SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

NEW APPROACHES TO THE EVALUATION OF STRESS URINARY INCONTINENCE AND THE ROLE OF DIETARY SUPPLEMENTS IN SUPPORTING CONSERVATIVE TREATMENT

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New Approaches to the Evaluation of Stress Urinary Incontinence and the Role of Dietary Supplements in Supporting Conservative Treatment

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1. Background and objectives of the doctoral thesis

Similar to developed countries, the population's aging process has accelerated in Hungary. At the same time, according to data from the Central Statistical Office (KSH), life expectancy at birth for women increased from 76.2 years in 2000 to 78.0 years in 2021. The relevant literature unanimously predicts that as the world's population ages, the incidence of pelvic floor disorders will also increase. In the United States alone, pelvic floor disorders currently affect an estimated 25 million women. By 2050, it is predicted that 43.8 million women, or nearly 33% of the adult female population in the United States, will be affected by at least one bothersome pelvic disorder. The increase in the prevalence of UI may be related to the aging population and the increasing prevalence of obesity. In addition, due to the 2019 coronavirus pandemic, a large portion of the population could not attend routine examinations, which increases the likelihood of undiagnosed pelvic floor conditions.

Female pelvic floor disorders include urinary and fecal incontinence, pelvic organ prolapse, and certain pain syndromes. Urinary incontinence may be a symptom reported by patients, a sign detected during examination, or a diagnosis confirmed by tests. These conditions have a significant impact on female functioning and quality of life and negatively affect women's well-being and health. Several risk factors for urinary incontinence have been identified, such as aging, obesity, and smoking, which are causally related to the condition, while the role of pregnancy and childbirth remains controversial. Urinary incontinence causes unnecessary social isolation and costs. In the most severe cases, women become increasingly isolated and confined to their homes. Although not life-threatening, urinary incontinence causes women to reduce their social and physical activities, which can lead to social isolation and depression.

Incontinence and prolapse can be a direct cause of sexual dysfunction due to physical discomfort or can cause distress that leads to a deterioration in intimacy and sexual

relationships. With an aging population, female pelvic floor disorders are a significant problem from both an individual and a societal perspective.

Our research aimed to determine whether the severity of stress incontinence correlates with any pelvic biomechanical parameters, and we also investigated whether the dietary supplement we developed increases the effectiveness of pelvic floor exercises.

Our first cross-sectional study aimed to explore the extent to which the biomechanical parameters of the female pelvis, which can be measured quantitatively using Vaginal Tactile Imaging technology, correlate with the clinical severity of stress urinary incontinence. Current diagnostic tools, including urodynamic testing, various questionnaires, and physical tests, provide important but limited information about the functional status of pelvic structures, especially under dynamic stress. The specific aim of the study was to compare the severity of incontinence determined using the MESA (Medical, Epidemiologic, and Social Aspects of Aging) questionnaire and the PGI-S (Patient Global Impression of Severity) scale with 52 biomechanical parameters recorded by VTI and to determine any significant correlations through statistical analysis. The aim of the research was also to identify specific VTI parameters that are sensitive to differences in clinical severity, particularly in mild and severe SUI. Our long-term goal is to make VTI suitable for more accurate mapping of the pathophysiological heterogeneity of SUI, thereby supporting personalized diagnostic and therapeutic decision-making.

The aim of the parallel randomized, double-blind, placebo-controlled clinical trial was to evaluate the effect of a specifically formulated dietary supplement containing a combination of creatine, leucine, zinc, calcium, and magnesium - has on the symptoms of women with stress - dominant urinary incontinence when used in combination with standardized pelvic floor muscle training (PFMT). Our hypothesis is that the ingredients in the dietary supplement may positively

affect muscle strength, muscle protein synthesis, and neuromuscular function, thereby enhancing the therapeutic efficacy of PFMT. During the study, participants will perform structured PFMT daily for six weeks while receiving either a dietary supplement or a placebo in a randomized manner. The primary endpoint is the change in the UDI-6 (Urogenital Distress Inventory) questionnaire score, while secondary endpoints include the IIQ-7 (Incontinence Impact Questionnaire), the PGI-S (Patient Global Impression of Severity), vaginal squeeze pressure measured with a perineometer, and the Biomechanical Integrity (BI) Score determined by VTI. The study also aims to determine the extent to which the biomechanical parameters measured by VTI reflect subjective symptom improvement and whether the dietary supplement contributes to functional regeneration of the pelvic floor.

