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Non-operative methods for the treatment of female stress urinary incontinence

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ABSTRACT

Purpose of research: Stress urinary incontinence (SUI) is a common health problem, especially among women which impairs daily functioning. The purpose of this research is to elucidate the pathophysiology of stress urinary incontinence (SUI), describe its diagnostic methods, summarize current treatments in light of recent studies, and outline examples of new potential therapies.

Methods: Databases such as PubMed, Medline, and ResearchGate were searched with particular attention to the current guidelines.

Basic results: The primary treatment of SUI is lifestyle modification, including weight reduction. Pelvic floor muscle training (PFMT) is recommended as first-line therapy, reducing the number of incontinence episodes and improving quality of life. Additional methods include electrical stimulation or biofeedback. At later stages of treatment, pharmacological therapy is recommended, mainly using vaginal oestrogens and duloxetine.

Conclusions. Non-operative therapies, such as lifestyle modification and PFMT, are effective treatments for SUI. In combination with pharmacotherapy, they significantly improve the quality of life of patients without invasive surgical procedures.

INTRODUCTION

Urinary incontinence is the involuntary, uncontrolled passing of urine. It is a problem that affects both men and women but is more common in the female gender [1]. There are four types of incontinence:

1. Urgency urinary incontinence, associated with a sudden and strong urge to urinate followed by involuntary micturition [2][3].

2. Overflow incontinence, in which a small amount of urine is periodically passed due to bladder overflow. This condition can be associated, for example, with impaired contractility of the bladder detrusor muscle.

3. Stress urinary incontinence, associated with involuntary micturition in conditions with increased intra-abdominal pressure, for example, during activities such as sneezing, coughing, or laughing.

4. Mixed form which often combines urgency and stress incontinence [2].

In this article, we will focus on discussing stress urinary incontinence issues. Stress urinary incontinence reduces quality of life, impairs daily functioning, excludes patients from sports and physical activity, and negatively impacts mental health. Risk factors associated with its occurrence include diabetes mellitus, obesity, smoking, pregnancy, childbirth, menopause, ageing, pelvic surgery and chronic constipation [4].

Anatomical pathogenesis of stress urinary incontinence

The onset of stress urinary incontinence is associated with the development of anatomical changes in the urethra, surrounding tissues or pelvic innervation. These changes include: Atrophy of the urethral mucosa and less secretion produced by it reducing its sealing action. It can be caused, for example, by low oestrogen concentrations.

- 1. Urethral sphincter dysfunction caused, for example, by childbirth, radiotherapy, or diseases of the central nervous system.
- 2. A reduction in the elasticity of the urethral wall harms its ability to deform under external forces that generally cause the urethral lumen to close. This situation can be caused, for example, by radiotherapy.
- 3. The collapse of the posterior wall of the bladder neck, causing it to be displaced downwards along with the proximal part of the urethra, resulting in a lower pressure inside the urethra than in the bladder (under normal conditions, it should be the other way around) and thus, with an increase in abdominal pressure, favours the occurrence of urinary incontinence. These changes are caused by a weakening of the bladder support structure and, on cystourethrography, form a funnel shape.
- 4. Damage to the pelvic fascia and the tendinous arch of the pelvic fascia which are responsible for maintaining the stability of the pelvic organs.
- 5. Damage to the pubovaginal ligament stabilises the urethra during periods of rest and increased abdominal pressure.
- 6. Dysfunction of the levator ani muscle. This muscle, together with the mediastinal fascia and the vagina, forms a 'hammock'-like structure that helps to maintain the position of the urethra. When the intra-abdominal pressure increases, the anal lever muscle contracts, thereby flexing the urethra and closing the urethral lumen.

Damage to the pelvic floor nerves and thus dysfunction of muscles such as the anal lever
 [5].

Diagnostics

Determining the type and severity of urinary incontinence is critical before implementing treatment. Diagnosis should start with a thorough history taking, including symptoms and their severity, risk factors and co-morbidities. The neurological and obstetric-gynaecological history should be remembered. The impact of symptoms on quality of life should also be assessed. Questionnaires help take a history and identify the type of incontinence. The next step is a physical examination, where particular attention should be paid to abdominal and gynaecological examination. A general urine examination should be ordered to exclude abnormalities such as glucosuria, erythrocyturia or proteinuria [6][7].

