

The Efficiency of Phytoestrogen Therapy in Patients with Natural Menopause

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Phytoestrogens are compounds of vegetal origin exhibiting estrogenic activity, both agonist and antagonist. Phytoestrogens seem to have increased affinity for the β-estrogen receptor class. This aspect is of particular relevance to organs rich in β receptors, such as coronary arteries and the brain. Phytoestrogens are low estrogen-like estrogens, their activity in human cell cultures being 500-fold weaker than estradiol. Hormonal therapy is beneficial in postmenopausal women, taking into account the results validated over time by observational studies, and is being discussed as primary prevention in cases without coronary artery disease at the age of 50 years under 60 years old and 10 years after the onset of menopause. For elderly women, the therapy is individualized, the benefit being dependent on age and the recommended dose. Menopausal hormone therapy has been shown to be effective especially for relieving climacteric symptoms, long-term effects on cardiovascular disease being still under study.

Keywords: menopause, oestrogens, hormone therapy

Estrogen is a hormone that plays an extremely important role in developing and enhancing the feminine qualities. Although this hormone is also produced by men's body, it is met in large quantities in the women's body, being considered a hormone of femininity [1]. Estrogen causes the development of breasts, pelvis and lack of facial hair. In women, estrogens are mainly synthesized in the ovaries and placenta during pregnancy. Liver, breasts and adrenal glands can contribute to the synthetisation of this hormone, but in small amounts. The level of estrogen secreted by the body depends mainly on two other hormones: LH (luteinizing hormone) and FSH (folliculostimulant hormone) from the hypothalamus. Blood gonadotropin levels are controlled by sex hormones (estrogen, progesterone, testosterone etc.) through negative feedback to the hypothalamus. This is why mental stress leads to the occurrence of a hormonal imbalance in the body [2-3].

Women, when reaching menopause, are predisposed to fluctuations of estrogen. A low level of estrogen can cause fatigue, osteoporosis and even depression. The increased level of this hormone, on the other hand, can cause cramps and insomnia. To combat this fluctuation, doctors sometimes prescribe non-steroids, which help maintain an optimal level of estrogen in the body, but they can have serious side effects [4].

Menopause, by modifying the hormonal profile (mainly by lowering estrogen hormones), is a risk factor in the development of atherosclerosis. Endothelial dysfunction plays a key role both in the pre-lesional and lesional stages of atherosclerosis [5].

Endothelial dysfunction induced by dyslipidemia, especially by oxidized LDL, is the first step in the initiation and evolution of the atherogenic process [6].

The decrease of estrogens in the menopause leads to a change in the lipid profile, with increases in triglycerides, total serum cholesterol, LDL cholesterol and lower HDL cholesterol (with an anti-atherogenic protective role) [7-9].

Studies have already shown that in the natural and surgical menopause the atherosclerotic process is based on endothelial damage caused by altered lipid metabolism. Hormonal treatment, mainly by ingesting estrogen, positively influences lipid metabolism and thereby decreases the risk of cardiovascular disease [5].

Today there is scientific evidence that estrogen has effects on almost all systems and apparatuses of the female body [10-11]. Because of this, various symptoms have been associated with decreased estrogen which occurs in menopause. It is important to emphasize that not all symptoms occur to any woman, but there are some that have a higher frequency, such as vaso-motor and urogenital symptoms [12-14].

Purpose and objectives

With all the immediate and long-term consequences of estrogenic deprivation, menopause is an important public health issue with social, personal and economic impact.

If immediate menopausal symptoms are sometimes noisy, the long-term, insidious consequences, especially cardiovascular and bone, are of major importance.

In order to eliminate trouble some symptoms and prevent long-term consequences, in order to provide a good quality of life for women in menopause, it is nowadays unanimously recognized that hormonal therapy is necessary in the context of respecting some recognized indications and contraindications and in the rigorous following of the therapy effects.

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One of the main objectives of the clinical trial was to evaluate the lipid and carbohydrate profile in natural menopause and the effects of hormonal therapy. The evolution of climacteric symptomatology under treatment was also observed.