2. Methods

2.1 Correlation between the female pelvic floor biomechanical parameters and the severity of stress urinary incontinence

We conducted a cross-sectional study at an outpatient clinic between 4/1/22 − 15/3/22 at the University of Debrecen, Department of Obstetrics and Gynecology authorized under approval from the Scientific and Research Ethics Committee of Hungary: 2876-13/2022/EÜIG. After taking a medical history, potentially eligible patients completed the MESA questionnaire. Women with stress or stress-predominant mixed UI (stress percent score more than urge percent score) on the questionnaire were selected for the study. Exclusion criteria were pregnancy or less than 12 months postpartum; more than three vaginal deliveries or prior operative delivery; pelvic organ prolapse (POP) > stage 2 prolapse according to the pelvic organ prolapse quantification system (POP-Q); and current medications for UI or prior surgical treatment for UI; collagen or connective tissue disease. POP was assessed by a standardized POP-Q examination after the International Continence Society recommendations. After enrollment based on the MESA questionnaire, women were asked to complete the Patient Global Impression of Severity question (PGI-S). After a standardized pelvic exam, the biomechanical integrity of the pelvic floor was evaluated by VTI.

2.1.1 Questionnaires

2.1.1.1 Medical, epidemiologic, and social aspects of aging questionnaire

The questionnaire is developed and validated to identify the urgency- or stress-predominant component of MUI and assess the severity of symptoms. The MESA is a self-reported questionnaire with nine questions on stress incontinence and six on urge incontinence. The four response categories range from "never" (0 points) to "often" (3 points), with higher scores

indicating more frequent symptoms of incontinence. We calculated the stress score (maximum = 27 points), the urge score (maximum = 18 points), the stress index, and the urge index, which are obtained by dividing each category's actual score by the maximum total possible. The MUI is categorized as stress-predominant if the stress index exceeds the urge index. To assess the severity of incontinence, the total score of stress (27) is divided into three degrees: scores 1 to 9 are assigned as mild, 10 to 18 moderate, and 19 to 27 as severe.

2.1.1.2. **Patient global impression of severity question**

The PGI-S is a universal measure utilized to assess the severity of a particular condition using a single-state scale. It has been validated specifically for women experiencing stress urinary incontinence. The PGI-S scale ranges from 0, indicating the absence of symptoms, to 4, indicating the presence of severe symptoms, with a minimal clinically important difference (MID) of 1.

2.1.2. **Vaginal tectile imager**

Biomechanical examination of the pelvic floor was performed using VTI (model: 2S) (Advanced Tactile Imaging, Inc., Ewing, NJ, USA). This device is equipped with 96 rows of pressure (tactile) sensors on both sides of the probe, as well as an orientation sensor and temperature controllers that maintain the probe temperature close to human body temperature during the examination. During the examination, the VTI probe records the pressure responses of the opposing vaginal walls along the length of the vagina. By integrating the pressure and positioning data obtained from each pressure sensor, we obtain a comprehensive picture of the deformation of the vaginal wall and the contraction of the pelvic floor muscles. The VTI examination procedure consists of eight sub-tests: 1) insertion of the probe, 2) elevation, 3) rotation, 4) Valsalva maneuver, 5) voluntary muscle contraction (anterior versus posterior compartment), 6) voluntary muscle contraction (left versus right side), 7) involuntary

relaxation, and 8) reflex muscle contraction (coughing). Tests 1, 2, 4, 5, 7, and 8 provide data on the anterior/posterior compartments, test 3 provides 360-degree data, and test 6 provides data on the left/right side. The VTI probe allows for 3-15 mm tissue deformation during probe insertion (test 1), 20-45 mm tissue deformation during probe lifting (test 2), and 5-7 mm deformation during probe rotation (test 3). In addition, it records dynamic responses during the Valsalva maneuver, pelvic floor muscle contractions, and relaxation (tests 4-8). The probe maneuvers performed during tests 1-3 record multiple pressure patterns from the tissue surface, enabling the creation of an integrated tactile image of the examined area using image composition algorithms. Within the tactile images obtained during examinations 1 and 2, the software calculates the spatial gradients ($\partial P(x, y)/\partial y$) for the anterior and posterior compartments. The y-coordinate represents the orthogonal direction originating from the longitudinal axis of the vagina and spanning the anterior and posterior compartments, while the x-coordinate is located on the longitudinal axis of the vagina itself. A VTI szoftver automatikusan kiszámítja az 52 paramétert, mely részletesen jellemzi a hüvely és az azt körülvevő szövetek tapintási leletét. Minden vizsgálati szempontot illetően követtük a gyártó utasításait. A BI-pontszám olyan összesített kompozit érték, mely összefoglalóan jellemzi a medencefenék biomechanikai tulajdonságait és amely magában foglalja a szövetek rugalmasságát, a medence alátámasztását, az izomösszehúzódást, az önkéntelen ellazulást és a mobilitást.

2.1.3. Statistics

For statistical calculations, we used IBM SPSS Statistics for Windows Version 25.0 statistical software (IBM Corp., Armonk, NY, USA). Descriptive statistics were computed for all variables of interest. The continuous outcomes were summarized using means and standard deviations, while categorical outcomes were presented as frequencies and percentages. Student's t-test was used to compare mean values between two groups. Simple correlation

analysis was used to examine the bivariate associations between selected parameters, indexes, and scores, and Pearson Correlation Coefficient (r) was calculated. Statistical significance was defined as a two-tailed test with a *P*-value threshold of < 0.05.

