ORIGINAL ARTICLE

THE EFFECTS OF SOY ISOFLAVONES AND HORMONAL REPLACING THERAPY ON THE INCIDENCE AND EVOLUTION OF POSTMENOPAUSAL FEMALE URINARY INCONTINENCE

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Abstract

The objective of our study was to determine the comparative effects of soy isoflavones and low doses of systemic hormonal therapy (SHT) on the evolution and incidence of urinary incontinence in postmenopausal women, who were continent at treatment initiation. This study lasted 12 months and included 215 postmenopausal women who were divided into three groups: the first comprised 78 women treated with soy extract (40% isoflavones); the second group 65 women with continuous combined hormonal preparation based on 1 mg oestradiol and 0.5 mg noretisterone acetate (NETA) p.o. daily; whereas the control group 72 women with no therapy. The *Revised Urinary Incontinence Scale* (RUIS) scores and the incidence of different types of urinary incontinence were determined at 0, 6, and 12 months. Our results showed that neither the first treatment nor the second significantly influenced the time-dependent evolution of these parameters. Therefore, the present study provides pertinent evidence that the two therapies investigated have no effect in preventing female post-menopausal urinary incontinence.

Rezumat

Obiectivul studiului nostru a fost evaluarea comparativă a efectelor unor isoflavone din soia şi terapia hormonală sistemică (THS), administrată în doze mici, asupra evoluţiei şi incidenţei incontinenţei urinare la femei în postmenopauză, continente la iniţierea terapiei. Studiul s-a desfăşurat pe o perioadă de 12 luni şi a cuprins un număr de 215 femei aflate la menopauză naturală, care au fost împărţite în trei loturi: lotul I - 78 de femei, tratate cu extract de soia cu un conţinut de 40% izoflavone, lotul II - 65 de femei, tratate cu un preparat hormonal combinat continuu: 1 mg estradiol şi 0,5 mg noretisteronă acetat (NETA) p.o., zilnic, şi lotul III - 72 de femei, fără terapie, lot de control. Pentru evaluare, s-au utilizat valorile scalei *Revised Urinary Incontinence Scale* (RUIS) şi incidenţa diferitelor tipuri de incontinenţă urinară au fost determinate la 0, 6 şi 12 luni. Rezultatele noastre au arătat că nici unul din cele două tratamente nu influenţează în mod semnifcativ evoluţia în timp a celor doi parametri. Astfel, prezentul studiu furnizează dovezi pertinente că cele două terapii investigate nu au nici un efect în prevenirea incotinenţei urinare postmenopauză la femei.

Keywords: systemic hormonal therapy (SHT), soy isoflavones, post-menopausal, urinary incontinence

Introduction

The female lower urinary tract is sensitive to the effects of oestrogens, due to the estrogenic receptors from the bladder trigone and urethral epithelium, which share a common embryological origin [7]. The biological effects of oestrogen and progesterone during the menopausal hormonal therapy are an important research topic, and as a result, a lot of work has been published regarding this issue [3, 6]. The lack of oestrogens during menopause affects all the oestrogen–sensitive tissues, including the genital and lower urinary tracts and is an essential etiological factor for the urogenital symptoms, following the menopause onset [12]. For example, the lower urinary tract anatomical and physiological changes that accompany this event are intimately involved in increasing the prevalence of urinary bladder symptoms, such as urinary frequency, urgency and incontinence [2, 8].

Urinary incontinence, regardless that we speak about urge incontinence (UUI), overflow incontinence, or stress incontinence (SUI), is a common disease that primarily occurs in elderly women [10], with a peak prevalence being recorded during menopause [11]. It is important to add that as women get older, the indication for SUI surgery decreases [1]. Therefore, it has been anticipated that the substitutive oestrogen therapy may have a positive effect on lower urinary tract symptoms (LUTS), and as consequence, until a few years ago, this

treatment was routinely used for treating the postmenopausal female urinary incontinence [8, 11]. However, a recent review indicates that the positive effects of hormonal therapy on urinary incontinence are rather controversial although its use in treating atrophic vaginitis is well established [11]. In addition, a recent Cochrane [3] and other important studies [7] regarding the systemic hormonal substitution therapy, using conjugated equine oestrogens in monotherapy or combined with progesterone, have concluded that it is associated with a higher risk of urinary incontinence in continent women, and moreover, with the worsening of symptoms in incontinent patients.

