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Review – Female Urology

Stress Incontinence Injection Therapy: What is Best for Our Patients?

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Abstract

Objective: Urethral injection (periurethral/intraurethral bulking) is an established, minimally invasive therapy for stress urinary incontinence (SUI). This review aims to determine which women should potentially benefit from, and be considered as candidates for, injection therapy and to elucidate what we are trying to achieve.

Methods: Based on MEDLINE database searches, all aspects of urethral injection were examined, including patient selection, safety, injection technique, efficacy, quality of life, goals and cost.

Results: Such therapy has a low complication rate, improves or cures about 3 out of 4 women, as shown in mainly short-term studies, and improves patients' quality of life. It can be used in the majority of patients with uncomplicated SUI. Therefore, injection therapy may be considered as a first-line treatment option for patients who have failed conservative therapy such as pelvic floor exercises and who decline or have a contraindication for pharmacological treatment. However, the decision of whether to use this type of treatment must be based on an informed discussion between the physician and patient – this dialogue should incorporate questions about patients' own treatment goals. Injection therapy appears to have the profile required to meet patients' goals, based on the findings that a procedure with an improvement in incontinence, minimal short-term risk, no long-term risk, and performed in a clinic, would be acceptable.

Conclusion: Investigating and trying to achieve patients' own treatment goals will ultimately enable us to do what is best for our patients, but current evidence suggests that injection therapy is a valid option worth discussing with many patients.

Keywords: Urinary incontinence; stress; Female; Injection therapy

1. Introduction

1.1. History of injection therapy

Urethral injection has been used to treat stress urinary incontinence (SUI) for many decades. The first report was in 1938 and used sodium morrhuate [1]. The injectable agents employed have evolved over the years, with the advent of polytetrafluoroethylene (PTFE, Teflon®) in the 1980s, and glutaraldehyde cross-linked (GAX) collagen (Contigen®), silicone (polydimethylsiloxane, Macroplastique®) and autologous fat in the 1990s. PTFE and autologous fat were associated with unfavourable safety profiles (e.g. particle migration/

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granuloma formulation and fat embolism, respectively) [2]. Therefore, their use is now discouraged [3], and they are not considered in detail here.

More recently, agents with improved safety profiles have emerged, including calcium hydroxylapatite (Coaptite®), carbon-coated zirconium beads (Durasphere®), ethylene vinyl alcohol (Uryx®) and NASHA/Dx gel – dextranomer (Dx) microspheres in a carrier gel of non-animal stabilised hyaluronic acid (NASHA). NASHA/Dx gel is notable, given that no major safety concerns have emerged during 7 years' follow-up in SUI [4], and a decade of use in the treatment of children with vesicoureteral reflux.

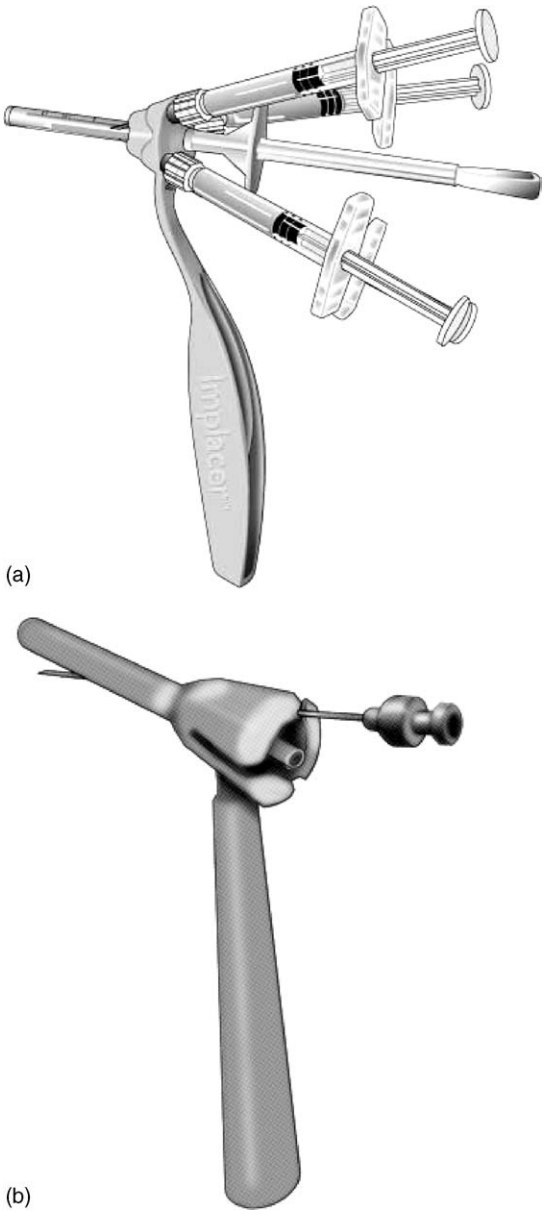

Fig. 1. (a) The Implacer™ for delivering non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) gel. (b) The Macroplastique® Implantation Device for delivering silicone. (b) reproduced with permission [5].