2.2. A randomized controlled pilot trial to assess the effectiveness of a specially formulated food supplement and pelvic floor muscle training in women with stress-predominant urinary incontinence

We have conducted a randomized, double-blind, placebo-controlled pilot trial with a six-week follow-up period at an outpatient medical center between 4/1/22 − 9/1/22. The trial was registered at ClinicalTrials.gov (Identifier: NCT05358769), and IRB approved by the Scientific and Research Ethics Committee of Hungary: 2876-13/2022/EÜIG.

The randomization was done in a 1:1 ratio and generated by SAS (SAS Institute, Cary, NC, USA) version 9.4. We have enrolled women with stress or stress-predominant urinary incontinence [based on the Medical, Epidemiologic, and Social Aspects of Aging (MESA) questionnaire]. Women who indicated stress UI or stress-dominant mixed UI (stress percent score more than urge percent score) were eligible for inclusion. Exclusion criteria were pregnancy or less than 12 months postpartum; more than three vaginal deliveries or any prior operative delivery; self-reported symptoms of pelvic organ prolapse or POP-Q stage > 2; history of supervised PFMT within 12 months; and current medications for UI or surgical treatment for UI; known zinc or copper deficiency or sensitivity; or collagen or connective tissue disease.

After enrollment, women were randomized to receive the specially formulated dietary supplement (Incoxil®, Fempharma, LLC, Debrecen, Hungary) (treatment group) or placebo (control group). Women in the treatment group were asked to take the oral dietary supplement every day for six weeks. Dietary supplement of the treatment group included creatine monohydrate 3 g/day, leucine 0.5 g/day, zinc sulfate heptahydrate 5 mg/day, calcium citrate

120 mg/day, and magnesium citrate 60 mg/day) as a water-soluble powder. While in the control group, women received daily supplementation with maltodextrin as a water-soluble powder. The color, texture, solubility, taste, and volume of the powder were similar between the two groups. After randomization, subjects received the dietary supplement in a sealed, uniform box. The completely identical boxes were labeled with codes. The codes were not known by the researchers participating in the clinical trial. The code could not identify the patients. Participants did not know what kind of preparations they were given; they were assigned randomly without being informed which group they belonged to.

After enrollment based on the MESA questionnaire, women were asked to complete the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). Standardized pelvic exam, including POP-Q measurement, Oxford scale assessment of the pelvic floor strength, the strength of voluntary contractions of vaginal muscles was measured by a perineometer device (Peritron, Laborie, Williston, Vermont, USA) in a standardized fashion, and the biomechanical integrity of the pelvic floor was evaluated by VTI. Patients received detailed pelvic floor muscle exercise instruction and training with the aid of the perineometer. Study participants were instructed to perform daily pelvic floor muscle exercises at an intensity of at least 65–75% of one repetition maximum of 45 pelvic floor muscle (PFM) contractions per day (15 PFM contractions performed three times per day) for six weeks as per previous protocols.

At the six-week visit, study participants were asked to complete the UDI-6 and IIQ-7 questionnaires again. In addition, repeat pelvic exams, including POP-Q measurement, Oxford scale assessment of the pelvic floor strength, the strength of voluntary contractions of vaginal muscles was measured by a perineometer device in a standardized fashion, and VTI evaluated the biomechanical integrity of the pelvic floor.

The primary outcome was the UDI-6 score. Secondary outcomes were the Incontinence Impact Questionnaire (IIQ-7) score, Patient's Global Impression of Severity (PGI-S), Patient's Global Impression of Improvement (PGI-I), Biomechanical Integrity score as measured by the Vaginal Tactile Imager, and vaginal squeeze pressure measured by perineometer.

2.2.1. **Questionnaires**

2.2.1.1. Medical, epidemiologic, and social aspects of aging (MESA) questionnaire

The MESA recording was performed as described in section 2.1.1.1.

2.2.1.2. **Urogenital distress inventory (UDI-6) and incontinence impact questionnaire (IIQ-7)**

UDI-6 is a short version of a condition-specific quality-of-life instrument. UDI-6 consists of six items. To specify the severity of urinary distress symptoms, patients' response options ranged from 0 ("no symptoms") to 4 ("quite a bit"). To calculate the score, the mean score of answered items within each component is multiplied by 25 to obtain the scale score (range 0–100). Higher scores in UDI-6 indicate a higher disability. IIQ-7 is a urinary incontinence-specific psychometric questionnaire. This questionnaire assesses the psychosocial impact of UI in women. It consists of 7 items. The total score ranges from 0 to 100. Higher score indicates a worse quality of life.