It is advisable to perform a cough test, which involves asking the patient to cough in the lithotomy position with a well-filled bladder. If urine leakage occurs at the beginning of this activity, this indicates stress urinary incontinence (positive result). If the test is negative, it should be repeated in a standing position. In most cases, the absence of urine leakage allows this type of incontinence to be ruled out. However, it is crucial to consider factors that can cause false-negative results, such as inadequate bladder filling or insufficiently strong cough. Inconclusive results require a urodynamic study [6].

A pad test and keeping a micturition diary by the patient for about 2-3 days may also be helpful in diagnosis. This may include information such as the amount of fluids drunk, frequency and volume of urine passed during controlled micturition and incontinence episodes, the circumstances under which the incontinence occurred and any accompanying symptoms [6][7].

It is also helpful to assess the volume of urine retained after micturition (PVR) to exclude overflow incontinence, which can result in hydronephrosis and impaired renal function. It is measured after the bladder has emptied using an ultrasound machine. This is the preferred method over measurement by catheterization [6].

Among the more specialised tests is the urodynamic test. It is not carried out routinely but should be considered, for example, in cases of inconclusive test results. A standard urodynamic test includes non-invasive uroflowmetry, measurement of post-micturition urine volume, invasive cystometry and pressure-fluid testing [8]. The urine volume passes during uroflowmetry, and the flow rate is measured. Cystometry involves inserting a catheter and

filling the urinary bladder with, e.g. physiological NaCl solution. Intrabladder pressure and abdominal pressure are measured during the test, from which the bladder pressure is calculated. The patient also reports their subjective sensations, such as the feeling of filling the bladder, the need to micturate, and feelings of discomfort or pain. The patient then urinates, the urine flow is examined, and pressure measurements are taken during micturition (flow-pressure study) [9].

In addition to the above investigations, cystoscopy, pelvic floor ultrasound, Bonney and Marshall test or Q-Tip test, among others, should also be considered [7].

Conservative treatment methods

The treatment depends on the type of incontinence and the severity of the symptoms [10]. As mentioned, the assessment of incontinence should include a detailed history and physical examination, as well as consideration of the patient's goals and expectations in the context of treatment. First-line therapy is behavioural and lifestyle modifications leading to weight reduction [11]. At later stages of treatment, patients may benefit from urine collection methods such as pads, catheterisation or support tampons [12]. Pelvic floor muscle training, other physiotherapeutic methods, pharmacological treatments, minimally invasive interventions, and surgery are also recommended [11].

Behavioural and lifestyle modification

Weight reduction. According to the recommendations of the European Society of Urology, lifestyle modification management should strongly encourage women with overweight and obesity and stress urinary incontinence to reduce and maintain their body weight [11].

Numerous studies point to obesity and overweight as significant risk factors for pelvic floor static disorders, including urinary incontinence [13]. An increase in BMI (Body Mass Index) has been shown to increase the risk of urinary incontinence [11].

Weight reduction results in a reduction in incontinence complaints. It has been shown that in patients undergoing a 6-month conservative intervention leading to weight reduction, a reduction in the number of reported incontinence episodes was observed compared to the control group [14]. According to a study of 150 women with a BMI of 42 ± 4.6 kg/m2 qualified for bariatric surgery, a reduction in the ICIQ score (International Consultation on Incontinence Questionnaire score) from 9.3 ± 3.9 to 3.3 ± 3.8 , (P <.001) [15] was observed in 37.3% of patients presenting baseline incontinence symptoms. The results of other studies evaluating improvements in quality of life in patients after bariatric surgery also demonstrate

a positive effect of significant weight reduction on the reduction of incontinence symptoms observed at around one year [14] [16] and 3 years after surgery [14].

Urine collection methods. Recommendations for urine collection methods come mainly from studies on patients with overactive bladder. They can improve the quality of life in patients with different types of incontinence in parallel to pharmacological methods or where other interventions might be too risky. Such methods include absorbent pads, catheterisation, internal urine collection devices and vaginal devices [12].