Over time, the injection technique has also developed, from endoscopic to non-endoscopic administration systems. The latter are: the Zuidex™ System, which consists of four NASHA/Dx gel syringes and a guiding device, the Implacer™ (Fig. 1a); and the Macroplastique® Implantation System (MIS), consisting of two silicone-filled syringes and the Macroplastique® Implantation Device (Fig. 1b) [5]. The viscosity of the silicone in the MIS and the resulting requirement for an injection gun has been considered by some to be a disadvantage. Both systems, in different ways, assist the user in determining how far the instrument should be inserted into the urethra.

Urethral injection continues to evolve, with tissue-engineered therapies showing particular promise. Autologous chondrocytes [6], bladder muscle cells [7] and myoblasts [8] as well as allogenic muscle-derived stem cells [9] are under investigation. Indeed, the first clinical results using transurethral injections of autologous fibroblasts and myoblasts are encouraging [10,11].

1.2. Aims of review

This review examines all aspects of injection therapy for the treatment of SUI in women, based on an extensive literature search. The initial aim was to determine which patients should receive injection therapy, and to elucidate what we are trying to achieve. For example, is it a complete cessation of leakage, or a reasonable improvement in symptoms with a lack of long-term side-effects? This should enable us to answer the question: what is best for our patients?

2. Literature search

MEDLINE was searched between 1966 and 2004 using 'incontinence' and 'inject*', 'collagen or Contigen', 'carbon coated beads or Durasphere ', 'silicone or polydimethylsiloxane or Macroplastique', 'polytetrafluoroethylene or PTFE or Teflon', 'dextranomer', 'calcium hydroxylapatite' or 'autologous fat'. The International Continence Society (ICS) website [12] was searched for abstracts between 1999 and 2003 in the female urology, quality of life (QoL), stress incontinence and treatment of incontinence categories. Reference lists from recent review articles and relevant non-MEDLINE indexed journals were also researched. Following deletion of duplicates, a library of 1013 references remained. The references were categorised and the following excluded: letters to the editor, non-English articles, reviews not directly concerning injectable agents or, excepting safety, not concerning SUI in women. The remaining references form the basis of

this article (n = 156). Additional references were also included. For objective efficacy, articles relating to collagen, carbon-coated zirconium beads, silicone or autologous fat were also identified during a supplementary literature search in which articles were selected based on several factors, including the number of patients, quality of the methods and timing of the publication.

3. Patient selection

Several factors require consideration when deciding which patients are suitable for injection therapy. Certainly, it is an option for women in whom more invasive surgical procedures are contraindicated, who don't desire surgery or who wish to have future pregnancies. The evidence for each factor is reviewed below, and recommendations are given in Table 1. Note that the evidence base to date supports the view that simple evaluation is adequate before injection therapy, with urodynamics reserved for patients with pelvic organ prolapse (POP) or SUI requiring more invasive and complex surgery [13], albeit many clinicians prefer urodynamic assessment before any invasive intervention for SUI.

3.1. General

The first point to consider is obviously whether the patient is troubled enough by her symptoms to request or require surgical intervention. Injection therapy should not be used if the patient has a urinary tract infection [14], is hypersensitive to the chosen agent [14] or has urethral mucosal fragility [15]. Caution is advised in patients with connective tissue diseases [16] or prior irradiation therapy.

3.2. Pelvic organ prolapse (POP)

Limited data exist on the treatment of SUI in women with POP, which also applies to injection therapy. However, SUI and POP coexist in many patients (one study reported 63.3% of patients with SUI also had POP) [17]. Injection therapy in such populations has the potential to benefit many women, and deserves investigation.

3.3. Pathophysiology

The pathophysiology of SUI is complex, with the two main components postulated to be intrinsic sphincter deficiency (ISD) and hypermobility. It appears that the two pathophysiologies coexist in the vast majority of patients [18], such that SUI may be considered as a continuous spectrum rather than existing as a dichotomy (Fig. 2). The pathophysiology of SUI must also be considered in the context of the overactive bladder symptom complex, as there is an association between detrusor overactivity-related filling symptoms, whether occurring with or without incontinence (wet or dry), and sphincteric weakness.

Table 1
Recommendations for selecting patients suitable for injection therapy to treat stress urinary incontinence (SUI)

Factor	Recommendation
General	Use where the patient is troubled enough by her symptoms to request or require surgical intervention Check that the patient is not hypersensitive to the chosen agent (specifically collagen) Treat urinary tract infections prior to therapy Caution is advised in patients with connective tissue diseases or prior irradiation therapy Patient preference should be central to the decision of whether to use injection therapy
Pelvic organ prolapse (POP)	Suggest treating significant POP prior to injection therapy Clinical opinion suggests that injection therapy after POP repair may be particularly suitable if the patient has poor prognostic factors for suburethral tape surgery (e.g. intrinsic sphincter deficiency) or weak bladder contraction during micturition Injection therapy may also be suitable in certain women with POP and SUI (e.g. frail, elderly women in whom injection therapy is performed at the time of POP repair, as well as those with a fixed urethra after previous vaginal surgery and/or risk of post-operative voiding dysfunction)
Pathophysiology: ISD vs. hypermobility	Suitable for all patients (there is no need to determine whether the patient's SUI is due to ISD or hypermobility)
Detrusor overactivity	Consider use if the condition can be managed
Age	Use is recommended in all age groups, apart from the very young, as many clinicians would feel uncomfortable administering injection therapy to this age group
Incontinence severity	It is generally accepted that injection therapy achieves the best results in patients with mild–moderate SUI
Previous surgery	Use is recommended in patients whether or not prior incontinence/prolapse surgery has been undertaken, though the prognostic influence of previous surgery should be considered