2.2.1.3. **Patient global impression of severity and improvement question (PGI-S and PGI-I)**

The Patient Global Impression of Severity (PGI-S) is a global index that may be used to rate the severity of a specific condition (a single-state scale). The PGI-S was validated on women with stress urinary incontinence. PGI-S, range 0 = no symptoms to 4 = severe symptoms,

MID = 1. The PGI-I is a seven-point transition scale comprising a single question asking patients to rate their urinary tract condition now compared to how it was before treatment on a scale from 1 (very much better) to 7 (very much worse).

2.2.2.Vaginal tactile imager

The VTI description was performed as described in section 2.1.2.

2.2.3. **Statistics**

We used SigmaStat/SPSS (Systat Software Inc., San Jose, CA, USA) software for statistical calculations. Descriptive statistics were calculated for all variables of interest. Means and standard deviations were calculated for continuous outcomes. Frequency and percentage were calculated for categorical outcomes. The Fisher's exact test was used to compare frequencies. The students' t-test was used to compare the mean values between the two groups. A paired t-test was used to compare the paired data obtained at baseline and six weeks later. The Wilcoxon signed-rank test was used to compare the VTI data. The study has adequate power to detect a difference after 32 patients' enrollment. Power analysis was performed [G*Power Statistical Power Analyses Software] based on our pilot study, which revealed that the baseline UDI score was 36 ± 15 in our population of women with SUI. To have a power of 80% and a significance level of 5% with a large effect size (Cohen's d = 1.06) to detect a decrease of 16 points in the UDI-6 score, a sample size of 32 was needed, with 16 patients in each arm of our RCT. The MCID for the UDI-6 questionnaire is 11 points. Calculating with a dropout rate of 10%, thirty-four women needed to be enrolled. Statistical significance was defined as a P-value < 0.05 using two-tailed tests.

3. Results

3.1. Correlation between the female pelvic floor biomechanical parameters and the severity of stress urinary incontinence

Thirty-one women participated in our study. The mean body mass index (BMI) was 27.6 ± 5.8 kg/m2. Among the participants, 18 patients (58%) were postmenopausal. In terms of incontinence severity assessment, the MESA questionnaire and PGI-S questions were utilized. According to the MESA questionnaire, seven patients (23%) had mild SUI, 15 patients (48%) had moderate, and nine patients (29%) had severe. Although all patients reported symptoms of stress incontinence as their main complaint, if the total score of the urge domain of the MESA questionnaire exceeded two, those patients were classified as mixed incontinence (MUI n = 13, 42%). As per the PGI-S question, eight patients (26%) experienced mild incontinence, while 23 (74%) reported severe incontinence.

Upon conducting a bivariate analysis to evaluate the associations between 52 VTI parameters and the MESA SUI Index, MESA SUI Score, MESA UUI Score, MESA UUI Index, and PGI-S Score, only the following correlations were found to be statistically significant. VTI parameters 4 and 27 displayed a moderate positive correlation concerning the MESA SUI Index and MESA SUI Score (VTI parameter 4 vs. MESA SUI Index r = 0.373, $P = 0.039$; VTI parameter 4 vs. MESA SUI Score r = 0.376, $P = 0.037$; VTI parameter 27 vs. MESA SUI Index r = 0.366, $P = 0.043$; VTI parameter 27 vs. MESA SUI Score r = 0.363, $P = 0.044$). Specifically, parameter 4 represents the maximum value of the posterior gradient, indicating the pressure change per posterior wall displacement in a direction orthogonal to the vaginal channel. Parameter 27 refers to the displacement of the maximum pressure peak in the anterior compartment.

Significant differences were observed when examining the distinction between mild and severe subgroups of SUI based on the PGI-S score. Specifically, VTI parameters 16, 22, 23, 24, 38,

and 39 demonstrated statistically significant differences between these two subgroups. Describing the above, parameter 16 refers to the maximum gradient at the perineal body posteriorly and can be interpreted as the strength of Level III support; parameter 22, 23, and 24 refers to the pressure response of the tissues and muscles behind the left and right vaginal wall; parameter 38 and 39 refers the maximum pressure change and value on the right side at voluntary muscle contraction which can be interpreted as a contraction strength of specific pelvic muscles.

Patients with stress incontinence were categorized according to the severity of incontinence as mild and moderate or severe according to the MESA score, as moderate or severe incontinence is more likely to require medical treatment than mild incontinence. The VTI parameter 49 showed a significant difference between the two groups (VTI parameter 49 in patients with mild SUI according to MESA SUI score vs. VTI parameter 49 in patients with moderate & severe SUI according to MESA SUI score, mean ± SD 14.06 ± 5.16 vs. 7.54 ± 7.46, $P = 0.04$). VTI parameter 49 describes the displacement of the maximum pressure peak in the anterior compartment, which can be interpreted as the mobility of anterior structures at reflex muscle contraction.

3.2 **A randomized controlled pilot trial to assess the effectiveness of a specially formulated food supplement and pelvic floor muscle training in women with stress-predominant urinary incontinence**

Of the fifty women screened, thirty-six met the entry criteria and were randomized. Eighteen women were randomly assigned to the control group and eighteen to the treatment group. Thirty-two women completed the trial. Of the fourteen excluded participants, ten did not meet the inclusion criteria, and four decided not to participate in the trial.