Studies comparing different types of absorbent pads have not shown a clear superiority for either of them. At the same time, it is believed that the effectiveness of specific designs may vary for different populations [17]. Regarding catheterisation, no correlation between the type of material or type of catheter and the effectiveness of the intervention has been proven. However, suprapubic catheterisation may be associated with fewer urological complications [18][19]. Anticholinergic drugs alleviate discomfort associated with the catheterisation procedure, but efficacy is not apparent [20] [21]. Another method may be botulinum toxin injection [22]. Antibiotic prophylaxis is recommended to prevent urinary tract infections but is associated with the risk of increasing antibiotic resistance [23].

Physiotherapy interventions. In the context of physiotherapy interventions, supervised, intensive pelvic floor muscle training (PFMT) of at least three months duration should be offered as first-line therapy to all women with stress urinary incontinence (SUI) or mixed incontinence (including older women and pre-and postnatal women). It is also strongly recommended that PFMT programmes are as intensive as possible and that the effectiveness and lack of side effects of PFMT be balanced with the expected outcome and complications of invasive SUI surgery [11].

Pelvic floor muscle training is used to improve the function and morphology of the structures that stabilise the urethra in the pelvic floor. It can be used to prevent urinary incontinence, for example, in women in the pre-partum period or as part of recovery after childbirth. Most commonly, however, it is used to treat an existing condition, sometimes in combination with a therapist's observation and/or palpation of muscle contraction or biofeedback (using measuring equipment that measures contraction through electromyography, manometry, dynamometry, ultrasound or MRI). Of the other methods using the exact mechanism, electrical stimulation and vaginal cones are also used [11].

The immediate effect of a single contraction of the pelvic floor muscles includes simultaneously narrowing the pelvic floor muscle area, increasing urethral closure pressure and elevating the bladder and rectum, thus preventing incontinence [24] [25]. Such changes resulting in increased muscle strength and endurance were observed in a randomised trial comparing intensive pelvic floor muscle training for six months with no treatment [26]. According to the Cochrane review, compared with the control group, women experiencing incontinence symptoms and using pelvic floor muscle training were eight times more likely to report a cure [27]. This group also experienced improved quality of life and reduced leakage by an average of one event per day, and these women lost significantly less urine in incontinence tests. Patients using pelvic floor muscle training were also more satisfied with their treatment and had better outcomes. Adverse events were described as rare and mild [11]. Biofeedback is a therapeutic technique that allows patients to control physiological processes

in the body that are usually unconscious, such as heart rate or muscle tension. Adding biofeedback to pelvic floor muscle training, according to the analysis of the Cochrane review, may have some additional effects [28]. However, when compared to using exactly the same dose of training and biofeedback between groups, the latter had no additional effect [29].

The use of vaginal cones to train the pelvic floor muscles is more effective than abandoning the therapy, but it is not possible to say conclusively whether it is more or less effective than structural PFMT [27][30]⁻ However, the inconveniences of this method are highlighted: some patients report difficulty keeping the cone inside, others report discomfort and problems with motivation, leading to frequent abandonment of this form of therapy [30].

There is the highest level of evidence (1a) to support PFMT in the treatment of SUI/MUI [27][31][32]. It has been observed that PFMT is less effective when women with MUI and UUI are included in studies, and intensive and supervised training is more effective. According to a literature review of NICE guidelines, PFMT is as effective as surgery in about half of women with SUI. Because of the postoperative risks and lack of adverse effects of PFMT, they recommend three-month supervised PFMT as first-line treatment for SUI and MUI [31].

In a study comparing the effectiveness of pelvic floor muscle training and midurethral sling MUS surgery involving 460 women with moderate to severe SUI, subjective improvement was reported by 90.8 per cent of women in the surgery group and 64.4 per cent of women in the physiotherapy group after one year [31].