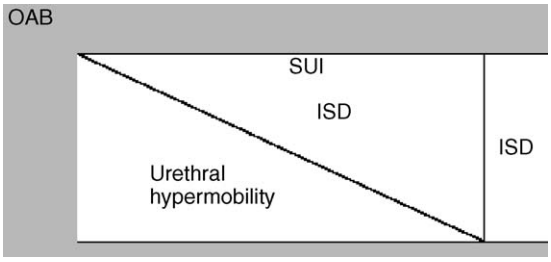

Fig. 2. Classification of female urinary incontinence. All patients with stress urinary incontinence (SUI) have some degree of intrinsic sphincter deficiency (ISD) with variable degrees of coexisting urethral hypermobility. There is a significant overlap in terms of storage symptoms with the overactive bladder symptom complex (OAB).

In the 1990s, the prevailing view was that injection therapy was most suitable for women with ISD [19–21]. This view has evolved, with current opinion suggesting that it is suitable for all forms of SUI (i.e. ISD and/or varying degrees of hypermobility) [2].

Several studies support this shift. Bent et al. showed that collagen produced cure or improvement in 66% of patients with urethral hypermobility and no ISD, in the 58 patients who reached the 12-month follow-up [22]. In probably the best article in this area [23], collagen was shown to be equally as effective in patients with hypermobility or ISD – a similar result was observed for NASHA/Dx gel administered under endoscopic guidance [24]. Equivalent efficacy was also the case in collagen-treated patients with ISD, in the absence or presence or urethral hypermobility [25]. McGuire and Appell reported that the dryness rate 1 year after collagen treatment was similar for women with ISD (46%) or hypermobility (47%) [26]. However, Gorton et al. showed that median continence duration following collagen treatment was shorter in women with ISD (15 months) than hypermobility (72 months) [27].

3.4. Detrusor overactivity

In previous review articles, it has been stated that injection therapy is contraindicated in cases of unmanaged detrusor overactivity [14,19,21], or that minimal or no detrusor overactivity should be present [28]. In a study of collagen in women with SUI ($n = 181$) or neurogenic incontinence ($n = 6$), detrusor overactivity was associated with a significantly lower cure/improvement rate (58%) than a stable bladder (78%) ($p = 0.0328$) [23]. Moreover, a lower success rate (59%) was observed following silicone injection of patients with urodynamic stress incontinence (USI) plus detrusor overactivity compared with patients only suffering from USI (76%) [29]. However, in another collagen study, cure rates in women with detrusor overactivity were not significantly different from the entire patient population [30]. Overall, it appears that the success of injection therapy is reduced in patients with detrusor overactivity, but its use should not be excluded outright if the underlying detrusor overactivity can be managed medically.

It is noteworthy that unlike surgical procedures such as colposuspension and suburethral slings, urethral injection has not been associated with *de novo* detrusor overactivity.

3.5. Age

Urethral injection offers potential advantages for elderly women compared with more invasive surgical procedures. These include use of local anaesthetic and a lower risk of post-operative complications, such as voiding difficulties that may necessitate self-catheterisation – often difficult for this population.

In the study by Herschorn et al., in which 186 women were treated with collagen, patient age did not affect treatment outcome, with results comparable between those aged <50 years, 51–70 years and >70 years [23]. However, in a study of silicone, the success rate in women with USI was higher in those aged 60 years or over (80%) than in those younger than 60 years (67%) [29]. Moreover, in another collagen study, those women who eventually required surgery for their incontinence despite collagen therapy were significantly younger than those who did not (57 years versus 69 years; $p = 0.01$) [31]. It is not clear whether this was related to a treatment effect, or whether younger women were more willing to undergo surgery. Note that in the three studies cited [23,29,31], no indication was given about whether incontinence severity was similar in the sub-groups analysed. Overall, there is no strong evidence that younger or older age affects treatment outcome.

3.6. Incontinence severity

In a study using collagen, a cure rate of only 13% was observed in patients with severe incontinence [31]. This result is complicated by inclusion of patients with mixed incontinence, and could also be attributed to the stringent outcome criteria used. In another study using collagen [23], a cure rate of 40% was observed for patients with mild SUI prior to treatment (Stamey grade 1) [32], compared with a rate of 20% for those with moderate-to-severe symptoms (Stamey grade 2 or 3). Therefore, logically it appears that collagen therapy is more effective in mild than moderate-to-severe SUI. However, the difference was not significant ($p = 0.19661$), with the authors concluding that no difference in outcome occurred in relation to pre-treatment grade of incontinence. Overall, the data are inadequate to allow definitive conclusions to be drawn, but most clinical opinion reflects the view that

incontinence severity does influence treatment outcome.

3.7. Previous surgery

Both collagen and silicone have been shown to improve incontinence in patients with previous incontinence or prolapse surgery [30,33–35]. In contrast, studies with NASHA/Dx gel have shown that injection therapy can produce significant improvements in incontinence in patients without previous incontinence surgery [36–38]. In one study using collagen, treatment produced similar success rates whether or not patients had undergone previous incontinence procedures [39], while in another, the success rate was higher in those patients who have had previous surgery (90%) than not (73%) [40].