Of the eighteen individuals randomly assigned to the treatment group, two did not complete the trial: one was lost to follow-up, and one withdrew from participation because of a lack of time. Of the eighteen women randomized to the control group, two did not complete the trial: one was lost to follow-up, and one withdrew informed consent before taking any supplement. In total, thirty-six women completed the trial: sixteen in the control group and sixteen in the treatment group.

There were no demographic differences between the two groups.

MESA stress urinary incontinence (SUI) scores were similar between the control and treatment groups (mean ± SD, 15.3 ± 5.5 vs. 13.2 ± 5.0; P = 0.25). Between-group analysis revealed no significant differences between the control and treatment group except for mean change (increase) in vaginal squeeze pressure [(cmH2O, mean ± SD), 5 ± 12 vs. 15 ± 15, P = 0.04] and mean change (decrease) in PGI-S score [(mean ± SD), -0.2 ± 0.9 vs. -0.8 ± 0.8, P = 0.04].

Out of the 52 examined VTI parameters, significantly more parameters improved in the treatment group compared to the control group (11/52 vs. 3/52, P = 0.04). Within-group analysis showed that UDI-6 and IIQ-7 scores improved significantly from baseline to six weeks in the treatment group but not in the control group [UDI-6 score (mean ± SD) 45 ± 21 vs. 29 ± 21, P = 0.02 (treatment group), 43 ± 18 vs. 33 ± 26, P = 0.22 (control group)] [IIQ-7 score before (mean ± SD) 50 ± 30 vs. 30 ± 21, P = 0.01 (treatment group) 48 ± 23 vs.40 ± 28, P = 0.36 (control group)].

Similarly, maximum vaginal squeeze pressure was significantly stronger in the treatment group compared to baseline after six weeks but not in the control group [Maximum vaginal squeeze pressure (cmH2O, mean ± SD), 30 ± 15 vs. 45 ± 28, P = 0.001 (treatment group) and 36 ± 18 vs. 41 ± 21, P = 0.13 (control group)]. PGI-S scores only improved in the treatment group from baseline to six weeks after treatment [PGI-S score (mean ± SD) 3.1 ± 0.8 vs. 2.3 ± 0.8, P = 0.0001].

Vaginal Tactile Imaging revealed that in the control group, only three VTI parameters improved (VTI #6, 10, 49), while in the treatment group, eleven parameters were better (VTI #1,5, 19, 37, 40–46). None of the VTI parameters worsened during the trial. BI-score, on average, improved significantly in the treatment (Fig. 2) and control group as well [SD unit, mean, from − 1.06 to -0.58, P = 0.001 (treatment group) and from − 0.66 to -0.42, P = 0.04 (control group)]. Nevertheless, women in the treatment, on average, improved twice as much in their BI-score as women in the control group (-0.49 vs. -0.24). There was a significant improvement in elasticity and relaxation in the treatment group, while in the control group, only in contraction.

4. Discussion

The aim of this doctoral thesis was twofold: on the one hand, to explore the relationship between the biomechanical parameters of the female pelvic floor and the severity of stress urinary incontinence (SUI), and on the other hand, to examine whether a specially formulated dietary supplement enhances the effectiveness of pelvic floor muscle training. SUI), and secondly, to investigate whether a specially formulated dietary supplement enhances the effectiveness of pelvic floor muscle training (PFMT). The two studies used different methodological approaches, but both aimed to contribute to a better understanding of the pathophysiology of SUI and its non-invasive treatment options.

To our knowledge, we conducted the first study to demonstrate a correlation between the biomechanical parameters of the female pelvic floor and the severity of stress urinary incontinence. Our cross-sectional study found significant differences between SUI severity subgroups classified based on the PGI-S and MESA questionnaires and selected female pelvic biomechanical parameters measured with VTI. SUI is the most common type of UI. To our knowledge, the cause of SUI is significantly more complicated than the often oversimplified theories that assume a single anatomical or neurological injury/lesion during childbirth. These injuries increase the likelihood of stress incontinence, which is influenced by both genetic (tissue strength, mechanical, and anatomical conditions) and behavioral (diet, smoking, and exercise) factors. While the Hammock Hypothesis seeks to explain how observed anatomy relates to vaginal, urethral, and bladder function, Integral Theory perhaps prompts us to consider how anatomy may also contribute to bladder overactivity. There is professional consensus that SUI can generally be attributed to two primary mechanisms: intrinsic sphincter deficiency and urethral hypermobility.

