Menopausal complaints, oestrogens, and heart disease risk: an explanation for discrepant findings on the benefits of post-menopausal hormone therapy

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There is a large discrepancy between the findings of observational and experimental studies on the effects of post-menopausal hormone therapy (HT) and coronary heart disease risk. Observational studies, mainly comprising peri-menopausal women, report risk reductions up to 30–50%, whereas the experimental studies, comprising elderly women, do not show coronary protection. Suggested explanations are methodological differences, such as confounding or healthy user bias, incomplete capture of early events, the stage of atherosclerosis at the start of HT, formulation or dose of HT, or early susceptibility to thrombotic events. We propose that the presence of climacteric complaints determines the susceptibility to hormone replacement therapy. Climacteric complaints are the main indication for HT in the population, whereas in the clinical trials women with climacteric complaints were either explicitly excluded or comprised only a minority of the total randomized population. There is some, albeit circumstantial evidence to support this hypothesis. Women with climacteric complaints of sweating not only appear to have lower levels of serum oestradiol, but also lose more bone than women without climacteric complaints. Consequently, sweating episodes may indicate potential benefits from HT. It has also been reported that hot flushes during menopause correlate with a higher level of oxidative stress and an increased cardiovascular reactivity to stressful situations. We suggest epidemiological approaches to test our hypothesis.

Oestrogens and coronary heart disease

Most women in westernized societies die of coronary heart disease (CHD). Importantly, pre-menopausal women are at lower risk than men of comparable age and post-menopausal women. Protection by endogenous oestrogens has long been considered a likely explanation for this risk difference. Around menopause, oestrogen levels decline by ∼80%. Early menopause, caused by bilateral oophorectomy, leads to an increased risk of cardiovascular disease in younger women, but not when supplementation with HT is given.[1,2] Observational studies support the hypothesis that longer duration of exposure to endogenous oestrogens decreases cardiovascular disease risk.[3] Recently, data from the Women's Ischaemia Syndrome Evaluation (WISE) study provided further evidence that low serum oestradiol levels increase risk of coronary artery disease also in pre-menopausal women.[4] These and other findings suggest that increasing oestradiol levels in post-menopausal women through hormone therapy (HT) will result in a cardioprotective effect of hormonal therapy in post-menopausal women. However, the data are not consistent.

Discrepancies between findings of observational and experimental studies

Extensive data from observational studies support a beneficial effect of HT on the occurrence of CVD in post-menopausal women, amounting to a risk reduction of 35–50%.[5–7] Moreover, observational data in women who have experienced a cardiac event or a coronary intervention are concordant with the data from healthy women on HT.[8]

There are plausible mechanisms for cardiovascular protection in HT-users. With respect to cardiovascular risk factors, oestrogen alone or in combination with a progestagen improves lipoprotein levels to the pre-menopausal state. No significant changes in blood pressure, insulin levels, and fibrinogen have been found.[9] However, oral administration of oestrogens increases levels of triglycerides and VLDL of which the clinical significance is less clear. The net balance of effects on thrombotic and fibrinolytic factors

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by HT-use is a two–three-fold increased risk of thromboembolic events, especially in the first year of treatment.[10] Direct oestrogenic effects on the vessel wall comprise a rapid activation of the nitric oxide synthesis in endothelial cells.[11] In small experimental studies, intravenous administration of 17-oestradiol caused direct vasodilatation in healthy women and in women with atherosclerotic disease.[12,13] However, cumulative data indicate a near-doubling of C-reactive protein with various forms of HT, including conjugated equine oestrogen or oestradiol, with or without a progestin, but not with transdermal oestrogen,[14] potentially promoting vascular inflammation and plaque instability[15] making it difficult to predict the net effect on clinical endpoints from all these mechanistic studies.

