Evaluation of the efficacy of dietary supplements based on Equisetum arvense, Soy Isoflavones, Lactoferrin and vitamin D3 on the control of climacteric symptoms

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ABSTRACT

The purpose of our study was to assess the impact of a food supplement of Equisetum arvense, Soy Isoflavones, Lactoferrin and vitamin D3 on climacteric symptoms. Were enrolled 85 patients of which 78 have completed the study. It has been administered to patients the modified Kupperman index (Modified Kupperman Index) and then we evaluated the climacteric symptoms, with the scale Menopause Rating Scale at the beginning of treatment, at 45 days (T45) and 90 days (T90). Statistical analysis showed a reduction in all parameters between T0 and T45, between T0 and T90 and to a lesser degree between T45 and T90. The product has been also evaluated by patients effective and well tolerated. The study shows that supplementation with a herbal and quantitative features such as used by us is effective in controlling the symptoms associated with menopause.

SOMMARIO

Lo scopo del nostro studio è stato quello di valutare l'impatto di un integratore alimentare a base di Equisetum Arvense, Isoflavoni di Soia, Lattoferrina e Vitamina D3 sulla sintomatologia climaterica. Sono state arruolate 85 pazienti di cui 78 hanno concluso studio. È stato somministrato alle pazienti l'indice modificato di Kupperman (Modified Kupperman Index) e poi abbiamo valutato la sintomatologia climaterica con la scala Menopause Rating Scale all'inizio del trattamento, a 45 giorni (T45) e a 90 giorni (T90). L'analisi statistica hpa mostrato una riduzione di tutti i parametri tra T0 e T45, tra T0 e T90 e in minor parte tra T45 e T90. Il prodotto è stato inoltre valutato dalle pazienti efficace e ben tollerato. Lo studio dimostra che l'integrazione con un fitoterapico con le caratteristiche quali e quantitative come quello usato da noi è efficace nel controllo dei sintomi associati al climaterio.

Keywords: menopause, climacteric, lactoferrin, isoflavones, Equisetum

INTRODUCTION

Climacteric represents the transition from fertile to menopause and it is due to a progressive depletion of ovarian function. This results, in addition to the known alterations of the menstrual cycle, in varied and multi-organ symptoms. The climacteric is marked by physiological and psychological changes that may impact heavily on the woman's life, sometimes affecting his social relations. It is characterized by the presence of vasomotor symptoms (VMS, hot flashes and night sweats), bone loss, urogenital atrophy of the mucosa, as urinary tract infections and urinary incontinence, increased cardiovascular risk, somatic symptoms and sexual dysfunction with decreased libido[(1)]. The social cost of the climacteric is high if we consider, for example, that bone mass is reduced, on average, of 1-2% year after menopause and that about 25% of postmenopausal women have severe osteoporosis and 50% of women not taking oestrogen will suffer a bone fracture in the course of life[(2)]. The impact of climacteric symptoms has gained importance with the rise in life expectancy of women, since they can expect to spend a significant part of their lives after menopause. This period should be a time highly productive and the maintenance of functional capacity and a good quality of life is of utmost importance. In recent years, following the publication of the Million Women Study (MWS) the use of hormone replacement therapy has decreased significantly[(3-4)] and clinicians have tried to avoid using preparations soy isoflavones[(5)] and other herbal components with the objectives of reducing autonomic symptoms associated with menopause. Among the herbal ingredients scientifically recognized for comprehensive management of symptoms literature arises from time attention on soy isoflavones. As amply demonstrated Soy isoflavones have the important property of binding the ER-beta oestrogen receptor expressed predominantly on the vaginal mucosa, on the heart and bone tissue. Given the specific affinity for the beta oestrogen receptor, isoflavones may be considered natural selective modulators (SERMs) so treatment with these drugs may be useful to control vasomotor symptoms associated with perimenopause and menopause, to improve the serum lipid profile and the metabolism of the bone tissue[(6-8)].