When assessing women with SUI, one of the first steps is to ask the patient to complete validated questionnaires. The MESA questionnaire is a reliable and validated tool

developed as part of the MESA project, an observational study funded by the National Institutes on Aging (NIA) in 1983. Its primary purpose is to identify the urgency or stress-dominant component of MUI and to assess the severity of symptoms. The PGI-S questionnaire uses a 5-point scale to ask the patient about the severity of the condition, which is not specific to incontinence. However, the severity of the condition can be assessed using the scale: in mild cases, the patient scores 1 or 2 points, and in severe cases, 3 or 4 points. In the literature, reports on individual studies have used both questionnaires and test procedures that measure certain biomechanical properties of the vagina or pelvic floor. Mariott et al. used an intravaginal pressure sensor to evaluate vaginal pressure profiles before and after anti-prolapse surgery, while Pires et al. used a perineometer to examine maximum voluntary contractions in female athletes. However, simpler biomechanical parameters can also be measured using a solid-body circular catheter or even the Oxford scale. However, neither method is capable of providing sufficient insight into the biomechanical components of the pelvic floor, which is essential when examining minor deviations or cases with a small number of subjects. As we have shown in the methods section, VTI is capable of measuring appropriate and sufficient biomechanical parameters, as has already been demonstrated in the case of POP. Our study shows a positive correlation between the MESA SUI score and VTI parameters 4 and 27. Parameter 4 refers to tissues/structures in the anterior compartment at a depth of 10-15 mm, while parameter 27 corresponds to the maximum pressure peak displacement in the anterior compartment. These two parameters fit well with urethral hypermobility, which is a common mechanism in the pathophysiology of SUI. Our results suggest that the parameters measured during VTI examination may bring us closer to a personalized understanding of pathophysiology. Since our goal was to examine the relationship between the biomechanical parameters of the female pelvic floor and the severity of SUI, we investigated this question using the PGI-

S and MESA questionnaires. The PGI-S cannot distinguish between different types of incontinence, so we examined all types in the correlations. Accordingly, several biomechanical parameters of the pelvic floor showed significant differences when severity was classified according to the PGI-S, which we interpreted not as an argument against the PGI-S severity versus severity classification, but as a reason for the different pathophysiological background of different types of incontinence. In contrast, when the MESA questionnaire was used to classify the study population according to SUI severity, only the VTI parameter of 49 showed a significant difference between the groups. This parameter may explain the mobility of the anterior structures during reflex muscle contraction, which we interpret as further evidence of urethral hypermobility as a pathophysiological factor.

We were not surprised that the biomechanical parameters of the anterior vaginal compartment correlate with SUI. The proximity of the urethra to the anterior vaginal wall allows for the assessment of vaginal condition using VTI, and it is well known that urethral hypermobility contributes to the pathophysiology of SUI. In contrast, we did not expect a correlation between the biomechanical parameters of the posterior vaginal wall and the severity of SUI. One possible explanation is that general pelvic floor weakness (both anterior and posterior parameters are abnormal) may indicate a generally weaker pelvic floor function, which manifests itself in more severe SUI. The pathophysiology of SUI is not fully understood, and our results suggest that VTI may be useful in the personalized assessment of women with SUI. In addition, VTI technology may help identify biomechanical weaknesses in the pelvic floor that cannot be identified by other methods or urodynamic testing. VTI may further improve the ability to provide appropriately personalized care for SUI patients, thereby increasing the chances of curing this common condition. One of the strengths of our study is that we were the first to examine the

relationship between the biomechanical parameters of the female pelvic floor and the severity of SUI. We used a non-invasive, easy-to-perform method to assess several critical biomechanical properties of the female pelvic floor. Compared to previous methods, such as manometry or vaginal pressure profiling, the new method used in this study provides a much more detailed insight into pelvic floor function due to the use of multiple sensors. Our study has a number of weaknesses that need to be addressed and improved in further studies. The number of participants was relatively low, although sufficient power was available for statistical analysis. In addition, the diagnosis of UI was based solely on questionnaires; no urodynamic testing was performed. The severity of SUI was also not assessed using the pad test, which is often used in research studies but less frequently in everyday clinical practice. A larger, multicenter study would be needed to confirm our findings.

In our second study, we reported on the effects of a specially formulated dietary supplement on urinary incontinence symptoms while study participants performed PMFT. We found that daily intake of the supplement, in addition to regular pelvic floor muscle exercises, performed over six weeks, with a maximum of 45 pelvic floor muscle contractions per day at an intensity of at least 65-75% of one repetition maximum (15 PMF contractions three times a day), Most professional guidelines recommend conservative treatment for first-line management of SUI.