Electrical stimulation may also be considered for the treatment of stress urinary incontinence (SUI) or as an adjunct to pelvic floor muscle contraction (PFM) teaching, but this is a weak

recommendation based on the possible benefits of the intervention and taking into account its unclear benefits, and potential increased side effects [33][34]. Electromagnetic stimulation (EMS) did not positively affect urinary incontinence treatment compared with pelvic floor muscle training, and the results of the incontinence tests were comparable to those of the placebo [35]. On the other hand, electroacupuncture (EA) is effective in treating stress urinary incontinence based on 15 randomised clinical trials. It was observed that ICIQSF scores improved and urine leakage per hour decreased in patients undergoing EA compared to those who received placebo EA, exercise or medication [36].

Pharmacological treatment

European recommendations for pharmacological interventions include the use of oestrogens and duloxetine [11].

Use of estrogens. Offering vaginal estrogen therapy to postmenopausal women with stress urinary incontinence (SUI) and symptoms of vulvovaginal atrophy and the recommendation that alternative forms of HRT should be discussed in women taking oral conjugated equine estrogens as hormone replacement therapy (HRT) who develop or worsen SUI stand out as strong recommendations [11].

Estrogen drugs are used as hormone replacement therapy (HRT) in women with natural or therapeutic menopause. In contrast to the systemic route of administration, vaginal estrogen treatment does not increase the risk of thromboembolism, endometrial hyperplasia or breast cancer[37][38][39]. Intravaginal treatment is mainly used to alleviate symptoms of vaginal atrophy in postmenopausal women.

Topical estrogen treatment has been shown to improve SUI symptoms in the short term [37]. A comparison of estrogen treatment with PFMT, ES and its use as an adjunct to surgery does not allow firm conclusions to be drawn [40]. Still, one study in postmenopausal women showed the benefit of adding vaginal estriol to electrostimulation and pelvic floor muscle training in the treatment of stress urinary incontinence [41]. No significant adverse effects were reported after two years of vaginal administration of estradiol for vulvovaginal atrophy [40][42].

Topical estrogen treatment can be given as conjugated equine estrogens, estriol or estradiol in the form of pessaries, vaginal rings or creams. The ideal duration of treatment and long-term effects have not been established, but improvements have been shown with vaginal rings over placebo, which were preferred to pessaries [42].

Numerous studies on systemic HRT to assess parameters other than urinary incontinence have shown that conjugated equine oestrogens increase the risk of developing or worsening UI compared with placebo and do not improve SUI [43][44][45][46][47][48]. In one, it was shown that of the estrogens used, raloxifene was not associated with the development or worsening of urinary incontinence[49]. A smaller study suggested that oral oestriol or oestradiol causes improvement in UI symptoms, although the evidence was unclear [31][50].

Use of Duloxetine. Duloxetine should be offered to those patients with stress urinary incontinence who do not respond to other conservative treatments and wish to avoid invasive procedures after careful discussion of the risk of side effects. The substance should be introduced and discontinued gradually due to the high risk of side effects [11].

In addition, it should be noted that duloxetine improves stress urinary incontinence in women, but the chances of cure are low. Duloxetine can also cause significant gastrointestinal and central nervous system side effects, leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of therapy (strength of evidence 1a) [11].

Duloxetine inhibits the presynaptic reuptake of the neurotransmitters serotonin (5hydroxytryptamine; 5-HT) and norepinephrine (NE). In the sacral spinal cord, increased concentrations of 5-HT and NE in the synaptic gap increase the stimulation of 5-HT and NE receptors on the motor neurons of the vulvar nerve, which in turn increases resting tonus and the strength of contraction of the striated urethral sphincter [51].

Duloxetine was evaluated as a treatment for women with stress urinary incontinence (SUI) or mixed urinary incontinence (MUI) in three systematic reviews (SR) [52][53][54]. Improvements in incontinence were observed compared to placebo, with no clear differences between SUI and MUI. One study showed a cure for incontinence in 10% of patients. No improvement in incontinence-related quality of life (UI QoL) was observed in the study that used this as the primary endpoint. In another study comparing duloxetine (80 mg daily) with pelvic floor muscle training (PFMT) alone, PFMT + duloxetine and placebo [55], duloxetine reduced urinary leakage compared to PFMT or no treatment. Global improvement and quality of life were better with combination therapy than without treatment. There were no significant differences between PFMT and no treatment in this study.