Experimental part

Materials and methods

Study groups. 83 patients with natural menopause, split in three groups:

Group I - 37 patients with natural menopause treated with Activelle (1 mg estradiol + 0.5 mg norethisterone acetate);

Group II - 22 patients with natural menopause fed with natural phytoestrogens;

Group III - 24 patients in untreated natural menopause.

Group I was made of women in menopause for at least 1 year, for which the incidence of bleeding was one of the main reasons why they were accepted in the study. They were recommended to get Activelle: 1 tablet daily, containing 1 mg of estradiol + 0.5 mg norethisterone acetate.

For group II, the treatment with natural phytoestrogens consisted of changing the diet based on the consumption of:

- nuts and oily seeds (sunflower and flax seeds);

- soya and soybean derivatives (for example tofu);

- isoflavone that can be found in the largest quantities in soya and red clover and lignans consumed from flax seeds.

Group III was made of women in menopause for at least 1 year, who do not get hormonal treatment.

We chose this because in the North-Eastern part of Romania, the plants that are rich in phytoestrogens have been used for centuries in treating menstrual problems and menopause, then we followed the clinical and paraclinical evolution of the patients under Activelle treatment (group I) in comparison with the administration of natural phytoestrogens (group II) or in the absence of a hormonal treatment (group III), in order to find a possible

answer to the question *Should the food be medicine or should the medicine be food?*

Study inclusion criteria: Anamnestic amenorrhea for at least 1 year; absence of hormonal treatment for at least 1 year.

Each patient had a chart filled in with information about: age, home, smoking, alcohol consumption, anthropometric data, heredo-collateral history, personal physiological and pathological history, timing of menopause, previous hormonal treatments, clinical symptomatology, paraclinical evaluation, type of menopausal treatment.

At the onset of the study, the presence of climacteric symptoms was evaluated and the following measurements were performed: waist, weight, blood pressure measurement; full clinical and genital examination; Pap smear; echography for measuring endometrial thickness; evaluation of lipid metabolism parameters: total serum cholesterol, triglycerides, LDL cholesterol, HDL cholesterol; blood glucose, TGP, haemoglobin; EKG; mammography and osteodensitometry.

Hormonal estrogen therapy. Estrogen administration is the main way to treat menopause [15-19].

Through follow-up visits (V0), 6 months (V6), 12 months (V12) and 24 months (V24), the patients were followed for 2 years.

Statistical analysis. Retrospective study. The data were selected from the observation sheets and processed using the statistical functions of the SPSS 18.0

Results and discussions

The patients' age varied from 40 to 62, with no significant differences of the mean age for the study groups analysed (table I).

The patients from the analysed groups came mainly from cities and towns, were married, graduated from high-school, with a reduced degree of obesity ($p>0.05$) (table 2).

Among the identified heredo-collaterals we noted (fig. 1):

Table 1
STATISTICAL INDICATORS OF
THE PATIENTS' AGE
COMPARATIVELY ON STUDY
GROUPS

Group	Mean	Std dev.	Std Err.	Min	Max	IC95%	Variant %	Median
I	51.70	4.89	0.80	40	62	49-54	9.46	52
II	51.68	2.55	0.54	48	58	50-53	4.94	51
III	52.13	3.13	0.64	45	56	50-55	6.00	52

Table 2

THE STRUCTURE OF THE GROUPS BASED ON EPIDEMIOLOGIC CHARACTERISTICS

Characteristics	Group I (n=37)		Group II (n=22)		Group III (n=24)		p
	n	%	n	%	n	%	
Urban environment	34	91.9	21	95.5	24	70.8	0.851
Married	29	78.3	19	86.4	23	95.8	0.799
High-school studies	33	89.2	17	77.3	14	58.3	0.867
Obese	7	18.9	2	9.1	3	12.5	0.900

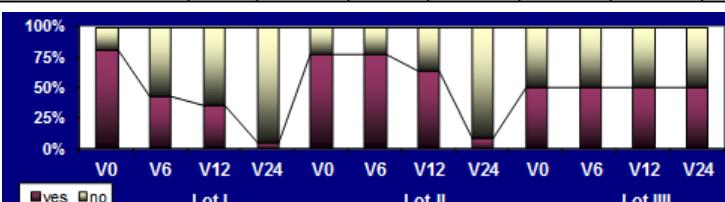
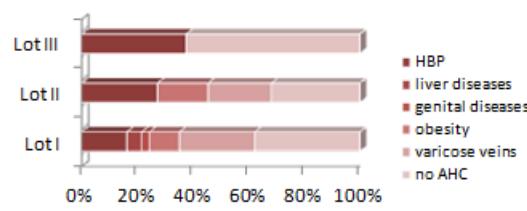