The number of women required to demonstrate reductions in risk in a trial is large because in spite of its importance as a cause of morbidity and mortality, heart disease rates in healthy post-menopausal women are still low. Consequently, to increase efficiency in trials, populations are sought with a higher disease risk, notably women with pre-existing CHD. In 1998, the results of the first large randomized trial on HT, the Heart and Estrogen/ progestin Replacement Study (HERS) were reported. HERS enrolled 2763 post-menopausal women with established coronary disease, younger than 80 years, and with an intact uterus. Women were treated with either 0.625 mg of conjugated equine oestrogens plus 2.5 mg of medroxyprogesterone acetate or placebo. After a follow-up of on average 4.1 years, there were no significant differences between groups in the incidence of myocardial infarction or CHD death, relative hazard (RH), 0.99 and 95% confidence interval (CI), 0.80–1.22.[16]

Soon after HERS, more groups published findings of clinical trials studying clinically manifest cardiovascular endpoints, such as WEST[17] and ESPRIT.[18] A number of studies reported on intermediate or surrogate endpoints, such as coronary angiography[19–21] or carotid itima media thickness,[22,23] but only one of these demonstrated overall benefits of HT on clinical event rate or the progression of atherosclerosis.[23]

The Women's Health Initiative trial (WHI) was a randomized controlled primary prevention trial in which 16 608 post-menopausal women aged 50–79 with an intact uterus at baseline were recruited by 40 US clinical centres between 1993 and 1998. Participants received conjugated equine oestrogens, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day, in one tablet ($n = 8506$) or placebo ($n = 8102$). After a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of oestrogen plus progestagen vs. placebo, because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic including all endpoints indicated risks exceeding benefits. Unexpectedly, in the WHI, the estimated hazard ratio (HR) for CHD was 1.29 (nominal 95% confidence interval 1.02–1.63) with 286 cases.[24] The WHI also compared unopposed CEE with placebo in 10 739 post-menopausal women, aged 50–79, with prior hysterectomy. The primary outcome was CHD incidence (non-fatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects. In February 2004, this trial was also stopped early, because the burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit [HRs (95% CI) for CEE vs. placebo for the major clinical outcomes after an average follow-up 6.8 years] were CHD, 0.91 (0.75–1.12) with 376 cases and global index, 1.01 (0.91–1.12). This study yielded an unexpected reduced risk of breast cancer [HR 0.77 (95% CI 0.59–1.01)].[25] The recently published Million Women Study confirmed the increased breast cancer risk reported for opposed HT,[26] indicating that HT is not suitable as a preventive agent in all elderly women.

Explanations for the discrepancy

Several explanations for the discrepancy between the findings of the observational studies and the trials have been postulated. Methodological flaws could have hampered the observational studies. In observational studies, women who use HT are usually more healthy and health conscious than non-users.[27,28] This imbalance could have led to an overestimation of the beneficial effects and an underestimation of the risks associated with HT-use.[29] An important disadvantage of many prospective studies is their limited ability to identify clinical events that occur early after the initiation of the therapy, especially when information on the determinant is only gathered at baseline. Selective follow-up of women that benefit from HT may lead to artefactual results.[30]

Also, pharmacological differences have been suggested as a cause of the discrepancy. In the trials, mainly conjugated equine oestrogens are used in combination with a continuous regimen of medroxy progesterone acetate, whereas in the observational studies, many women used conjugated equine oestrogens only or in a cyclic combination with medroxy progesterone acetate.[30,31] Therefore, although the regimes were sometimes different, the compounds are merely the same. The dosage may play a critical role here; whereas for early post-menopausal women 0.625 mg of conjugated equine oestrogens and 2.5 mg of medroxyprogesterone acetate are an adequate dose, half of this dose might be safe for late post-menopausal women and seems equally effective in reducing cardiovascular risk.[7] Furthermore, the number of years since menopause differs substantially between women in the observational studies and women in the trials, with younger women dominating in the observational studies. On the one hand, the women enrolled in the trials may therefore have had a more advanced stage of atherosclerosis, and it has been suggested that a healthy endothelium is necessary for beneficial effects of oestrogens. In rabbits, it was shown that oestrogen benefits were reversed in the presence of endothelial damage.[32] Monkeys with a shorter interval between ovariectomy and initiation of HT showed a 50–70% reduction in the progression of atherosclerosis, whereas monkeys with a longer lag between ovariectomy and HT showed no benefit of replacement therapy.[33] Also in women, atherosclerosis abrogates the effect of HT on vasodilation.[34] On the other, the most important difference between women using HT in trials and HT in real life is that outside trials women tend to receive HT because of a reason, e.g. for an indication. The most common indication is menopausal