Interpretation of the data is difficult as many studies have used a mix of patients with or without previous incontinence/prolapse surgery. Nevertheless, the data suggest that the success of injection therapy is not influenced by the presence or absence of previous surgery, assuming a similar degree of severity. However, clinical experience suggests that all surgical procedures for incontinence are influenced to some extent by previous surgery, and this is also likely to be the case for injection therapy. Moreover, the effect of injection therapy on subsequent surgery needs to be considered.

4. Safety

A recent review has stated that the complication rates with commercially available agents are acceptably low [41]. Safety concerns may occur that are generic to all substances (e.g. suburethral swellings, haematuria, urinary retention) or are agent specific (e.g. particle migration, granuloma formulation, hypersensitivity).

Reports of suburethral swellings are rare, and have been observed with collagen [42], PTFE [2,43], carbon-coated zirconium beads [3,44] and NASHA/Dx gel [36,37]. Their aetiology in SUI is unclear, but is presumably related to an increased risk of a tissue reaction to the injectable agent that has been placed outside the urethral wall, and they appear to resolve in many cases with simple needle drainage.

Particle migration was a major concern with PTFE. Among current materials, it is much less of a concern with biodegradable agents (e.g. collagen, NASHA/Dx gel) than non-biodegradable agents (e.g. silicone, carbon-coated zirconium beads). Indeed, permanent accumulation of non-biodegradable agents may be a problem, particularly where there is a risk of granuloma formulation or other potential adverse effects (e.g. carcinogenicity).

Among agents more commonly used today, particle migration has been observed with silicone in dogs [45], though it has been stated that this agent does not migrate to vital organs [46], and with carbon-coated zirconium beads [47]. Migration has been attributed to small particles within the injectable agent [48]. Therefore, given that carbon-coated zirconium beads are relatively large (251–300 μm), the migration may be due to technical problems rather than being a property of the agent. Particle migration has not been reported for collagen [2], NASHA/Dx gel [49] or calcium hydroxylapatite [50].

Another potential safety concern is hypersensitivity, which is restricted to collagen and attributable to previous collagen exposure. Hypersensitivity affects approximately 3% of patients [51], and necessitates skin testing in all patients, 30 days before treatment.

Silicone gel has been linked to connective tissue and autoimmune diseases [52]. Although the silicone used in SUI is a solid elastomer and not a gel, these theoretical safety concerns have been voiced relating to its use in SUI. Furthermore, solid silicone elastomers have shown carcinogenic potential in a rat model, albeit at a low level [53].

In summary, few of the early agents were free from safety concerns. Newer agents with much improved safety profiles are emerging, thereby increasing the potential for urethral injection therapy.

5. Injection technique

Different injection techniques are possible, but whatever the procedure, it is important that the material is injected accurately to minimise the risk of complications.

Most urologists currently use transurethral, as opposed to periurethral injection, as they have most experience with this [2]. Schulz et al. reported no significant differences in efficacy between the two methods using endoscopically administered NASHA/Dx gel [24]. However, transurethral injection was associated with a trend for improved efficacy at 1-month post-injection [24,54], and produced a lower rate of urinary retention (5% versus 30%, $p < 0.05$) [24]. In a study using collagen by Faerber et al., no significant differences were observed in both outcomes and complication rates between the two routes [55]. In both studies, periurethral injection required a significantly greater injection volume. This is important as it may be associated with higher cost and, theoretically, may

increase the potential for the development of complications related to the presence of non-absorbable agents.

The injection technique can also be varied in terms of the number of implants and the needle size. The ideal injection site has yet to be determined, with the proximal site usually chosen. However, the mid-urethra is also commonly used, and there is no evidence to suggest that either site is superior.

Non-endoscopic injection is a major development – it allows outpatient treatment and avoids the need for surgical facilities. Nevertheless, some physicians may feel more comfortable with the endoscopic procedure as it enables the bolus to be visualised and injection to be continued until adequate coaptation is achieved. However, clinical experience and published data suggest that endoscopically confirmed coaptation does not necessarily correlate with long-term improvement in continence [56].

6. Objective efficacy

Studies investigating the efficacy of collagen, carbon-coated zirconium beads and silicone identified during the supplementary search are reviewed in Table 2. The majority of the studies are level IV (good quality case series), with only two level I types identified (randomised, controlled studies): autologous fat versus saline [57] and carbon-coated zirconium beads versus collagen [58].

Studies for ethylene vinyl alcohol, calcium hydroxylapatite and NASHA/Dx gel were identified during the main search. In a multicentre, 1-year study of ethylene vinyl alcohol versus collagen involving 237 women, 46% of whom had failed surgery, ethylene vinyl alcohol appeared to be more effective [59]: the dry rate (defined as no leakage by pad weight) was 64% and 42%, respectively. A trend for greater improvements in incontinence has also been observed for calcium hydroxylapatite compared with collagen [50,59].

The initial study of endoscopically administered NASHA/Dx gel involved 20 patients, 6 of whom had previously received surgery for SUI or prolapse [60]. Objective cure was defined as leakage <8 g/24 hours in the 48-hour pad test or <1 g in the short-term pad test, objective improvement as a 50% reduction in incontinence in the 48-hour pad test and/or short-term pad test. At 3–7 months' follow-up, an objective cure or improvement rate of 85% was observed (45% and 40%, respectively). In a follow-up study, only 25% of patients reported recurrence of their incontinence after a mean of 6.5 years [4].