Two open-label studies with follow-up of more than one year assessed the long-term effect of duloxetine in the control of SUI. Both studies had a high number of patient withdrawals due to lack of efficacy and a high rate of side effects, including nausea and vomiting (in more than

40% of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue [56][57].

A systematic review showed significant efficacy of duloxetine compared to placebo in women with SUI, but with an increased risk of side effects [54]. Adverse effects of duloxetine include mental health problems and suicidal thoughts. A meta-analysis of four randomised controlled trials (RCTs) involving 1,910 women with SUI found no cases of suicide, violence or akathisia, but suggested that the rate of treatment discontinuation due to side effects was about one in seven patients and that the harms may outweigh the benefits of treatment [58]. A meta-analysis of twelve placebo-controlled trials involving almost 3,000 patients found that in patients with major depressive disorder, there was no significant difference in the rate of suicide-related events between duloxetine and placebo [59].

Therapy development

Promising therapies for the treatment of urinary incontinence have emerged in recent years, such as midodrine, gepotidacin and TAS-303. The new drugs offer potentially greater efficacy and fewer side effects, expanding therapeutic options for patients.

Midodrine is a substance that stimulates alpha-adrenergic receptors in the urethral smooth muscles, leading to their contraction and an increase in urethral closure pressure. The result is an improvement in urethral closure function, which may reduce incontinence episodes [60].

In clinical trials, midodrine has shown efficacy in increasing urethral opening pressure in patients with SUI. These studies indicate that midodrine can significantly improve continence control by increasing urethral opening pressure by up to 9.3 cmH2O compared to placebo and consequently reduce the frequency of incontinence episodes [60].

Gepotidacin is an antibiotic of the triazacenafitylene class. It exhibits its action through a unique mechanism of inhibiting bacterial DNA replication and binding to a unique site, resulting in balanced inhibition of two type II topoisomerase enzymes. The EAGLE-2 and EAGLE-3 studies were randomised, multicentre, double-blind trials to evaluate the efficacy and safety of oral gepotidacin compared with nitrofurantoin in women with uncomplicated urinary tract infections. It was shown that gepotidacin was no worse than nitrofurantoin and even more effective in some cases, so it may be a promising therapeutic option for women with coexisting urinary incontinence [61].

TAS-303 is a novel selective inhibitor of norepinephrine uptake against serotonin or dopamine transporters. In preclinical in vitro and in vivo studies, TAS-303 was shown to selectively and effectively inhibit [3H]norepinephrine binding to human NET. Oral

administration of TAS303 (3 mg/kg) significantly increased blood levels of norepinephrine, while it had no significant effect on levels of adrenaline, dopamine and serotonin. The substance increased basal urethral pressure in healthy rats and leakage point pressure in rats with vaginal distension, showing a maximal effect comparable to duloxetine. In the forced swim test, TAS303 (100 mg/kg) showed no significant effect on immobility time in rats, suggesting that this drug may have minimal central nervous system side effects at an effective dose for urethral function. These results demonstrate that TAS-303 has therapeutic potential in treating patients with SUI [62].

CONCLUSIONS

Stress urinary incontinence (SUI) is a significant health problem that significantly reduces the quality of life of many women. Effective diagnosis, including a detailed history, physical examination and urodynamic testing, is crucial for correct diagnosis and selection of appropriate treatment methods. Non-operative methods of treating UC, such as lifestyle modification. pelvic floor muscle training (PFMT), electrical stimulation and pharmacotherapy, play a fundamental role in treating this condition. Lifestyle modification, including weight reduction, can significantly reduce incontinence complaints. PFMT, as a first-line therapy, effectively reduces the number of episodes of incontinence and improves patients' quality of life. Additional methods, such as electrical stimulation and biofeedback, can complement PFMT. In cases where these methods are unsuccessful, pharmacotherapy with vaginal oestrogens and duloxetine can be effective. New potential therapies like midodrine, gepotidacin, and TAS-303, offer possibly greater efficacy and fewer side effects. A combination of different therapeutic approaches tailored to the individual patient's needs allows optimal management of the symptoms of SUI. A therapeutic approach based on nonoperative methods of treating SUI not only improves the physical condition of patients but also their psychological and social comfort, which is essential for the overall improvement of quality of life.

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