Oestrogen and the cardiovascular system

Nitric oxide (NO), a potent vasodilator, has cardioprotective effects, including regulation of blood flow and inhibition of platelet aggregation. In vascular endothelium, oestrogens increase synthesis of NO and expression of NO synthase (NOS) [1]. In this issue of Clinical Science, Teerlink et al. [2] report the results of a long-term controlled trial in healthy postmenopausal women, which showed that oestrogen replacement therapy with oral conjugated equine oestrogen (CEE) produced an 8% decrease in plasma levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NOS, but had no effect on the levels of the inactive symmetric dimethylarginine (SDMA). The decrease in ADMA was consistent over 2 years of CEE therapy and was not observed in either the placebo-treated group or in the group given the selective oestrogen receptor modulator (SERM) raloxifene.

The effect of CEE on ADMA adds to our understanding of the mechanisms of oestrogenic effects on the cardiovascular system. How does oestrogen produce this effect? The authors [2] suggest that oestrogens may decrease ADMA levels indirectly via an effect on oxidized low-density lipoprotein (LDL), leading to decreased inhibition of the enzyme dimethylarginine dimethylaminohydrolase, which hydrolyses ADMA, but not SDMA. Another possibility is that the changes in ADMA might be mediated by changes in circulating or tissue levels of homocysteine. There is now strong supporting evidence for a role of ADMA in homocysteine-induced impairment of the NO synthesis pathway [3–5]. The study by Teerlink et al. [2] does not report changes in either oxidized LDL or homocysteine levels. Although it is a bit premature for the authors to conclude that ADMA is ‘a cardiovascular risk factor’, the ability of CEE to induce changes in ADMA points towards a potentially important pathway for modification of the vascular NO system.

There have been many studies, with various surrogate end points, suggesting beneficial effects of oral oestrogens on the cardiovascular system [6–8]. Endothelial dysfunction occurs in the development of atherosclerosis [6] and endothelial functional markers correlate with cardiovascular outcomes [9]. ADMA concentrations have also been shown to correlate with the risk of acute coronary events in a prospective case-control study in men [10]. However, there are significant pitfalls in extrapolating from surrogate markers directly to the clinical setting. This is perhaps best exemplified by the effects of oral oestrogens on the cardiovascular system. Oral oestrogens improve lipid profiles [11]. It is tempting to extrapolate from oestrogenic effects on surrogate end points, especially those as robust as lipid profiles, to net clinical benefit. However, oestrogen has pleiotropic effects on the cardiovascular system that are complex, including both beneficial and adverse effects. Adverse effects include coagulation activation, as well as increases in inflammatory markers [12,13]. The net effect of oral combined oestrogen therapy is a small, but significant, increase in cardiovascular events, as well as unwanted effects on the reproductive system, including a small increase in breast cancer risk [14,15].

The potential to selectively induce beneficial effects of oestrogen, via receptor modulation or non-receptor actions, while avoiding the adverse effects, is perhaps the most enticing area in current research into the cardiovascular effects of sex steroids [8]. Teerlink et al. [2] have demonstrated yet again how the effects of a SERM, in this case raloxifene, can differ from those of oestrogen [16]. Raloxifene decreases osteoporotic fractures, but prothrombotic effects persist [17]: its cardiovascular effects are yet to be clarified. Development of future generations of SERMs are aimed at improving selectivity to induce oestrogenic benefits and exclude adverse effects. These advances are awaited with interest [17]. Unravelling the various vascular effects of oestrogens and SERMs and the interactions with oxidized LDL, homocysteine and the NO system may yet lead to new therapeutic approaches to the management of cardiovascular disease.

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REFERENCES


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