

# HORMONE REPLACEMENT THERAPY'S EFFECT ON CARDIOVASCULAR RISK FACTORS

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**Abstract:** Background: hormone replacement therapy (HRT) is still a controversial therapy, its effects over cardiovascular system being contradictory. Methods and material: we evaluated the HRT's effects on cardiovascular risk factors on a 238 women (38 with and 200 without HRT) sample, between April 2007 and April 2008. For every woman, we investigated the cardiovascular risk factors' presence. Results: at the beginning, the prevalence of smokers was greater in women with HRT and those without HRT were more frequently hypertensive. After a year, we do not recorded statistical significant differences between the two groups regarding the prevalence of diabetes mellitus, overweight, obesity, smoking, or hypertension. Conclusion: even if we can not say for sure that HRT is influencing in a direct way the cardiovascular risk factors, we registered favorable changes of those, an important step being represented by the recognition of cardiovascular risk. In the same time, we did not registered important differences regarding the evolution of risk factors.

**Keywords:** hormone replacement therapy, cardiovascular risk

**Rezumat:** Terapia de substituție hormonală (TSH) reprezintă, cel puțin până în prezent, o terapie controversată, efectele sale asupra aparatului cardiovascular fiind contradictorii. Metodă și material: Am evaluat efectele TSH asupra factorilor de risc cardiovascular pe un eșantion compus din 238 de femei (38 cu și 200 fără TSH) în perioada aprilie 2007-aprilie 2008. Inițial și la evaluarea de la un an, s-a investigat prezența sau absența factorilor de risc cardiovasculari. Rezultate: Inițial, procentul subiectelor fumătoare a fost mai ridicat în rândul celor cu terapie de substituție hormonală, în timp ce procentul celor hipertensive a fost mai ridicat în rândul celor fără substituție. La reevaluare, nu am înregistrat diferențe semnificative din punct de vedere statistic între cele două grupuri (cu vs fără terapie de substituție) în ceea ce privește prevalența diabetului zaharat, supragreutății, obezității, atenuându-se și diferențele existente anterior. Concluzie: Chiar dacă nu se poate afirma cu certitudine influența directă a TSH asupra unor factori de risc cardiovasculari, s-a constatat modificarea favorabilă a acestora, o componentă importantă fiind reprezentată și de conștientizarea

riscului cardiovascular, dar nefiind înregistrate diferențe notabile pe evoluția factorilor de risc.

**Cuvinte cheie:** terapie de substituție hormonală, factori de risc cardiovascular

## INTRODUCTION

Background: the presence of estrogen hormones, being in relationship with both women's risk factors (as birth control or menopause), but also with anti-atherosclerotic protection, displaces ischemic manifestation after the age of 55. Many studies have been made in order to decide if the effect of hormone replacement therapy (HRT) is favourable or not, the effects being different depending on the moment of therapy's initiation. There are some studies which showed favourable effect of HRT, **Error! Reference source not found.** but in the same time, the combatants of this theory (like WHI, HERS studies).(2,3,4) Further analysis of previous studies reveals new facts, accentuating the importance of timing of HRT's initiation, but also the importance of patient's approach way.(5) Thus, whereas these pros and cons of hormone replacement therapy, the controversy is still open.(6) Even an editorial published in New England Journal of Medicine **Error! Reference source not found.** had shown that important clinical questions regarding hormone replacement therapy's use are still without answers, studies like ELITE, KEEPS being capable and responsible to give future answers.

The purpose of present study was to determine the hormone replacement therapy's impact on cardiovascular risk factors.

## METHODS

We studied 238 women (38 with, and 200 without hormone replacement therapy) between April 2007 and April 2008, mean age 55.66±7.9 years. We considered as hormone replacement therapy any kind of estrogenic treatment (conjugate estrogen, estradiol, estropipat) conjugated or not with progesterone, but also estrogen receptors' modulators (as raloxifen). Birth control pills or just progesterone alone were not considered as hormone replacement therapy. HRT was prescribed by gynaecologist or by endocrinologist. We studied menopausal women (with natural or post

## CLINICAL ASPECTS

surgical menopause), without cardiovascular disease. Data about weight, height, heredocolateral antecedents, smoking habit, educational status, blood pressure, plasma lipids values, glycaemia and ECG were collected. Uncomplicated hypertension was not registered as a cardiovascular disease, being considered a cardiovascular risk factor. All the patients were evaluated two times - at the beginning of the study and a year later.

The data was analyzed using SPSS 8.0 for Windows. We calculated mean and standard deviation for normal distributed quantitative variables. Differences between quantitative variables were examined using Student test (paired or not paired), and for qualitative variables we performed  $\chi^2$  test. A p value less than 0.05 was considered significant from statistical point of view.