Fig. 2. The presence of hot flashes during monitoring

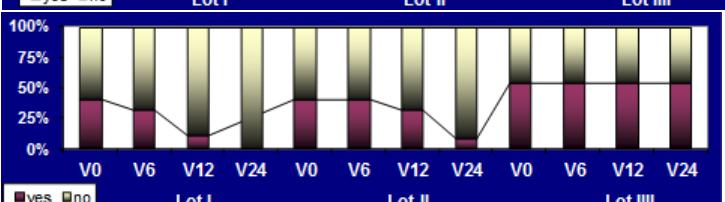


Fig. 3. The presence of migraines during monitoring

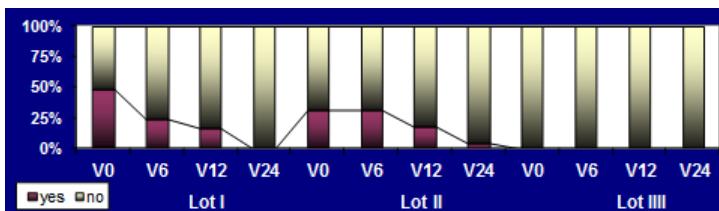


Fig. 4. The presence of asthenia during monitoring

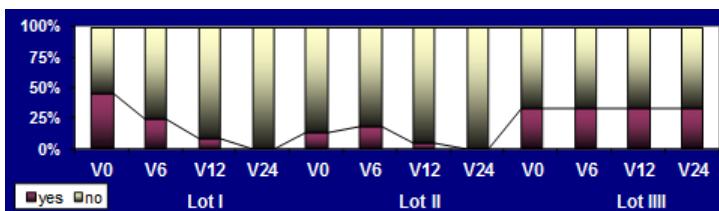


Fig. 5. The presence of insomnia during monitoring

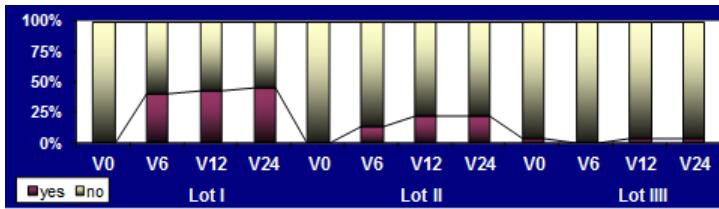


Fig. 6. The presence of libido during monitoring

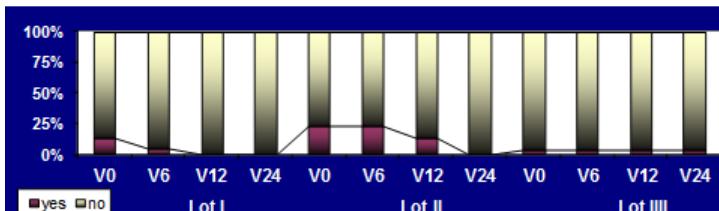


Fig. 7. Presence of vaginal dryness during monitoring

-for group I, 25% varicose veins and about 15% hypertension (HBP);

-in group II HBP is predominant (27%) and also varicose veins (23%);

-for group III we found only HBP in 35% of the monitored patients.

The age of natural menopause in the group treated with Activelle (lot I) ranged from 1 to 10 years with a very wide range of values (71.02%) and a mean of the group of 3.57 ± 2.53 years. In the lot fed with natural phytoestrogens (lot II), the age of menopause varied between 1-6 years, the mean of the lot being of 2.45 ± 1.37 years, significantly lower compared to the patients in lot I ($p=0.041$).

In patients treated with synthetic estrogens there was an increased frequency of hot flashes, migraines, asthenia, insomnia, reduced libido and vaginal dryness. Hormonal therapy removes all these symptoms and, in addition to the immediate improvement in the quality of life, exerts a long-term protective role on the risks of osteoporotic fractures, cardiovascular disease and the risk of Alzheimer's disease (figs. 2-7).