In this context, the objective of this work was to assess the effects of some phytochemical substances with oestrogen-like effects (soy isoflavones) on the incidence and evolution of urinary incontinence in post-menopausal women, who were continent at treatment initiation using the low doses of systemic hormonal therapy (SHT) as a comparison benchmark.

Materials and Methods

This research, which is part of a larger study that investigates the effects of hormonal and phyto-oestrogen therapies, in preventing postmenopausal osteoporosis [15], lasted 12 months and included 215 middle-aged postmenopausal women. It was carried out in accordance with the WMA Declaration of Ethical Helsinki – Medical Research Involving Human Principles for Subjects, and approved by the Ethics Committee of the Faculty of Medicine and Pharmacy, University of Oradea, Romania.

The continent patients were randomly distributed in three groups: the first group (ISO) that contained 78 women treated with soy extract (40% isoflavones); the second group (SHT) that comprised 65 women with continuous combined hormonal preparation based on 1 mg oestradiol and 0.5 mg noretisterone acetate (NETA) p.o. daily - Activelle® (NovoNordisk); and a third group (CTR) including 72 women with no therapy, which was used as a control.

The patient's clinical assessment underwent in gynaecologic and orthostatic positions. The Valsalva manoeuvre and the full-bladder coughing test were performed to exclude stress urinary incontinence. The supra-pubic ultrasound examination ruled out the inhabited bladder or the inflammation diagnosis. The valve examination did not find any vaginal wall or cervix lesions. Moreover, the results of urine tests, which were performed for 52% of the treated women, were negative. The assessment for urinary incontinence was completed using an appropriate and specific index, i.e., the Revised Urinary Incontinence Scale (RUIS), which was measured at 0, 6, and 12 months. This short five-element scale derives from the Urogenital Distress Inventory-6 and Incontinence Severity Index (ISI), and was designed and standardized as a urinary incontinence assessment tool, as well as for monitoring the post-treatment results [11]**.** The total RUIS scores were calculated by summing up the scores obtained for each question of the questionnaire. The score increases by one point, once the severity of symptoms rises, subjectively perceived, for each of the 5 items. Total RUIS score ranges between 0 (asymptomatic) and 16 (the most severe symptoms). The interpretation of RUIS scores implies that the scores lower than 4 belongs to patients that do not suffer (do not show) symptoms of a very mild urinary incontinence; the scores between 4-8 indicate a mild urinary incontinence; the scores between 9 and 12 are considered as markers of a medium incontinence; whereas those higher than 13 show a severe urinary incontinence [13].

Statistical analysis was performed by using Statistica 10 software package (Statsoft Inc.). Normality and homogeneity of variance for RUIS scores measured at each time point for each group were verified by using an Anderson-Darling test and a Brown Forsythe test, respectively. If these assumptions were met, a one-way ANOVA was performed to identify differences existing in RUIS scores at each time point, followed by the application of Tukey's HSD tests for post hoc analysis in case of significant differences. Repetitive-measures ANOVA were also used for each treatment to check whether there are significant changes in the temporal evolution of RUIS score. Next, Chi-square ($\chi 2$) tests were conducted at 6 and 12 months to analyse the incidence of different types of urinary incontinence among the groups. A p value < 0.05 was considered significant.

In order to interpret the magnitude of change in RUIS scores at different time points the "effect size" (ES) was measured at each time point using Cohen's *d*.

The interpretation of this index was compiled from the statistical literature, that is: small effect size (ES = 0.20), medium effect size (ES = 0.50), large effect size (E_s = 0.80) [4]. ES is important when expressing the findings of a quantitative study because a p value can identify if there is an effect, but cannot reveal the magnitude of the effect [14].

Results and Discussion

Urinary incontinence affects 15% to 50% of postmenopausal women [6]. In everyday practice, the use of this substitution therapy aimed at improving urinary incontinence symptoms has gradually decreased due to recent studies that changed the wrong positive perception, and moreover, led to the conclusion that this therapy

should not be prescribed for preventing or improving UI [3, 7]. Given the adverse effects and risks associated with SHT, the oestrogen-like substances have been extensively studied in recent years as an alternative to SHT.