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Supplementation with vitamin D3 (Vit D3) plays a key role on the stabilization of the bone. It is known as the dominant function of vitamin D3 is related to the elevation of plasma calcium and phosphate levels, necessary for bone mineralization. Vitamin D3 stimulates the absorption of calcium especially at the level of the duodenum and jejunum and acts on the distal renal tubule ensuring greater retention of calcium itself. It is also demonstrated an effect of immunoregulation mediated by Vit D3, in which calcitriol apparently promotes the proliferation of regulatory T cells and their accumulation in the sites of inflammation[9].

Equisetum arvense, rich in silicon, it is known in the literature to reduce osteoclast activity as to be suggested in the bone regeneration[10].

Our study evaluated the integration of soy isoflavones (from Glycine max), vitamin D3, silicon and lactoferrin.

Lactoferrin stimulates the proliferation and differentiation of osteoblasts, and on the other hand inhibits osteoclasts. In addition, lactoferrin may act on bone cells through the inhibition of osteolytic cytokines such as TNFa, IL-1β and other cytokines that increase in concentration during the inflammatory processes. For these properties, lactoferrin can be used as a regulator for the control of bone physiology and supplementation of lactoferrin may thus help to improve the bone mineral density and bone strength[11-13].

MATERIALS AND METHODS

The study was conducted at the U.O. of Gynecology and Obstetrics of Montevarchi in collaboration with the study group consisting of: Gabriele D'Egidion MD; Gabriella Scorpio MD; Giovanni Cavallo MD - Gynecology and Obstetrics U.O. of Modica (RG). After acquisition of adequate informed consent were recruited 85 women in these centers. The criteria for inclusion and exclusion are shown in Table I. The patients were subjected to a preliminary test for the evaluation of climacteric symptoms using the modified Kupperman index (Modified Kupperman Index) as shown in Table II[14]. The patients were given a dietary supplement of soy isoflavones, lattofferrina, vitamin D3 and Equisetum arvense with the compositions shown in Table III. The product was recommended at a dose of one tablet per day for a total of ninety days. The patients were subjected to the evaluation of the clinical symptoms at baseline (T0), after 45 days (T45) and after 90 days (T90) using the scale Menopause Rating Scale, Table IV[15].

Tolerability to treatment was investigated asking to indicate the degree of nothing, poor, fair, good and excellent to 90 days (T90).

The efficacy perceived by patients was investigated asking them how they judged it at T90 in terms of: excellent, good, fair, poor or null.

RESULTS

Were included 85 postmenopausal women from 43 to 63 years (mean: 51.3 ± 3.6 years); of these 78 have concluded the study. All subjects included had a normal physical examination. Among the subjects included 15 patients out of 85 (17.6%) were taking drugs. Among those who completed the survey that number stood at 13 of 78 (16.6%).

In particular:

- 8 taking drugs for thyroid disease (6 excluding the drop-out)
- 1 was taking drugs for thyroid disease, anti-inflammatories and antioxidants
- 3 taking drugs for hypertension
- 1 took steroids (0 excluding drop-out)
- 1 took steroids and metamizol
- 1 had undergone hormone replacement therapy

The Kupperman index of the included patients

Table I:
Inclusion and exclusion criteria.

INCLUSION CRITERIA
Outpatients aged between 45 and 55 years of age
Perimenopause with oligomenorrhea and autonomic symptoms associated
Patients with index of Kuperman between 15-35
Informed consent to participate in the study
EXCLUSION CRITERIA
Ongoing treatment with hormone replacement therapy, with products similar pharmacological effect or individual components to similar action
Diseases compromising the cooperation of patients for evaluation (cognitive deficits, psychiatric illness, alcoholism, drug abuse)
Diabetes mellitus
Renal insufficiency (serum creatinine> 2.0 mg / dl)
Severe hepatic impairment (GOT and / or GPT> 2 times the upper limit of normal)

Table II:
Modificated Kupperman Index.