Regarding the climacteric symptomatology in natural menopause, we have to mention the following:

- at the start of the study, hot flushes dominated the patients proposed for hormone treatment ($p=0.033$), asthenia ($p=0.0007$);

- after 6 months of treatment, it was noted: increased asthenia ($p=0.038$).

After 12 months, in hormone treatment groups, particularly in the Activelle group, the hot flashes decreased significantly ($p=0.024$), and so did migraines ($p=0.001$) and vaginal dryness ($p=0.035$) and libido appeared more frequently ($p=0.002$).

After 24 months, in the symptoms of patients in hormone treatment groups, the frequency of hot flashes was significantly reduced ($p=0.001$) and also migraines ($p=0.001$); insomnia disappeared ($p=0.001$) and the libido

frequency increased ($p=0.001$), data comparable to those in the literature [20].

In menopause, estrogen deficiency leads to changes in lipid profile, with atherogenic potential, hormone therapy having the role of cardiovascular protection [21-22].

It is considered today that, with the exception of absolute contraindications and taking into account the necessary precautions in a number of general illnesses, 80% of women could benefit from hormonal therapy. For the control of menopausal symptoms, hormonal therapy given for up to 5 years is appropriate, with a prolongation for another 5 years, if the symptom recurs at interruption. Hot flushes, palpitations, insomnia and psychological problems improve after estrogen therapy for 3 months in 90% of cases [23-25].

During the 2-year follow-up, serum total cholesterol, triglycerides, LDL and HDL cholesterol were evaluated every 6 months (table 3), as well as glycemic, transaminase and hemoglobin levels (table 4).

In patients with natural menopause, hypercholesterolemia is an atherogenic risk factor due to estrogen deficiency.

Total serum cholesterol values decreased after treatment, as follows:

- in the Activelle group from 196.95 mg / dL to 146.49 mg / dL;

- in the group of patients with natural phytoestrogens from about 202 mg / dL to 149 mg / dL;

- in the group of untreated natural menopause, the evolution of mean total cholesterol had an increasing trend during monitoring ranging from 165.83 mg / dL to 189.17 mg / dL.

The highest mean triglyceride values are observed in the untreated group, which shows the importance of estrogens in triglyceride metabolism.

The evolution of mean triglyceride values during monitoring was significantly reduced in the groups of hormone-treated menopausal patients ($p<0.05$):

Group	V0	V6	V12	V24
Cholesterol total, mg/dl				
I	196.95 ± 40.64	179.68 ± 45.75	160.54 ± 40.96	146.49 ± 38.75
II	201.68 ± 33.44	187.73 ± 44.50	167.73 ± 46.39	148.64 ± 41.67
III	165.83 ± 30.63	176.25 ± 23.37	183.33 ± 22.00	189.17 ± 21.85
Triglyceride, mg/dl				
I	132.10 ± 55.86	124.58 ± 41.83	115.32 ± 34.93	104.59 ± 28.79
II	115.50 ± 42.75	116.45 ± 43.31	110.18 ± 40.11	103.81 ± 35.41
III	105.40 ± 56.14	98.35 ± 42.06	101.04 ± 46.65	95.28 ± 35.06
LDL cholesterol, mg/dl				
I	121.86 ± 33.24	122.32 ± 36.32	111.19 ± 34.19	102.27 ± 32.31
II	126.95 ± 30.83	115.73 ± 29.81	107.73 ± 26.37	95.91 ± 24.23
III	91.67 ± 25.14	102.92 ± 21.56	111.25 ± 22.32	117.08 ± 22.16
HDL cholesterol, mg/dl				
I	54.20 ± 17.60	58.95 ± 14.40	65.84 ± 11.93	71.41 ± 11.80
II	57.36 ± 19.66	63.45 ± 16.57	66.41 ± 12.17	69.91 ± 8.96
III	44.17 ± 6.02	46.04 ± 7.94	43.92 ± 7.95	41.08 ± 8.04