NASHA/Dx gel via the Implacer™ has been investigated in two European studies, both involving surgery-naïve patients in whom ISD or hypermobility was not determined [36,37]. In the first study ($n = 42$), significant improvements in median provocation test urine leakage and number of incontinence episodes/24 hours were observed at 12 months (both $p < 0.0001$ versus baseline) [37], with 24% reporting no leakage, as assessed by provocation test. Improvements were sustained to 24 months in a follow-up population ($n = 20$) [61]. In the second study ($n = 142$), a ≥50% reduction in provocation test urine leakage versus baseline was observed in 73% of patients at 6 months, with 33% dry (<1 g leakage) [36]. Correspondingly, the median number of incontinence episodes/24 hours decreased from 3.0 at baseline to 0.8 at 6 months ($p < 0.0001$). These improvements were sustained out to 12 months.

The durability of any clinical benefit has yet to be adequately addressed, with several studies using collagen, carbon-coated zirconium beads and silicone showing that improvements in incontinence decrease with time (Fig. 3) [22,23,46,62].

Overall, the efficacy literature is difficult to interpret as the studies lack uniform definitions of pathophysiology and use heterogeneous patient populations, different injection methods, variable outcome criteria, and

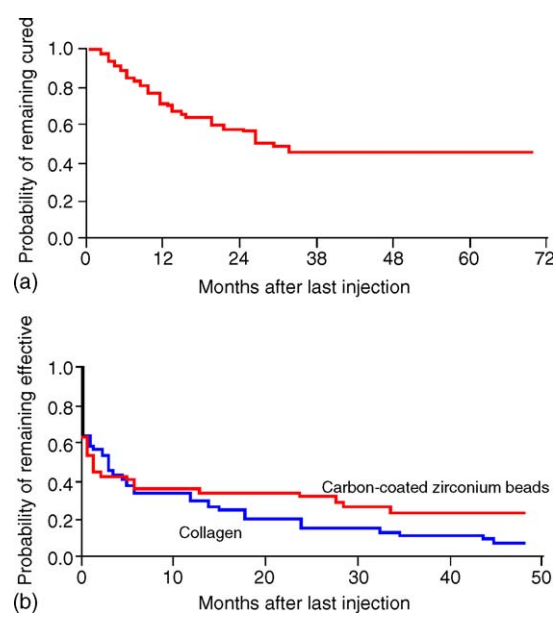

Fig. 3. Kaplan–Meier curves showing durability of cure/improvements in incontinence. (a) Durability of cure after last collagen injection [23]. Cure was defined as no incontinence symptoms or pad use on questioning. Reproduced in an adapted form with permission [23]. (b) Durability of efficacy after injection with collagen or carbon-coated zirconium beads [62]. Efficacy was based on an incontinence questionnaire regarding current leakage, frequency of leakage and length of injection effect. Reproduced with permission [62].

Table 2
Studies reporting the efficacy of collagen, carbon-coated zirconium beads and silicone in the treatment of SUI

Reference	Agent[a]	SUI patient population	Follow-up	Outcome parameter	Success rate (cure + improved)	Level of evidence[b]
Bent et al. [22]	Collagen ($n = 58$)	Urethral hypermobility (Type I, IIA or IIB [Blaivas classification]) [78]	12 months	**Cure:** Stamey grade 0 **Improvement:** decrease of at least one Stamey grade	66%	IV
Winters et al. [79]	Collagen ($n = 58$)	ISD (ALPP <60 cm H_2O) ($n = 49$) Urethral hypermobility (Q-tip) ($n = 37$) Previous incontinence surgery ($n = 31$)	2 months	**Cure:** 'no leakage at all' or ≤1pad per day	79.3%	IV
Groutz et al. [31]	Collagen ($n = 63$)	Urodynamically confirmed sphincteric incontinence Mixed incontinence (41%) Concomitant urethral hypermobility ($n = 8$) Previous incontinence surgery ($n = 18$)	Mean 12 months	**Objective outcome score** **Cure:** no SUI by a diary, <8 g leakage by pad test and patient considers herself cured **Improvement:** good or fair	40%	IV
Corcos and Fournier [80]	Collagen ($n = 40$)	Type I ($n = 8$), Type II ($n = 20$), Type III ($n = 12$) (Blaivas classification) [78]	49 months	**Cure:** symptomatic dryness, negative pad test and no VLPP leakage **Improvement:** patient satisfaction, and >50% improvement in VLPP and pad test	70%	IV
Cross et al. [81]	Collagen ($n = 139$)	ISD (ALPP <60 cm H_2O) No urethral hypermobility	Median 18 months	**Substantial improvement**: ≥70% reduction in daily pad usage or grade 0 incontinence	74%	IV
Khullar et al. [39]	Collagen ($n = 21$)	USI Previous incontinence surgery (43%)	2 years	**Cure:** pad test leakage <1 g **Improvement:** ≥50% decrease in pad test leakage	57%	IV
Smith et al. [82]	Collagen ($n = 94$)	ISD (ALPP <65 cm H_2O)	Median 14 months	**Cure:** dry as reported by the patient **Socially continent:** ≤1 pad/day	67%	IV
Faerber et al. [83]	Collagen ($n = 12$)	Type I (VLPP >60 cm H_2O)	Mean 10.3 months	**Cure:** not defined	100%	IV
Herschorn et al. [23]	Collagen ($n = 187$)	SUI ($n = 181$) Neurogenic incontinence ($n = 6$) Detrusor overactivity ($n = 31$) Previous incontinence surgery (63%)	Mean 22 months	**Cure:** no incontinence symptoms or pad use on questioning **Improvement:** any decrease in grade of incontinence	75%	IV
Kreder and Austin [84]	Collagen ($n = 22$)	ISD (ALPP <60 cm H_2O or open bladder neck at rest) Majority had failed previous incontinence surgery	Mean 22 months	**Cure:** 'completely continent or rarely requiring a pad' **Improvement:** 50% decrease in pads/day	40%	IV
Richardson et al. [85]	Collagen ($n = 42$)	ISD (LPP <60 cm H_2O)	Mean 46 months	**Cure:** incontinence grade 0 **Improvement:** incontinence improved by 1 or 2 grades vs. baseline	83%	IV
Monga et al. [30]	Collagen ($n = 29$)	Proven USI All had prior unsuccessful incontinence surgery	24 months	**Subjective cure:** dry **Improvement:** change from daily to intermittent incontinence	68%	IV
O'Connell et al. [86]	Collagen ($n = 44$)	ISD (median LPP = 56 cm H_2O) Concomitant urethral hypermobility ($n = 2$)	Up to 7 months	**Cure:** no pads **Improvement:** <2 pads	63%	IV
Herschorn et al. [87]	Collagen ($n = 31$)	SUI ($n = 29$) Neurogenic incontinence ($n = 2$) Previous incontinence surgery ($n = 18$)	Mean: 8.4 months (cured) 4.5 months (improved)	**Cure:** 'no incontinence at all' **Improvement:** ≤2 pads/day and/or improvement of ≥1 incontinence grades	90.3%	IV