### RESULTS

Mean age of hormone replacement therapy women was  $49.13 \pm 5.39$  years of age, in comparison with  $56.90 \pm 7.7$  registered in those without hormone replacement therapy. At the beginning of the study, no significant statistical difference was registered between two groups (with vs without HRT) regarding mean values of glycaemia ( $97.15 \pm 18.96$  vs  $106.72 \pm 34.98$ ,  $p=NS$ ), total cholesterol ( $213.76 \pm 39.27$  vs  $215.18 \pm 43.02$ ,  $p=NS$ ), LDL-cholesterol ( $136.84 \pm 35.16$  vs  $131.79 \pm 41.02$ ,  $p=NS$ ), HDL-cholesterol ( $46.81 \pm 12.80$  vs  $47.26 \pm 10.64$ ,  $p=NS$ ) or seric triglycerides ( $146.52 \pm 75.52$  vs  $147.99 \pm 59.81$ ,  $p=NS$ ). Also, we did not register significant differences regarding the prevalence of diabetes mellitus (13.2% vs 16%,  $p=NS$ ), dyslipidemia

(84.2% vs 77%,  $p=0.396$ ), overweight (28.9 % vs 41%,  $p=NS$ ) or obesity (31.6% vs 47%,  $p=NS$ ). Instead, the smoking women percentage was significantly higher in HRT group (23.7 % vs 6%,  $p=0.002$ ), while the hypertension was met more frequently in those without HRT (50% vs 74%,  $p=0.006$ ).

At the second evaluation, no significant statistical differences were registered between the two groups (with vs without HRT) regarding prevalence of diabetes mellitus (25% vs 21.5%,  $p=NS$ ), dyslipidemia (75% vs 73%,  $p=NS$ ), overweight (50% vs 35.6%,  $p=NS$ ), obesity (31.3% vs 49.2%,  $p=NS$ ), smoking habit (6.3% vs 6.3%,  $p=NS$ ) or hypertension (50% vs 37.7%,  $p=0.424$ ). No differences between the two groups regarding mean values of total cholesterol, LDL-cholesterol, HDL-cholesterol, or seric triglycerides were recorded.

In the same time, in HRT group, we noticed an increased prevalence of diabetes mellitus (in 2007 13.2% vs 25% in 2008,  $p=0.425$ ) - more important than that one registered in women without HRT (in 2007 16% vs 21.5% in 2008,  $p=NS$ ) - of overweight patients' prevalence (in 2007 28.9% vs 50% in 2008,  $p=0.212$ ), but also the reduction in smoking prevalence (in 2007 23.7% vs. 6.3% in 2008,  $p=0.249$ ), and in dyslipidaemia prevalence (in 2007 84.2% vs 75% in 2008,  $p=0.459$ ). In turn, in no replacement therapy group, no significant evolution of cardiovascular risk factors was registered, excepting the changing in hypertension prevalence (in 2007 74% vs 37.7% in 2008,  $p<0.001$ ). Synthesizing, the both groups' characteristics are presented in.

**Table no. 1: Characteristics of patients – in 2007, respectively 2008**

	Initially			After a year		
	With TSH	Without TSH	p	With TSH	Without TSH	P
Age (years)	49.13±5.39	56.90±7.7	<0.05			NS
Weight (kg)	71.92±14.91	77.7±13.04	0.015	73.00±14.95	78.61±13.62	NS
Height (cm)	161.29±5.74	161.45±6.22	NS	161.06±7.25	161.71±5.87	NS
BMI (kg/m <sup>2</sup> )	27.65±5.77	29.82±5.13	NS	28.04±4.92	30.11±5.1	NS
Glycaemia (mg %)	97.15±18.96	106.72±34.98	NS	97.62±33.09	97.03±21.92	NS
Total cholesterol (mg %)	213.76±39.27	215.18±43.02	NS	216.18±32.4	205.61±41.28	NS
HDL (mg %)	46.81±12.80	47.26±10.64	NS	52.12±8.04	56.54±34.91	NS
LDL (mg %)	136.84±35.16	131.79±41.02	NS	126.81±37.65	130.85±40.49	NS
Triglyceride (mg %)	146.52±75.52	147.99±59.81	NS	155.43±88.89	143.98±51.91	NS
Diabetes mellitus (%)	13.2	16	NS	25	21.5	NS
Dyslipidemia (%)	84.2	77	NS	75	73.3	NS
Overweight (%)	28.9	41	NS	50	35.6	NS
Obesity (%)	31.6	47	NS	31.3	49.2	NS
Smoking habit (%)	23.7	6	0.002	6.3	6.3	NS
HBP (%)	50	74	0.006	50	37.7	NS

## DISCUSSIONS

Cardiovascular diseases represent the first mortality cause in women(8)(9)(10)(11)(12)(13)(14), in Europe, almost 55% from women's registered deaths being due to cardiovascular disease, in particular to ischemic heart disease and stroke. The number of cardiovascular deaths is exceeding the sum of next seven death causes.(9)

Menopause is responsible for a change in cardiovascular risk profile characterized by changes in lipids metabolism (high triglycerides, low HDL-cholesterol), changes in fat distribution,(15) impaired fasting glucose, growing of sympathetic tone, and appearance of endothelial dysfunction.(16)

Whereas these realities, it has been tried to find new possibilities to reduce cardiovascular mortality and morbidity, especially in postmenopausal women, one of these being the hormone replacement therapy. At the beginning, HRT was used for relief of menopausal symptoms (such as sweating, hot flashes, sleeping disorders, and urogenital troubles), (17) but, for a while, it was also suggested that HRT can play an important role in influencing cardiovascular mortality and morbidity.