Name:						**Date:**	
Which of the following symptoms apply to you at this time? Please provide the raw score according to the severity of each symptom. For symptoms that do not apply, please fill in "0"							
SYMPTOMS	**WEIGHTING FACTOR**	**SEVERITY SCALE**				**SCORE**	
		0	1	2	3	RAW SCORE	WEIGHTED SCORE
Sweating hot flusches	X4	None	<3 times/day	3-9 times/day	≥10 times/day		
Paresthesia	X2	None	Relationship with climate	Fell tingling, burning, pricking or numbness frequently	Lose sense of warm and pain		
Insomnia	X2	None	Once in a while	Frequent need sleping pill	Affects life and work		
Nervousness	X2	None	Once in a while	Frequent	Frequent, cannot control		
Melancholia	X1	None	Once in a while	Frequent, can self-control	Losing faith in life		
Vertigo	X1	None	Once in a while	Frequent	Affects daily life		
Fatigue	X1	None	Once in a while	Fell difficult when climbing the 4th floor	Affects daily life		
Arthralgia myalgia	X1	None	Once in a while	Frequent, not affecting function	Affects function		
Headache	X1	None	Once in a while	Frequent	Requires treatment		
Heart palpitation	X1	None	Once in a while	Frequent, not affecting daily life	Requires treatment		
Formication	X1	None	Once in a while	Frequent	Requires treatment		
Sexual complaints	X2	Normal	Reduced libido	Sexual problems	Loss of Libido		
Urinary tract infection	X2	None	Once in a while	More than 3 times per year, not requiring medication	More than 3 times per year, needing medication		
Notes: Raw score, severity score of each symptom; weighted score, raw score x weighting factor; total score, sum of the weighted score. Classification of the modified Kupperman Index is "no complaint" (total score 0-6), "mild" (total score 7-15), "moderate" (total score 16-30) or "severe" (total score >30)							

Table III:
Composition of phytotherapic used.

Average content of ingredients characterized by daily amount	
components	1 tablet
Equisetum arvense dry extract 10% Intake of silica	400 mg 40 mg
Glycine Max dry extract 40% Intake of soy isoflavones	200 mg 80 mg
Lactoferrin tit. min 90%	100 mg
Vitamin D3	0.02 mg

Table IV:
Menopause Rating Scale (MRS).

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

was on average 25.3 ± 5.0, with values between a minimum of 15 (1 case) and a maximum of 35 (1 case). For statistical analysis of the results we used the software STATISTICA 12 (StatSoft, Inc. 2013). To test the differences in the questionnaire MRS (Menopause Rating Scale) at T0 and T45, T0 and T90 and T45 and T90 has used the Wilcoxon signed-rank test for paired samples, nonparametric test that does not use the media and does not require additional assumptions of normal distribution.

In Tables V-VII shows the averages (used for the graphic representation 1 and 2), the number of non-null differences used for the test, and the significance (p) of the observed differences between T0 and T45 (Table V), between T0 and T90 (Table VI) and between T45 and T90 (table VII).

Scores MRS have been reported on the chart number 1 while the graph number 2 we reported MRS scores at T0, T45 and T90 grouped by group of symptoms (somatic, psychological and urogenital).

The tolerability of phytotherapic was investigated asking to indicate the degree in terms of: poor, fair, good and excellent. For 53.9% of the patients tolerability was excellent, it was good for 32.9%, discrete for 9.2% and low only for 3.9%. The data are shown in Figure 3.

Regarding the perception efficacy the food supplement in the T90 patients have assigned the following ratings: excellent (51.3%), good (31.6%), moderate (10.5%), poor (5.3%) or null (1.3%). The results are reported in Figure 4.

Statistical analysis shows that between T0 and T45 all variables showing differences extremely significant. Almost all p values are <0.001; exception Question 9 (bladder problems) that still gives rise to a p of about 0.003, which it is also significant.

Between T0 and T90 all variables showing differences extremely significant. It is also repeated here the partial exception of the application 9, which still gives a value of p = 0.0012 slightly greater than 0.001.

Between T45 and T90, the situation is slightly more varied than the previous tables, with some differences non significant, a significant difference at the 5% (question 5, irritability) and other extremely significant, well over 1%.

The results of this third test, compared with the previous two, could indicate that in some cases (applications 5,6,9) treatment effects were already achieved after 45 days and that little has changed after another 45, which intuitively can be confirmed by comparing the average response to these questions.

DISCUSSION.

The results show how the use of a food supplement with the qualitative and quantitative characteristics of the one we used has an important role on climacteric symptoms. In particular, it shows that the impact on both the somatic symptoms, psychological on the urogenital manifest already after 45 days of use. This benefit persists over time and is implemented, albeit slightly to 90 days. The degree of compliance to the integration with the product was high with about 80% of the patients participating in the study which was considered tolerable between very good and good.