Table I

The temporal dynamics of RUIS scores

Study group	Sample size	Month 0	Month 6	Month 12
Isoflavone (ISO)	78	1.71 ± 1.05	1.92 ±1.16	2.28 ± 1.71
Hormonal therapy (SHT)	65	1.75 ± 1.07	2.23 ± 1.52	2.82 ± 2.09
Control group (CTR)	72	1.82 ± 1.04	2.11 ± 1.34	2.53 ± 1.96

Table I shows the mean with ± standard deviation for RUIS scores at different time points, as well as the sample size, for each group examined here. Statistical analysis revealed that the conditions for normality were met for all variables (Anderson-Darling test, in all cases $p > 0.05$). The sample size for all groups was large enough ($n \geq 65$) to provide reliable information when testing the normality. In addition, it is known that for a sample size larger than 30 or 40 the parametric procedures can be used without major problems even when the data are not normally distributed [5]. Moreover, the groups investigated were homoscedastic, irrespective of time point (Brown Forsythe test, month 0: $p = 0.891$; month 6*:* $p = 0.126$; month 12: $p = 0.638$).

During this research, there was no urinary incontinence case with surgical indication recorded. At the start of the experiment, all women were continent, with the highest RUIS scores being observed for the CTR group. However, no significant differences were found among the study groups (ANOVA, $p = 0.801$); this attests to the validity of sampling procedure. At 6 months, the RUIS scores were between 0 and 8, with the patients showing, at most, mild urinary incontinence. At 12 months, however, the measured values ranged from 0 to 12, and the first cases of moderate incontinence were reported, with at least one patient for each group. The RUIS scores that were determined at 6 months for the SHT group were the most elevated, trend which was also seen at the last time point. In contrast, for the ISO group, it remained below that assessed for the control group, and interestingly, the difference between the measured values increased with time. However, there were no significant differences in RUISE scores at both 6 months (ANOVA, $p = 0.383$) and 12 months (ANOVA, $p = 0.253$) although this index increased significantly during the experiment for all treatments (Repeated-measures Anova, ISO: $p < 0.001$; SHT: $p < 0.001$; CTR: $p < 0.001$). Such results provide evidence that both SHT and soy isoflavone administration may not significantly influence the temporal dynamics of urinary incontinence.

The incidence of different types of urinary incontinence is given in Table II, with the highest value being observed for the SHT group at 12 months. No consistent differences were found in the present work among groups at 6 months ($\chi 2$ test, $p = 0.749$) and at the end of the study ($\chi 2$ test, $p = 0.463$). As a result, it appears that there is no consistent effect of either isoflavone administration or SHT on the incidence of urinary incontinence despite the fact that, for the latter group, there is some evidence suggesting a negative impact on it [3, 7]. However, a longitudinal survey on the effects of isoflavones on urinary incontinence in postmenopausal women also did not found any association between the isoflavone in-take and the urinary incontinence incidence [16], thus partially confirming our results.

Table II

Incidence and evolution of the urinary incontinence

Urinary incontinence	ISO group		SHT group		CTR group	
	No.	%	No.	%	No.	%
At 6 months						
Without UI	73	93.59	58	89.23	68	94.44
Mild UI	5	6.41	7	10.77	4	5.56
Moderate UI	0	0	0	0	0	0
At 12 months						
Without UI	68	87.18	52	80.00	62	86.11
Mild UI	9	11.54	11	16.92	8	11.11
Moderate UI	1	1.28	2	3.08	2	2.78

It is important to mention that effect size (ES) was between -0.1 – -0.2, irrespective of time point, more precisely, at 0 months it was -0.11, at 6 months -0.14, and at 12 months -0.13. This corresponds to a small effect size, with the negative values indicating that mean of the ISO group is always lower that those observed for the CTR and SHT group. In studies with a small sample size, the

probability of identifying statistically significant differences among groups worth to be considered only if the effect size is large [14]. Therefore, there are pertinent premises that our results are valid for the population investigated.

This study provides pertinent evidence that SHT and soy isoflavone administration may not influence the temporal trends in incidence and evolution of urinary incontinence in post-menopausal women. Future research must, however, should be conducted on larger population samples to provide a higher statistical power, thus preventing the risk of not detecting a potential effect of SHT and/or soy isoflavone administration on urinary incontinence in postmenopausal women.

Conclusions

Daily administration of the continuously combined hormonal preparation (1 mg oestradiol and 0.5 mg NETA) and of soy extract (isoflavones – 40%) did not show any similarity compared to control group, with a change over time in the evolution of urinary incontinence in postmenopausal women. Similar literature results were also found regarding the incidence of different types of urinary incontinence and their possible therapeutic approaches. Therefore, our results suggest that the both therapies investigated are controversial in preventing female post-menopausal urinary incontinence.

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