New evidences revealed that HRT's effects are complex: being involved in reducing blood pressure and norepinephrine's values (if the therapy is started soon after first symptoms of menopause),(18) influencing lipid profiles (growing HDL-cholesterol, lowering LDL-cholesterol)(19,20,21,22), determination of a lower subclinical cardiovascular disease's prevalence and coronary calcification, **Error! Reference source not found.** reducing in a significant way the number of cardiovascular events in younger women (less than 10 years after first symptoms of menopause)(5). But, in the same time, HERS (2,3) and WHI (4) studies have shown no influence on primary or secondary prevention of cardiovascular events in HRT women, the total risk being significantly greater than the benefits.

However it seems that hormone replacement therapy's benefit can be under the influence of the moment of starting therapy, but also of its length (the efficiency being greater in younger women, with recent installation of menopause) (23,24). Considering these new evidences (pro, but also against), the controversy is still open 6), hormone replacement therapy's action mechanism is not completely known.

The analyses of our sample showed that, at the first evaluation, the two subgroups were comparable, being differences only regarding smoking prevalence (greater in HRT group) and hypertension prevalence (greater in no HRT group). So, the cardiovascular risk profile did not differ significantly in the two groups, showing that cardiovascular risk factors' evolution and cardiovascular risk changes under hormone replacement therapy can be – in postmenopausal women – edifying about the HRT's effect on cardiovascular risk, but also about HRT's value in cardiovascular primary prevention.

Previous studies have shown favourable influence on lipid profile of hormone replacement

therapy, HRT being responsible for HDL-cholesterol growing and LDL-cholesterol lowering (19)(20)(21)(22). In agreement with these, we registered an improvement of lipid profile in HRT women (decrease of LDL-cholesterol, increase of HDL-cholesterol, diminish of dislipidemic patient percentage's), while, in non-HRT women, even if we recorded a favourable tendency in HDL-cholesterol and triglycerides mean values, no reduction in dislipidemic patient's percentage was noticed.

In accord with Pentti's study which showed that HRT patients present a lower body mass index (BMI) (25), on our sample, women submitted to HRT had presented, at one year evaluation, a lower BMI (even if not significant difference was present). On the other hand, if in HRT group increased the overweight women's percentage, in non-HRT group we found a raise in obese women's percentage.

On our sample, we found a reduction in hypertension prevalence in non-HRT women, being however constant in HRT women.

Regarding smoking prevalence, in women with HRT it decreased from 23.7% to 6.3% and in women without hormone replacement therapy it increased in a not significant way (from 6% to 6.3%). This finding supports the idea of indirect benefic influence of HRT on smoking habit, an effect probably derived from awareness of postmenopausal increasing cardiovascular risk. The results are in accordance with literature, being known that smoking prevalence decreases when women are submitted (for a long period, especially over 5 years) to hormone replacement therapy ().

Unlike other studies (showing that HRT has a favourable effect on glycaemic control (26)(27)(28)(29)), on our sample prevalence of diabetes mellitus significantly increased in women with hormone replacement therapy (from 13.2% to 25%). On the other hand, the prevalence maintained at an approximate same value in non-HRT group (16% in 2007 vs 21.5% in 2008). We do not have a clear explanation of this raising, being probably in relationship with previous cardiovascular high risk of these women.

Globally, analyzing the obtained data, we can say that, even if we can not affirm for sure the direct influence of HRT on cardiovascular risk factors, we established a favourable evolution of those, an important part being represented by the awareness of cardiovascular risk. Likewise, no significant differences were registered regarding the cardiovascular risk factors' evolution in menopausal women, no matter of one-year treatment taken (with or without HRT)

This fact is in concordance with literature, showing that in cardiovascular primary prevention the results of using HRT are not spectacular, HRT being recommended neither in cardiovascular disease primary prevention, nor in cardiovascular disease secondary prevention.(10)

Limits of the study are represented by the small sample of women taking HRT (due to their preconceived

ideas about HRT's effects, but also to the prohibitive costs), numerical difference between the two groups (the reasons being already exposed).

## CONCLUSION

The effects of hormone replacement therapy are very diverse, not fully understood, and despite of theoretical premises, in clinical practice, with no significant success in reducing the cardiovascular risk. As a consequence, at least for the moment, HRT will not be indicated to postmenopausal women just for a cardiovascular preventive goal.

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