This percentage corresponds to the number of patients who considers the product efficently with a grade between excellent and good in controlling the climacteric symptoms.

In conclusion, climacteric is even more a crucial period for the psychological well-being of women and is a social duty and therapeutic to address complaints related to it. The compliance of patients to hormone replacement therapy in recent years has decreased substantially while alternative therapies have made their way especially based on herbal remedies. The literature abounds with studies on the rational use of food supplements for the control of climacteric disorders. Unfortunately, few studies have been conducted evaluating the effectiveness of the integration with products based on active principles. In particular, for example, would be useful studies to assess the impact of these products on the bone profile of the patients and on cardiovascular risk in the long term. These, however, require a long period of observation, and a considerable economic cost to perform examinations and laboratory control.

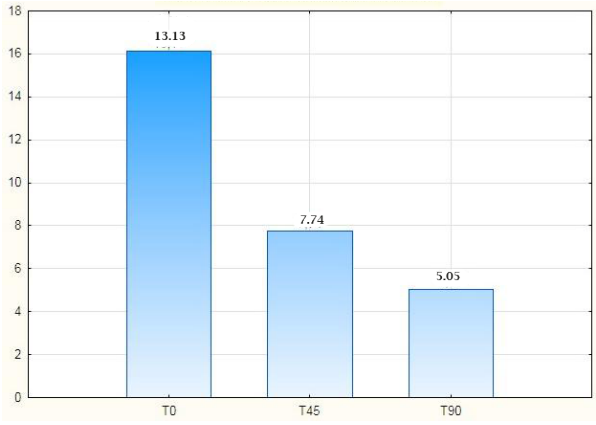

Figure 1: *MRS Score - media at T0, T45, T90.*

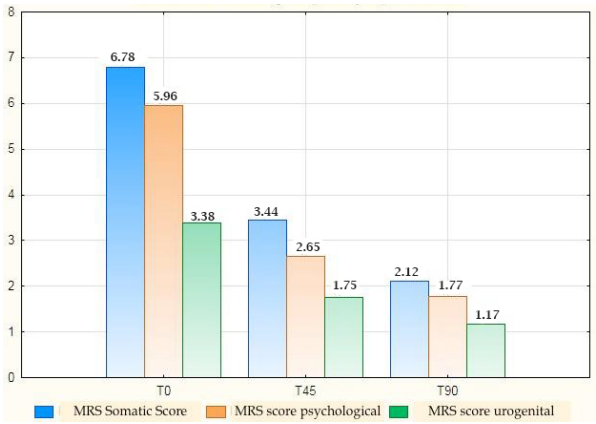

Figure 2: *Score for the group of symptoms.*

Table V*:*
MRS score Significant differences at T0 and T45.

Item MRS (score 0-4)	Media T0 (N=78) (*)	Media T45 (N=78) (*)	Number of difference non-null	P (Test di Wilcoxon)
1. Hot flushes, sweating (episodes of sweating)	2.23	1	70	<0.001
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	1.15	0.58	34	<0.001
3. Sleep problems (difficulty in falling asleep, diffi culty in sleeping through, waking up early)	1.94	0.96	57	<0.001
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	1.46	0.71	48	<0.001
5. Irritability (feeling nervous, inner tension, feeling aggressive)	1.51	0.69	49	<0.001
6. Anxiety (inner restlessness, feeling panicky)	1.41	0.51	50	<0.001
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	1.58	0.74	49	<0.001
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	1.5	0.68	40	<0.001
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	0.59	0.31	22	0.0031
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	1.29	0.67	41	<0.001
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	1.46	0.9	37	<0.001
Somatic MRS score (sum of items 1,2,3,11)	6.78	3.44	70	<0.001
Psychological MRS score (sum of items 4,5,6,7)	5.96	2.65	34	<0.001
Urogenital MRS score (sum of items 8,9,10)	3.38	1.65	57	<0.001
MRS total score (sum of all 11 items)	16.13	7.74	48	<0.001

Table VI:
Significant differences MRS at T0 and T90.

