism or with the mucosal vascularity. It should also be durable.

The injection technique has undergone modifications over time, yet the ideal technique has yet to be described. It should be reproducible and consistent. The optimal sites along the urethra, the radial location(s), and the injection volume have to be identified. Ideally, the technique should involve a small volume, small needle, no extrusion of the agent, and no need for reinjections.

Histologic studies in experimental animal models showing the site of the deposit in the urethral wall as well as the effect on surrounding structures would be helpful. In addition, long-term data from prospective studies as well as randomized prospective trials comparing injectables with other treatments are needed. These studies should include economic discussions of cost and cost-effectiveness.

*Injectable agents are used for buttressing the ISD component of the incontinence, but patients with concomitant hypermobility may benefit as well.*

### Conclusions

Considerable progress has been made since the introduction of collagen injections. Injectable agents are used

### Main Points

- Patients with intrinsic sphincter deficiency with or without hypermobility, along with normal detrusor function, are candidates for the use of injectable agents for stress urinary incontinence. However, the search continues for the ideal, cost-effective agent and technique.
- Injectables are administered under local anesthesia with cystoscopic control, either periurethrally or transurethrally, with the agent implanted within the urethral wall, ideally at the bladder neck or proximal urethra.
- Injection of GAX collagen (after proper skin testing) generally is associated with no inflammatory response, granuloma formation, or migration, and complications are rare. Short-term success rates are 72% to 100%, but re-injection is often necessary to maintain results longer-term.
- The diameter of most silicone microparticles makes migration unlikely, and associated side effects (hematuria, dysuria, frequency, and retention) are usually self-limited and not common; still, concern remains over long-term tissue response to this injectable and the durability of the results.
- Carbon beads have demonstrated results similar to those of collagen, but more studies are needed to determine the pros and cons of this agent. Teflon, used since the 1960s, is no longer popular; although generally safe, Teflon can migrate to distant sites and offers no durability advantage over other agents.
- Autologous fat offers a biocompatible alternative for injection, but a significant portion of the graft may not survive, and results have not been impressive compared with other agents.

for buttressing the ISD component of the incontinence, but patients with concomitant hypermobility may benefit as well. They have also been administered to elderly patients who are not surgical candidates. However, there are still a number of important areas in which further study is needed.

Durability is an ongoing concern. Although long-term successes have been reported with collagen and Teflon, the results of both deteriorate over time. Similarly, autologous fat and silicone microparticles yield poorer long-term than short-term results. There are no long-term results reported with any of the other injectable agents. Comparisons between injectables and between injectables and surgery have been done to a limited degree, and prospective studies have yet to be reported. Despite the ease of the technique and the attractiveness to patients of an outpatient procedure that can be repeated if necessary, the cost-effectiveness of injectable agents relative to other treatments, such as newer minimally invasive surgical procedures, still has to be addressed.

Safety of the material is another concern. All of the injectables have excellent safety profiles, although the risk of migration and granuloma formation with Teflon has prevented its widespread use. Rare but serious complications have also been reported with collagen and autologous fat. The long-term risks of silicone microparticles are unknown and the actual migration risk of Durasphere has yet to be elucidated.

Longer-term and comparative studies may settle many of these issues. ■

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