Eckford and Abrams [40]	Collagen ($n = 25$)	USI Previous incontinence surgery ($n = 10$)	3 months	**Cure:** 'complete cessation of stress incontinence' **Improvement:** 'reduction in the degree of stress incontinence but the patient still requiring to change underclothes or wear protection'	80%	IV
Haab et al. [35]	Collagen ($n = 22$) vs. autologous fat ($n = 45$)	ISD (open bladder neck and proximal urethra at rest associated with a low VLPP) Minimal hypermobility (22% of patients) At least 1 failed incontinence procedure	Mean 7 months	**Cure:** totally continent **Improvement:** not clearly defined Outcome based on a visual analogue scale, diary, pad test and clinical evaluation	Collagen: 86% Autologous fat: 43.2%	IV
Lightner et al. [58]	Collagen ($n = 68$) vs. carbon-coated zirconium beads ($n = 61$)	ISD (ALPP <90 cm H_2O) Prior surgery allowed	Mean 14 months	**Cure:** not defined **Improvement:** improvement of $\geq$1 Stamey grade	Collagen: 69.1% Carbon-coated zirconium beads: 80.3%	I
Tamanini et al. [88]	Silicone[c] ($n = 21$)	Urodynamically verified SUI ISD (VLPP <90 cm H_2O) Previous incontinence surgery (19%)	12 months	**Cure/improvement**: assessed by Stamey grade	76.1% (patient view)	IV
Peeker et al. [33]	Silicone ($n = 16$)	USI All had undergone prior incontinence/ prolapse surgery 'Damage or functional defect of the intramural sphincter' No urethral hypermobility (Q-tip)	>24 months	Assessed by questionnaire/standardised quantification test **Improvement:** excellent (dry) or good (improved but not completely dry)	87.5%	IV
Barranger et al. [34]	Silicone ($n = 21$)	ISD (MUCP <30 cm H_2O or <[110−age] × 80) All had undergone prior incontinence/ prolapse surgery	Median 31 months	**Cure:** 'dry all in all circumstances' **Improvement:** 'only rare or minimal leakage'	48%	IV
Koelbl et al. [89]	Silicone ($n = 32$)	ISD (VLPP <65 cm H_2O) Prior incontinence surgery ($n = 28$)	12 months	**Cure/improvement:** not clearly defined, but based on a questionnaire and stress test	59%	IV

[a] Patient group with longest follow-up reported.
[b] Criteria as used in the International Consultation on Incontinence: level I (randomised, controlled trials); level II (good quality, prospective cohort studies); level III (good quality, retrospective case-control studies); level IV (good quality case series); and level V (expert opinion).
[c] Macroplastique® Implantation System.

ambiguous descriptions of the extent of prolapse and number of repeat injections. Current evidence suggests that approximately 3 out of 4 women are improved or cured following injection therapy in the short term, albeit there is a dearth of long-term, follow-up data, with no strong evidence that any one agent is superior. It is clear that randomised, controlled, comparator studies with long-term follow-up are required.

