Are endogenous sex hormones important for atherosclerotic cardiovascular disease risk in men?

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Editorial

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In spite of many studies published during several last decades, the effects of endogenous sex hormones on atherosclerosis, particularly on atherosclerotic cardiovascular disease (CVD), remain unclear. Different studies have showed contradictory findings. This is particularly true when endogenous sex hormones in men are concerned. For instance, one study suggested that high serum testosterone is associated with reduced risk of CVD events in elderly men, while another study showed that elderly men with low serum testosterone and estradiol have increased risk of mortality, and subjects with low values of both testosterone and estradiol have the highest risk of mortality [1,2]. The association of low values of endogenous testosterone with increased risk of CVD in men has been linked to endothelial dysfunction [3]. A meta-analysis of observational studies showed that low endogenous testosterone concentrations in aging men could be a possible CVD risk factor [4]. However, a most recent meta-analysis did not find any association of endogenous testosterone with CVD deaths or with all-cause mortality [5]. Concerning treatment with exogenous testosterone, i.e. testosterone replacement therapy, the results of a meta-analysis performed 15 years ago weakly supported the conclusion that such a therapy in men was not associated with important cardiovascular events [6]. Nevertheless, since a number of studies have suggested that testosterone replacement treatment increased the risk of CVD, the US Food and Drugs Administration (FDA) released in 2015 a warning statement about the potential cardiovascular risks of this therapy requiring labeling change to inform of possible increased risk of CVD, and stressing that testosterone therapy should be prescribed only to men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [7].

Appiah et al. in their study on 954 young and middle-aged men published in this issue of *Atherosclerosis* [8] showed that low levels of endogenous total and free estradiol were associated with elevated risk of CVD mortality. They also found that this elevated risk was largely limited to non-Hispanic white men. These results are in accordance with the results of a study performed on 3650 men ≥65 years old, who were followed for mortality over 12 years, which showed a nonlinear association of total and free estradiol with all-cause mortality and these associations were stronger for CVD mortality [9]. Moreover, the results were in accordance with the results of an older study, which showed an association (although a weak one) between the degree of retinal artery atherosclerosis and lower estradiol levels [10]. It has to be mentioned that previously a strong correlation between the extent and severity of retinal artery atherosclerosis and the extent and severity of coronary arteries atherosclerosis, i.e. coronary heart disease, was proven [11].

The importance of these findings is stressed by the fact that, in spite of the widespread perception, levels of serum estradiol in men are in average higher than those in postmenopausal women. It is interesting that the results of these studies are different than the results of a recently published 2-sample Mendelian randomization study which used gene-based genetic instruments to assess the association between endogenous estradiol genetically predicted by 22 variants in the aromatase CYP19A1 gene region and the risk of thromboembolism (5815 cases) in 170,593 unrelated men. It has to be mentioned that the genetic determinants explaining the majority of the identified variance in circulating estradiol levels are located in the CYP19A1 gene region. This study showed that endogenous estradiol genetically predicted by variants in the *CYP19A1* gene region was inversely associated with the risk of thromboembolism and ischemic stroke in men [12]. This is important since it is well known that sex hormones may influence the risk of CVD also because of their effect on thromboembolism as well as because the process of thrombus formation is closely related to atherosclerosis so that the term atherothrombosis is often used for this process.

Most studies, observational, *in vitro* and *in vivo,* performed so far (although done predominantly in postmenopausal women) suggested that endogenous estrogens had protective cardiovascular effects. Possible protective mechanisms of estrogens recently summarized suggested that, by their binding to estrogen receptors ERα, ERβ and GPER1 (G-protein coupled estrogen receptor 1; formerly GPR30: G-protein coupled receptor 30) on vessel wall smooth muscle cells and endothelial cells, estrogens can reduce inflammation through the presence of sex

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steroid receptors on neutrophils, monocytes, macrophages and platelets, they act as potent antioxidants, decrease monocyte adhesion to endothelial cells, upregulate NO synthase (NOS), improve endothelial function but that they can also decrease plasma LDL-cholesterol levels and its deposition in arterial wall, and alter gene expression [13]. Estrogens do not only increase the synthesis of NOS in vascular endothelial cells but they also increase NOS activity by phosphorylation, thus enabling NO-induced vasodilation, and they enhance production of another vasodilator – prostacyclin. Higher levels of endogenous estradiol are associated with lower levels of plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator levels thus interfering with thrombogenesis. Therefore, lower levels of endogenous estradiol would act exactly in the opposite way [14]. However, it must be mentioned that in one study the authors found that endogenous estradiol was associated with the presence of vulnerable carotid plaque by the presence of calcification, lipid core, and intraplaque hemorrhage (they were analyzing plaques by ultrasound and magnetic resonance imaging), as well as an increased risk of stroke in women but not in men, while no consistent associations were found for endogenous testosterone in either sex [15].

It might be concluded that, in spite of some still open questions, the results of Apiah et al. [8] support the majority of existing data suggesting that low levels of endogenous estrogens are associated with elevated risk of atherosclerosis and, subsequently upon this, also with atherosclerotic CVD morbidity and mortality in men. Therefore, based on these data and other studies on the effects of endogenous sex hormones on atherosclerotic CVD in men, it seems that the answer to the question from the title of this article should be clearly positive.

Declaration of competing interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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