Postmenopausal sex hormones: comparing apples and pears

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The sex hormone story in relation to cardiovascular disease is always good for a surprise. Where we assumed that increased levels of female sex hormones were protective against the development of cardiovascular disease, our colleagues Mei Dong et al. from Yantai, China suggest quite the opposite. In their paper published in this edition of the Netherlands Heart Journal the authors describe a relation between the occurrence of a myocardial infarction (MI) in post-menopausal women and levels of sex hormones [1]. They report that high levels of oestradiol and increased waist-to-hip ratio (WHR) are related to the occurrence of acute MI.

This story is confusing. From an epidemiological perspective it was shown that in women there is a relation between the onset of the menopause and the risk of MI. Based on these observations studies were initiated to supply sex hormones in order to postpone the onset of atherosclerosis. Yet the beneficial effects of hormone replacement therapy were off set by the induction of thrombosis, likely in subjects who already had coronary artery disease [2]. However, recent publications might change this view, as a recent paper by Schierbeck from Denmark demonstrated that an early start of hormone replacement therapy seems to benefit and decreases future atherosclerotic events [3]. Moreover, it is well known that women with premature menopause have an earlier onset of atherosclerosis.

An important restriction of the paper by Dong et al. is the patient selection and moreover the control population. It is

obvious they selected pears and apples. The control group had lower WHR and lower levels of sex hormones. They also had a lower body mass index (BMI). These are clearly the pears with a preserved waist size, and they were recruited at random with two controls matched for age only. The infarct patients had higher BMI and higher WHR describing the apple shape. The value of the waist-to-hip ratio with increase in BMI is relative and some studies suggest that with a BMI above 30 the relevance of the WHR is lost. In addition the cases more often had hypertension and diabetes. These are all changes related to the postmenopausal status and it is well known that all these factors contribute to an increased risk for MI. So clearly the groups are very different. The question is to what extent do the sex hormone levels contribute independently? It has been reported that sex hormone levels are positively related to the total amount of fat tissue, with an inverse relation to sex hormone binding globulin [4]. So it is not unlikely that in the current study the observed higher oestrogen levels are an association with known risk factors that lead to MI rather than being causative. In fact, in postmenopausal women androgen secretion originates from the ovarian hilus driven by high gonadotropins and the adrenal gland driven by adrenocorticotrophic hormone and the oestrogens come from peripheral conversion of these androgens. Their fat tissue is the predominant source of oestrogens via its high aromatase potential.

It is also relevant in this context to mention another much larger study from China that found, after control for age and body composition, no differences in reproductive hormone profiles in a large group of postmenopausal patients with coronary stenosis compared with controls [5].

Theoretically, these findings by Dong et al. do not exclude the possibility that the different levels observed post MI relate to post-infarction stress since the measurement was performed within 24 h of the event. With only one measurement reported the temporal changes in sex hormone

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levels are not available. The controls only fasted for 8 h. In their discussion the focus in literature is on the lowering of testosterone in males during stress and a lowering of oestrogens in females. As we know, surgical stress induces a marked and sustained increase of adrenal androgen secretion in postmenopausal women within the early days post-surgery [6].

But let us assume that the oestradiol levels were elevated prior to the acute event. Can we think of a possible mechanism by which it may cause MI? In this regard it is relevant to mention the outcome of the Heart Estrogen/Progestin Replacement Study (HERS), where it was shown that in the setting of a plaque rupture in the patients aged 70 years an acute thrombotic event was related to higher oestradiol levels [2]. Oestrogens induce matrix metalloproteinase which digests the fibrous cap of a plaque exposing the underlying thrombogenic collagen which is believed to be the mechanism involved in the adverse thrombotic effects of oestrogens in the presence of established atherosclerosis [7]. In addition to the higher oestradiol levels the reported higher levels of testosterone may be of interest. Women with polycystic ovarian syndrome (PCOS), an ovulation disorder associated with increased androgen levels, are more at risk to develop cardiovascular disease. To what extent the hyperandrogenism itself is mechanistic is unclear since the syndrome often comes with obesity and insulin resistance as known cardiovascular risk factors. There are no indications that long-term administration of androgens to women, as occurs in the treatment of female-to-male transsexuals, is associated with a substantial increase of cardiovascular risk factors [8]. But in healthy postmenopausal women, higher androgen levels were associated with increased metabolic markers for the risk of coronary artery disease whereas slightly higher normal testosterone levels seem to relate to lower progression of atherosclerosis. In men higher testosterone levels are associated with a reduced prevalence of metabolic syndrome and an elevated prevalence in women [9]. So, although inconclusive there are indications that testosterone may contribute to the progression of atherosclerosis in general and coronary artery disease more specifically.

In conclusion, whether in this study the observed elevated oestrogens were instrumental in causing the infarction or epiphenomenal to an adrenal stress response and increased peripheral sex hormone conversion potential still remains to

be answered. However, it is important for postmenopausal women to try to preserve to pear phenotype as cardiovascular disease is still the major cause of death in women [10]. Not only the distribution of the fat tissue is crucial, also the other risk factors should be checked and treated, especially diabetes and hypertension. Maybe the Wear Red Day should be promoted in the People's Republic of China, a country where the colour red can expect a warm welcome.

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