7. Quality of life (QoL)

Over 20 years ago, Norton noted that the surgical incontinence literature referred to the 'embarrassment' of incontinence but then ignored this factor and concentrated on objective variables [63]. She subsequently questioned the value of objective outcome measures, and devised a scale to measure the restriction incontinence imposes on the individual [63]. An explosion in the use of QoL, health status and symptom questionnaires followed, as evidenced by a MEDLINE search (Table 3). Many incontinence-specific instruments have been developed, which have recently been comprehensively reviewed (see Appendix A) [64]. A generic QoL instrument (e.g. the Short Form 36; SF-36) is also useful because it may detect QoL changes not identified by disease-specific questionnaires.

Information about the impact of injection therapy on QoL is relatively limited – poorly defined or unvalidated questionnaires and heterogeneous patient populations have often been used, and follow-up is frequently too short. Nevertheless, several agents have been shown to significantly improve QoL (Table 4). In one study, autologous fat was more effective than placebo in improving QoL, though validation of the incontinence questionnaire used was not referenced [57].

One of the limitations of most QoL instruments is their relative lack of interpretability. Little evidence exists to confirm that a significant change in score equates to a clinically meaningful improvement in symptoms, though an improvement of at least 5 points in King's Health Questionnaire (KHQ) domains appears to be meaningful to patients and clinically relevant [65]. Patient satisfaction is an alternative outcome measure, which may be affected by pre-operative counselling, patients' expectations and goals, and complications.

Table 3
Number of articles cited in MEDLINE using the search terms 'urinary incontinence' and 'quality of life'

Publication year	Articles cited in MEDLINE (*n*)
1976–1980	0
1981–1985	1
1986–1990	1
1991–1995	21
1996–2000	124

7.1. Patient satisfaction

Surgeons have measured satisfaction by direct questioning for over a century and it is well recognised that this may be biased because of patients' desire to please the medical profession. However, even when anonymous questionnaires are used, patients' satisfaction is frequently greater than objective cure. Black et al. found that if success was assessed in its most empirical form (i.e. 'no urinary leakage and no complication'), then cure rates were very low at 28%, but 65% of women were satisfied with their surgery [66].

Few data are available on patients' satisfaction with injectable agents, though satisfaction levels are similar to surgery [67], where complication rates are higher. In a study comparing carbon-coated zirconium beads and collagen, only 21% and 5% of patients, respectively, claimed that the treatment remained effective at the last follow-up (median follow-up: 51 and 62 months) [62]. However, a third were satisfied with the outcome of treatment.

In summary, there appear to be subtle differences between QoL, patient satisfaction and objective outcomes. These terms remain poorly defined, and further empirical work is required to understand women's perception of the outcome of SUI treatment. This may lead in the future to a robust and clinically useful definition of cure.

7.2. Patient preference

Patient preference is vital in the choice of SUI therapy. A study by Robinson et al. suggested that women would choose to undergo less-invasive procedures with a lower risk of complications, even though the chance of cure may be lower than a major operation [68]. This reflects the views of patients in tertiary care clinics and not necessarily those of women in the general population. Nevertheless, a valuable insight is provided into patients' general preference for non-invasive or minimally invasive treatment of SUI, though the inherent trade-off in choosing a less-invasive treatment (i.e. a lower success rate) needs to be stressed.

8. Patients' goals

Physicians' goals have generally been to achieve a complete cure of incontinence. A recent Cochrane review, whilst highlighting the lack of an adequate

Table 4
Studies investigating the impact of injection therapy on quality of life

Reference	Agent	QoL assessment	Outcome
Corcos et al. [67]	Collagen ($n = 66$)	SUI patient population not defined Multicentre, randomised open trial of collagen vs. surgery (bladder neck suspension, sling or Burch colposuspension) 12 months SF-36, IIQ and satisfaction index	No significant differences were observed between collagen and surgery
Winters et al. [79]	Collagen ($n = 58$)	ISD (ALPP <60 cm H_2O) ($n = 49$) Urethral hypermobility (Q-tip) ($n = 37$) Previous incontinence surgery ($n = 31$) Assessment by telephone interview at the end of the study	18/40 (45%) women reported a moderate or maximal improvement in QoL
Yokoyama [90]	Collagen ($n = 66$)	SUI patient population not defined	88% of women found the procedure useful or slightly useful
Anders et al. [91]	Collagen ($n = 26$) or silicone[a] ($n = 34$)	Urodynamically diagnosed with moderate or severe urethral sphincter-related incontinence Women were unfit for major surgery ($n = 19$) or had failed surgery ($n = 41$) 12 months Disease-specific QoL questionnaire (not specified)	QoL was significantly improved in all women ($p < 0.05$) No differences were observed between the 2 groups
Anders et al. [92]	Collagen ($n = 14$) or silicone[a] ($n = 26$)	Above population was followed up for 5 years King's Health Questionnaire	Significant improvements were observed vs. pre-treatment in 5/9 King's Health Questionnaire domains ($p \leq 0.19$) No differences were observed between the 2 groups
Kothari and Pitkin [29]	Silicone	'Pure' SUI ($n = 42$), SUI with detrusor overactivity ($n = 27$) or SUI with voiding dysfunction ($n = 5$) Mean follow-up of 11 months Visual analogue scale	QoL was improved in 66/74 (89%) patients
Tamanini et al. [88]	Silicone ($n = 21$)	Urodynamically verified SUI ISD (VLPP <90 cm H_2O) Previous incontinence surgery (19%) 12 months King's Health Questionnaire	Significant improvements were observed in 9/9 King's Health Questionnaire general domains and 6/10 disease-specific symptoms vs. baseline ($p < 0.047$)
van Kerrebroeck et al. [93]	NASHA/Dx gel[b] ($n = 42$)	Open, multicentre study SUI verified by demonstrable leakage on coughing or Valsalva manoeuvre Pathophysiology not determined No previous incontinence surgery 12 months King's Health Questionnaire	Significant improvements were observed in 7/10 King's Health Questionnaire domains vs. baseline ($p < 0.005$)
Haab et al. [38]	NASHA/Dx gel[b] ($n = 142$)	Open, multicentre study Urodynamically verified SUI Pathophysiology not determined No previous incontinence surgery 6 months King's Health Questionnaire	Significant improvements were observed in 8/9 King's Health Questionnaire domains vs. baseline ($p < 0.0025$)[c]