Most professional guidelines recommend conservative treatment as the first-line treatment for SUI. The European Association of Urology (EAU) recommends that all women with SUI be offered supervised intensive pelvic floor muscle training (PFMT) for at least three months as first-line therapy. Similarly, according to the ACOG, voiding therapy and pelvic floor muscle exercises improve urinary incontinence symptoms and can be recommended as a first-line, non-invasive treatment for all women. Although PFMT is widely used, there is no consensus on the number, duration, and intensity of exercises. In our study, we used a set of

exercises similar to those used in the ESTEEM study. This specific amount of PFMT proved to be manageable in terms of adherence to the exercises, while improving UI symptoms. A recent Cochrane review compared PFMT with no treatment and found that PFMT can cure or improve SUI symptoms. Women with SUI were eight times more likely to report a cure in the PFMT group. In addition, vaginal grip strength was used as a marker of pelvic floor function. PFMT has been shown to increase vaginal grip strength and improve UI symptoms. We observed a greater increase in vaginal grip strength in the treatment group, which likely contributed to the improvement in PGI-S change. There are very few publications examining the relationship between nutrition and PFMT, and they focus almost exclusively on the role of nutrition in obesity. We believe that our specially formulated dietary supplement contributed secondarily to the improvement in pelvic floor muscles due to its unique composition. Our key ingredients were creatine, leucine, zinc, calcium, and magnesium. Evidence suggests that creatine supplementation may improve health status as individuals age and may increase strength and/or muscle mass. Increased pelvic floor muscle strength and activity may result in improved urinary function, particularly in women with SUI. Previous studies have shown that long-term creatine supplementation (up to 30 grams of creatine per day for five years) is safe and well tolerated in healthy individuals and the elderly. Along with creatine, leucine was one of the most important components of the supplement. It is directly involved in protein synthesis, as it directly stimulates protein synthesis in muscles, but it has not previously been shown to contribute to pelvic floor muscle strength. Leucine may also prevent age-related muscle weakness, and research has shown leucine to play a beneficial role in enhancing muscle protein synthesis. The third key ingredient in the supplement is zinc. It is essential for connective tissue biosynthesis and homeostasis. It has been shown that zinc levels decline with age, and therapeutic interventions for vaginal atrophy increase vaginal zinc levels. In addition, calcium and

magnesium are critical elements in muscle function for maintaining physical fitness. Altered calcium homeostasis, which is common in older adults, plays a role in increased muscle damage, decreased muscle mass, and decreased muscle contractility, along with oxidative stress. On the other hand, magnesium is involved in protein and ATP synthesis and is responsible for muscle relaxation. A randomized clinical trial showed that elderly women who received a daily magnesium supplement for 12 weeks, in addition to an exercise program, improved their physical performance, suggesting that magnesium supplementation plays a role in maintaining muscle function and delaying sarcopenia. Our results suggest that the unique composition of our dietary supplement, which contains all key ingredients (creatine, leucine, zinc, magnesium, and calcium) in specific ratios, may be partly responsible for the observed beneficial effects on pelvic floor muscle strength and UI symptoms. Our study showed that only three VTI parameters improved in the control group. In contrast, eleven parameters improved in the treatment group, and none of the VTI parameters deteriorated during the study. These results are reassuring and consistent with our clinical findings that women in the treatment group experienced greater improvement in UI symptoms, similar to the improvement in pelvic floor biomechanical integrity. The BI scores of women participating in the treatment improved on average twice as much as those of women in the control group. It is not entirely clear how PFMT improves UI symptoms, but it is likely through improved pelvic floor muscle integrity and coordination. The treated group showed significant improvement in flexibility and relaxation, while the control group showed improvement only in contraction, which is consistent with the actual effect of PFMT through improved muscle function.

The strength of the study lies in its randomized nature and the fact that it is the first study to examine the effect of dietary supplements combined with PFMT in women suffering from stress-dominant UI. An important strength of the study was that the participants were blinded

to the allocations. Another strength of the RCT was that the evaluators performing perineometry, vaginal palpation, and pelvic floor assessment were also blinded to the allocations. In addition, objective measurements of pelvic floor integrity using VTI were supplemented by patients' subjective assessments based on validated questionnaires. Another strength of the study was that our participants reported high adherence to supplement intake and daily PFMT (~90%). The discontinuation rate in the treatment group was similar to that in the control and treatment groups. The main weakness of our study was that it lacked the power to detect differences in several secondary outcomes; overall, we enrolled relatively few women in the study. In addition, we assumed a very large effect size (Cohen d=1.06), which is difficult to achieve in 6 weeks.

A weakness of the study was that urinary incontinence was assessed using validated questionnaires rather than urodynamics or pad tests. Another weakness was the homogeneous, non-diverse study population. Finally, our study does not provide precise insight into the mechanism of action of supplementation. It is possible that the observed effects are secondary to a general improvement in muscle strength rather than a direct effect on the pelvic floor muscles and extracellular matrix.

Overall, my dissertation presented the results of two independent studies that offer a new approach to understanding the pathophysiology and non-invasive treatment of female stress incontinence. The first study demonstrated that pelvic floor biomechanical parameters, particularly in the anterior compartment, are associated with SUI severity. The results of the second study showed that targeted dietary supplementation can enhance the effectiveness of PFMT according to both objective and subjective measures.

Future large-scale, multicenter studies are needed to confirm these findings and to investigate the long-term safety and mechanism of action of nutritional supplements. The integration of VTI-based assessment into clinical practice may offer a new dimension to

personalized SUI care. My research contributes to a deeper understanding of female pelvic floor function and promotes the development of targeted, more effective therapeutic strategies.