Item MRS (score 0-4)	Media T0 (N=78) (*)	Media T90 (N=78) (*)	Number of difference non-null	P (Test di Wilcoxon)
1. Hot flushes, sweating (episodes of sweating)	2.23	0.64	75	<0.001
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	1.15	0.32	49	<0.001
3. Sleep problems (difficulty in falling asleep, difficulty insleeping through, waking up early)	1.94	0.53	66	<0.001
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	1.46	0.38	57	<0.001
5. Irritability (feeling nervous, inner tension, feeling aggressive)	1.51	0.51	57	<0001
6. Anxiety (inner restlessness, feeling panicky)	1.41	0.4	50	<0.001
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	1.58	0.47	57	<0.001
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	1.5	0.47	45	<0.001
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	0.59	0.24	23	0.0012
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	1.29	0.45	49	<0.001
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	1.46	0.63	43	<0.001
Somatic MRS score (sum of items 1,2,3,11)	6.78	2.12	77	<0.001
Psychological MRS score (sum of items 4,5,6,7)	5.96	1.77	74	<0.001
Urogenital MRS score (sum of items 8,9,10)	3.38	1.17	61	<0.001
MRS total score (sum of all 11 items)	16.13	5.05	77	<0.001

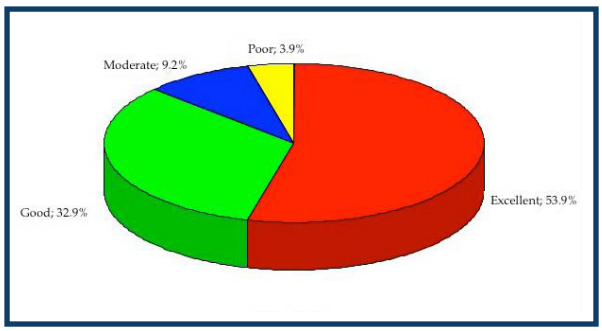

Figure 3: *Tolerability.*

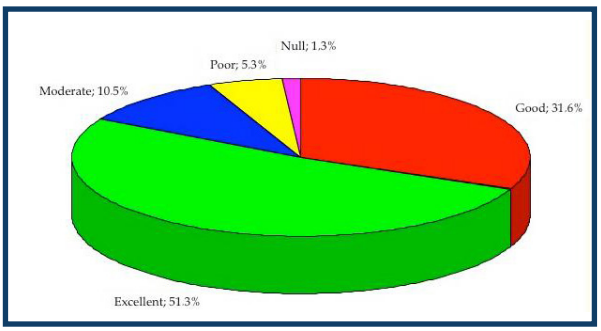

Figure 4: *Efficacy.*

Table VII:
MRS score Significant differences at T45 and T90.

Item MRS (score 0-4)	Media T45 (N=78) (*)	Media T90 (N=78) (*)	Number of difference non-null	P (Test di Wilcoxon)
1. Hot flushes, sweating (episodes of sweating)	1	0.64	26	<0.001
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	0.58	0.32	20	<0.001
3. Sleep problems (difficulty in falling asleep, diffi culty insleeping through,wakingupearly)	0.96	0.53	31	<0.001
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	0.71	0.38	29	<0.001
5. Irritability (feeling nervous, inner tension, feeling aggressive)	0.69	0.51	22	0.0162
6. Anxiety (inner restlessness, feeling panicky)	0.51	0.4	18	0.0777
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	0.74	0.47	26	0.0012
8. Sexual problems (change in sexual desire, in sexualactivity and satisfaction)	0.68	0.47	16	0.0018
9. Bladder problems (difficulty in urinating, increa sed need to urinate, bladder incontinence)	0.31	0.24	9	0.1386
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intecourse)	0.67	0.45	20	0.0042
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	0.9	0.63	24	<0.001
Somatic MRS score (sum of items 1,2,3,11)	3.44	2.12	57	<0.001
Psychological MRS score (sum of items 4,5,6,7)	2.65	1.77	50	<0.001
Urogenital MRS score (sum of items 8,9,10)	1.65	1.17	30	<0.001
MRS total score (sum of all 11 items)	7,74	5,05	65	<0,001

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