[a] Macroplastique® Implantation System.
[b] The Zuidex™ System.
[c] 12-month data now available, showing significant improvements in 6/9 domains ($p \leq 0.0001$ vs. baseline).

evidence base in the published literature, concluded that injection therapy appears to be less effective than open surgery at 12 months, but this is compensated by a better safety profile [54].

In terms of patients' goals, the study by Robinson et al. showed that women with lower urinary tract symptoms have realistic expectations about their treatment, with only 17% expecting a complete cure [68]. In two studies of pelvic floor surgery for prolapse and/or incontinence [69–72], patients' goals were investigated in the context of actual treatment procedures. In the Hullfish et al. study, the main treatment goals included

resumption of previous lifestyle or activities (40.2%) and relief of symptoms (38.1%) [72]. Patients with perioperative complications were less likely to report long-term goal achievement. Similar to the Hullfish study, Elkadry et al. showed that goals were highly personal, and their achievement was the main reason for patients deciding to undergo surgery. As assessed by a 5-point Likert scale, all or most goals were met in 75% of patients at 3 months post-treatment [69], with the situation similar at 1 year [70]. However, objective cure did not predict patient satisfaction or goal achievement. In fact, dissatisfaction was evident despite high cure rates, attributable to surgery-related complications that were worse than the initial problem.

Achieving patients' goals is something to which we should all aspire. Identifying and addressing these prior to surgery may increase satisfaction rates, with the caveat that rates observed during clinical trials may be higher than in clinical practice because more time is spent counselling patients and expectations are more realistic.

Injection therapy appears to have the profile required to meet patients' goals, based on the findings that a procedure with an improvement in incontinence, minimal short-term risk, no long-term risk, and performed in a clinic, would be acceptable. To date, no studies have evaluated whether and to what extent injection therapy achieves patients' goals. Clearly, a study investigating this question, rather than just examining the criteria that patients would find desirable, is required.

9. Cost

SUI can be associated with considerable costs for both purchasers and patients, with pads being a major source of expenditure. A treatment that reduces pad usage is likely to be extremely beneficial, so it is noteworthy that NASHA/Dx gel has been shown to decrease this by 40–50% [73].

The health economics data for SUI injection therapy is limited. An early study showed the cost of collagen injection therapy to be 2.1 times lower than fascia lata sling cystourethropexy, though the sling may be more cost-effective when its greater success rate is considered [74]. Decision-tree analysis comparing collagen injection with surgery, after initial surgical failure, predicted that collagen therapy would be cost-effective if the number of injections is minimised and post-surgery hospital stays are relatively long [75].

Studies have also compared injection therapy with tension-free vaginal tape (TVT). The mean cost per patient of NASHA/Dx gel was SEK22,435 (€2481), compared with a higher estimated cost for TVT (SEK28,954–32,019; €3202–€3541) [76]. NASHA/Dx gel may be considered as more cost-effective at 3 months, though longer-term data are required to confirm this finding. In contrast, economic modelling predicted a higher treatment cost for injection therapy than TVT (£1305 versus £1014, respectively) [77].

Given current cost constraints, further injection therapy cost analyses are needed. These should include long-term follow-up and secondary interventions (e.g. treatment of urinary retention), utilise health economics models, carefully consider actual cost data, and compare urethral injection with the recently released pharmacological therapy, duloxetine, and not just surgery.

10. Conclusions

Although the literature base is generally limited, it is clear that injection therapy produces short-term improvement or cure in approximately 3 out of 4 women and a significant improvement in QoL, as well as having a low complication rate. It can be used in the majority of patients with uncomplicated SUI. Therefore, it may be considered as a first-line treatment option for the vast majority of patients with SUI who have failed conservative therapy and who decline or have a contraindication for pharmacological treatment. Given that there is no strong evidence to distinguish the injectable agents, the choice of injectable agent is likely to depend on safety considerations, ease of use, cost and physician preference.

The decision of whether to use injection therapy must be based on patient preference following an informed discussion between the physician and patient. Only by emphasising patients' own treatment goals will we be able to do what is best for our patients.

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Appendix A. QoL questionnaires

King's Health Questionnaire (KHQ)
Contilife
Incontinence Impact Questionnaire and Urogenital Distress Inventory (IIQ, UDI)
Bristol Female Lower Urinary Tract Symptom (BFLUTS) questionnaire
Symptom Severity Index and Symptom Impact Index (SSI+SII)
Incontinence Quality of Life (I-QoL) Questionnaire

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