5. New scientific findings of the thesis

1. We were the first to prove that biomechanical parameters measured using Vaginal Tactile Imaging (VTI) correlate with the severity of SUI.

2. We demonstrated significant differences in certain VTI parameters between mild and severe SUI groups classified based on the MESA and PGI-S questionnaires.

3. We were the first to define that VTI parameter 4 (maximum posterior gradient value) and parameter 27 (anterior pressure peak displacement) correlate significantly with the MESA SUI score and index.

4. We identified that the VTI parameter 49 (displacement of the maximum pressure peak in the anterior compartment) differs significantly between mild and moderate/severe SUI.

5. Six of the VTI parameters (e.g., 16, 22–24, 38, 39) showed statistically significant differences in the PGI-S subgroups, revealing new correlations between the biomechanical roles of the anterior and posterior pelvic floor segments in SUI.

6. The study opened up new clinical possibilities for the diagnostic application of VTI, as it can provide objective data for personalizing treatment.

7. We conducted the first randomized controlled trial evaluating the effect of a dietary supplement specifically formulated for SUI (creatine, leucine, zinc, calcium, magnesium) in addition to PFMT.

8. Significant improvements were observed in the treatment group in the following areas: Reduction in PGI-S score ($p = 0.0001$); increase in vaginal tightness pressure ($p = 0.001$); improvement in UDI-6 and IIQ-7 questionnaire results; improvement in BI score ($p = 0.001$)

9. There was also improvement in the control group, but the change in BI score was twice as large in the treatment group.

10. Of the 52 biomechanical parameters measured with VTI, 11 improved in the treatment group, compared to only 3 in the control group ($p = 0.04$) – these are the first documented diet-induced biomechanical changes in the pelvic floor.

11. The research also pointed out that nutritional supplementation and PFMT may have a synergistic effect on pelvic floor function.

12. The study demonstrated a safe, well-tolerated, and clinically relevant intervention that represents a new opportunity in the field of non-pharmacological treatment.

6. Certified list of publications on which the dissertation is based and other publications

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Registry number: DEENK/159/2025.PL
Subject: PhD Publication List

Candidate: Erzsébet Koroknai
Doctoral School: Doctoral School of Nutrition and Food Sciences

List of publications related to the dissertation

1. Takács, P., Pákozdy, K., **Koroknai, E.**, Erdődi, B., Krasznai, Z. T., Kozma, B.: A randomized controlled pilot trial to assess the effectiveness of a specially formulated food supplement and pelvic floor muscle training in women with stress-predominant urinary incontinence.
   BMC Womens Health. 23 (1), 1-12, 2023.
   DOI: http://dx.doi.org/10.1186/s12905-023-02476-z
   IF: 2.4

2. **Koroknai, E.**, Rátonyi, D., Pákozdy, K., Sipos, A. G., Krasznai, Z. T., Takács, P., Kozma, B.: Correlation between the female pelvic floor biomechanical parameters and the severity of stress urinary incontinence.
   BMC Urol. 23 (1), 198-204, 2023.
   DOI: http://dx.doi.org/10.1186/s12894-023-01375-7
   IF: 1.7

List of other publications

3. Takács, P., Rátonyi, D., **Koroknai, E.**, van Raalte, H., Lucente, V., Egorov, V., Krasznai, Z. T., Kozma, B.: Biomechanical Integrity Score of the Female Pelvic Floor for Stress Urinary Incontinence.
   Int. Urogynecol. J. 35 (6), 1245-1253, 2024.
   DOI: http://dx.doi.org/10.1007/s00192-024-05797-1
   IF: 1.8 (2023)

4. Rátonyi, D., **Koroknai, E.**, Pákozdy, K., Sipos, A. G., Takács, P., Krasznai, Z. T., Kozma, B.: The impact of short-term pelvic floor muscle training on the biomechanical parameters of the pelvic floor among patients with stress urinary incontinence: a pilot study.
   Eur. J. Obstet. Gynecol. Reprod. Biol. 302, 283-287, 2024.
   DOI: http://dx.doi.org/10.1016/j.ejogrb.2024.09.037
   IF: 2.1 (2023)

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5. Rátonyi, D., **Koroknai, E.**, Takács, P., Krasznai, Z. T., Kozma, B.: A női medencefenék biomechanikai vizsgálata hüvelyi taktilis képalkotás módszerrel.
Magy Noorv Lapja. 86, 267-271, 2023.
6. **Koroknai, E.**, Deli, T., Krasznai, Z. T., Kozma, B.: Postpartum vena ovarica thrombophlebitis és acut appendicitis.
Magy Noorv Lapja. 86, 250-253, 2023.

Total IF of journals (all publications): 8
Total IF of journals (publications related to the dissertation): 4,1

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

25 April, 2025

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