complaints. None of the trials has included women on the basis of the presence of this indication, and frequent presence of menopausal complaints was an exclusion criterion for the trials because it was a hard treatment indication. Women enrolled in the observational studies will usually have started HT because they experienced menopausal complaints.

Hypothesis

We hypothesize that the presence of climacteric complaints determines a woman's susceptibility to the benefits of hormone replacement therapy. There is suggestive circumstantial evidence to support this hypothesis.[35] A small study in 40 peri-/post-menopausal women aged 45–56 found that women with climacteric complaints of sweating not only had lower levels of serum oestradiol, but also had a lower forearm bone mineral density than women without climacteric complaints.[36] Furthermore, these women gained more in BMD when they started HT than did the women who started HT, but did not have complaints of sweating. In multivariate analyses, sweating was an independent predictor of bone loss, even with serum oestradiol concentration in the regression model. It has been suggested that sweating episodes indicate the need for HT.[36,37]

The results of two Spanish studies indicate that hot flushes during menopause are associated with a lower level of total plasma antioxidant activity, and an increased stress induced electrodermal activity or cardiovascular reactivity to stressful situations.[38,39] The effect of hot flushes on total plasma antioxidant capacity could be reversed by HT, again an indication that women suffering from complaints might benefit most from HT. Still, these studies were very small and do not permit definitive conclusions. Preliminary analysis of the WHI data could confirm or exclude the hypothesis due to the small number of cases in the subgroups of women with menopausal complaints.[40] However, the combined evidence from two large, similar cohorts representing the experience of over 4000 healthy, younger post-menopausal women with menopausal complaints[41,42] revealed a low incidence of CHD and other vascular events within the first year of HT-use.[43]

Testing the hypothesis

Our hypothesis could be tested in a well-defined large cohort study of peri-menopausal women, where detailed information is gathered relating to climacteric complaints, most importantly sweating and flushes, and with several years of follow-up for clinical cardiovascular events. Such a cohort should be sought in countries where HT is not prescribed to the majority of women with menopausal complaints. Associations between HT-use and CHD risk can be stratified for women with and without menopausal complaints, and the statistical significance of the interaction can be tested in a regression model. As we do not really know what the true mechanism of 'menopausal complaints' is, it is difficult to select women on more objectively defined intermediate measurements, such as levels of serum oestradiol, bone mineral density, or total plasma antioxidant activity. However, several cohorts are available that gathered precise information on which menopausal complaints

were suffered, most importantly being sweating and hot flushes, and in which frequency.

Smaller randomized intervention studies with HT, stratified for presence of menopausal complaints, could learn us about the mechanisms of action by studying various endpoints, such as cardiovascular risk factors, vessel wall reactivity, and measures for generalized atherosclerosis, which include carotid intima–media thickness or coronary calcium scores as assessed with computed tomography scanning. A randomized placebo-controlled trial with CHD endpoints in women suffering from menopausal complaints will provide the final answer, but requires substantial numbers of participants and follow-up time.

Conclusion

The hypothesis that menopausal complaints are a marker for susceptibility to beneficial effects of HT provides an explanation for the discrepancy between the findings of observational studies and the clinical trials regarding the cardiovascular protective effects of HT.

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