Estrogens and Cardiovascular Disease in Men

To the Editor:

The role of estrogens in the prevention of cardiovascular disease is currently of particular interest. Recently, Wenger[1] reviewed various randomized clinical trials to assess the effect of hormone replacement therapy in cardiovascular disease and concluded that postmenopausal hormone therapy does not prevent clinical cardiovascular events in healthy women or women with heart disease. The question remains to be fully resolved, however, since the effect of treatment with estrogens at an earlier stage, at different dosages, or via other routes of administration is still not known. Clinical and experimental evidence is also available that obliges us to consider the role of estrogens in cardiovascular disease in men.

Although the precise actions of estrogens are not well known, they are thought to be essential for correct male development, as is apparent from rare cases of estrogen deficiency, caused by a defective aromatase enzyme, or estrogen resistance due to abnormalities of the cellular estrogen receptor. Phenotypically, they have been associated with osteoporosis, tallness, delayed epiphyseal closure, genu valgum, and eunuchoid proportions; metabolically, they are associated with changes in lipid profile, hyperglycemia, and insulin resistance. These manifestations vary according to the mechanism underlying the reduction in estrogen activity: in a patient with estrogen resistance, low levels of high-density lipoprotein (HDL-C) cholesterol were observed along with low levels of low-density lipoprotein (LDL-C) cholesterol and normal levels of triglycerides (TG), while in men with aromatase deficiency low levels of HDL-C have been observed along with high levels of LDL-C and TG.[2] In healthy men, estradiol level is associated with levels of apolipoprotein E and regulation of systolic and diastolic blood pressure. In addition, it acts along with testosterone to maintain normal levels of insulin sensitivity. The effects of estrogens can also be explained by their action as regulators of nitric oxide.[3]

The results of animal studies, as in humans, have been disparate. While in young men estradiol levels are negatively correlated with LDL-C and fasting glucose levels, a later study found no relationship between different cardiovascular risk factors and estrogens.[4,5] In a prospective cohort study in men in which the relationship between circulating sex hormones and cardiovascular disease was assessed, an association was observed between elevated levels of estradiol and reduced risk of disease for men older than 56 years, without a significant association with male sex hormones, although a cardioprotective effect for those hormones could not be ruled out.[6] In healthy men of fertile age subjected to estrogen suppression, a reduction was observed in plasma levels of HDL-C, particularly fraction 2, and a significant reduction in flow-mediated vasodilation.[7,8] Estrogen supplementation in healthy men aged more than 65 years reduces the levels of homocysteine, fibrinogen, and plasminogen activator inhibitor (PAI), and has a favorable effect on very low-density lipoprotein (VLDL-C) cholesterol, LDL-C, and HDL-C. In young men, vascular reactivity (flow-mediated vasodilation) is greater in those receiving estrogens and testosterone than in those receiving testosterone alone.[9] A reduction in the vasoconstrictor response to substances such as angiotensin II and noradrenaline has also been observed.[10] In contrast, an earlier study found no change in vessel diameter in older men following estrogen supplementation, whereas a change was observed in postmenopausal women of a similar age.[11] In transsexuals receiving chronic estrogen therapy, it has been observed that there is greater vascular reactivity than in control subjects, as well as increased levels of HDL-C and TG, increased visceral and subcutaneous fat, and reduced LDL-C levels, LDL-C particle size, and insulin sensitivity.[12,13] These conflicting results may be explained by the different doses of estrogens used in the studies and the use or not of antiandrogens, which would abrogate the possible influence of testosterone.

There is experimental and clinical evidence supporting a beneficial effect of estrogens in men, despite the presence in some studies of conflicting results, which may be explained by the study characteristics. More data is needed on the physiologic levels of estrogens in men, their physiologic effects, and the cardiovascular effects of estrogen supplementation in

order to assess their usefulness in the prevention and treatment of atherosclerotic disease.

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Response

To the Editor:

We appreciate the interesting and well-documented Letter to the Editor written by Dr Fleta-Asín. We totally agree, as is reflected in the section entitled "Unanswered questions" of the review article,[1] in that future research will still be necessary to determine whether or not hormone therapy, initiated in the early stages of the menopausal transition, confers cardioprotection or reduces cardiovascular risk. In particular, we need to have greater knowledge on the efficacy of different doses, formulations and modes of administration.

We also concur with respect to the idea that we need more data on the possible beneficial effects of estrogens in the prevention and treatment of atherosclerosis in men. However, some previous results from the Coronary Drug Project of the United States have pointed out the development of serious adverse effects associated with treatment with high-dose conjugated equine estrogens in men who had had a myocardial infarction. Thus, we consider that we need to be extremely cautious when assessing the potential beneficial effects on the lipid profile, since they may be counteracted and overcome by adverse effects on inflammatory markers and on the thrombotic mechanisms.

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