Group	V0	V6	V12	V24
Glycemia a jeun, mg/dl				
I	90.67 ± 19.54	90.95 ± 7.69	91.03 ± 5.44	90.08 ± 5.30
II	101.68 ± 10.75	94.51 ± 5.73	92.00 ± 6.13	91.18 ± 5.18
III	93.38 ± 4.48	96.71 ± 7.30	101.33 ± 10.98	103.08 ± 8.16
TGP, UI/l				
I	23.90 ± 7.78	25.52 ± 9.21	25.70 ± 9.41	25.86 ± 8.55
II	23.77 ± 8.45	21.55 ± 1.84	21.14 ± 1.17	21.09 ± 1.19
III	27.71 ± 3.38	28.67 ± 3.21	28.79 ± 3.40	29.21 ± 3.45
Haemoglobin, g/ml				
I	11.70 ± 0.75	11.30 ± 0.77	11.26 ± 0.69	11.26 ± 0.65
II	11.80 ± 1.09	11.40 ± 0.58	11.18 ± 0.50	11.09 ± 0.53
III	12.00 ± 0.26	11.70 ± 0.46	11.31 ± 0.46	11.21 ± 0.41

Table 3
MEAN VALUES OF LIPID METABOLISM
PARAMETERS IN STUDY GROUPS

-for the group of patients with natural menopause, treated with Activelle from values of 132.10 mg/dL to 104.59 mg/dL;

-for the group of patients with natural menopause with phytoestrogens in their diet from about 116 mg/dL to 103.81 mg/dL;

-in the group of patients with untreated natural menopause, the evolution of mean triglyceride values had an increasing trend during the monitoring ranging from 149.20 mg / dL to 167.50 mg / dL.

Regardless of the type of menopause, LDL cholesterol records significant decreases in mean values in the hormone treated groups:

-for the group of patients treated with Activelle from values of 121.86 mg/dL to 102.27 mg/dL;

-for the group of patients treated with natural phytoestrogens from 126.95 mg/dL to 95.91 mg/dL;

-for the group with no treatment, in natural menopause, the evolution of the mean values of LDL cholesterol had an increasing trend.

It is known that LDL, by its oxidized form, plays a key role in the pre-lesional stage of atherosclerosis. Consequently, the results of the study demonstrated the protective role of treatment in cardiovascular prevention in patients with natural menopause. Van der Mooren's studies (1994) show this relationship: hormonal treatment - reducing LDL cholesterol.

The mean HDL cholesterol values increased significantly in the hormone treated groups ($p < 0.05$), as follows:

-for the group of patients with natural menopause, treated with Activelle from values of 54.20 mg/dL to 71.41 mg/dL;

-for the group of patients with natural menopause treated with natural phytoestrogens from 57.36 mg/dL to 69.91 mg/dL;

HDL cholesterol has an anti-atherogenic role, being involved in cardiovascular protection.

Hormone-treated patients showed increases in HDL cholesterol, demonstrating the beneficial effect of hormone therapy, as literature proves.

It is noteworthy that in the group of untreated natural menopause patients the evolution of mean HDL cholesterol had a decreasing trend during the monitoring, ranging from 44.17 mg / dL to 41.08 mg / dL, which shows the lack of the protector effect of estrogen in this context.

Average blood glucose levels decreased in all treatment groups. In the group of patients without hormonal therapy, significant increases in mean blood glucose levels occurred after 2 years of follow-up.

During monitoring, the hormone-treated natural menopausal consignments showed significant increases in mean TGP values; the exception was the group treated with natural phytoestrogens.

Haemoglobin decreased in all investigated groups; after 2 years of treatment the mean values of haemoglobin become homogenous on study groups (11.09-11.37 g/mL).

Conclusions

The patients started therapy in less than 5 years from the debut of menopause, thus respecting the window of opportunity.

The moment when the treatment began was around the age of 50 years old.

The patients who consumed natural phytoestrogens had a normal body weight, while the patients treated with synthetic phytoestrogens were overweight.

The treatment with phytoestrogens, be they synthetic or natural, brought an improvement of the debut symptoms: flushes, migraine, asthenia, insomnia, reduced libido and vaginal dryness. The climacteric symptomatology resolved under treatment.

Under hormonal treatment changes in the lipid profile with a cardiovascular role have been obtained by the anti-atherogenic effect of total cholesterol lowering.

Patients with or without natural menopause treated with phytoestrogens recorded significant decreases in mean haemoglobin.

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