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Prevention of coronary artery disease in men: Male hormone, female hormone, or both?

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SUMMARY

Sex hormones play an important role in coronary artery disease. Although both male and female hormones have been well-documented to be able to influence vascular biology, the preventive use of sex hormones in CAD is not established. Recent progress suggests a necessity of rethinking of the use of sex hormones for CAD in both sexes. We hypothesize that a long-term and appropriate low-dose combination of male hormone and female hormone could be an effective preventive strategy for men with a high risk of but not developed CAD. This hypothesis is supported by the fact that estrogen has favorable profiles on several key CAD-associated risk factors regardless of sexes. Testosterone supplementation has been linked to a reduced risk of CAD specifically in men. In animal models the reduced risk of CAD in males administrated with testosterone is due to the conversion of testosterone into estrogen; and sex hormone ratio changes rather than each individual sex hormone were found to be the predictor of CAD in a human study, suggesting the importance of a proper ratio of estrogen:testosterone in the development of CAD. In addition, the controversy surrounding the use of hormone replacement therapy in women in turn indicates a potential beneficial effect of sex hormones in men in the prevention of CAD because of the fundamental difference between sexes. Therefore, the combined use of estrogen and testosterone for CAD in men deserves a full investigation and could provide useful information in understanding of the preventive and/or therapeutic application of sex hormones in both sexes.

Introduction

Coronary artery disease (CAD) is a major threat to public health and the leading cause of death in industrial countries [1]. Although atherosclerosis might be the primary underlying pathology of CAD, the cause and mechanism of this disease are not well-understood. Since CAD is an age and sex-dependent disease that is two to five times more common among middle-aged men than their women counterparts [2,3], it is likely that female hormones play an important role in a lower risk of CAD seen in women. The speculation that female hormones can protect women against aging associated diseases including CAD leads to a wide use of hormone replacement therapy (HRT) among postmenopausal women. While whether the preventive use of female hormones has a favorable cardiovascular effect on CAD in women is still controversial, given the fundamental difference of hormones between sexes, it is possible that the profile of exogenous sex hormones on CAD in men might be different from the one in women. Based on recent progress in the understanding of the association of both male and female hormones with the risk of CAD, we hypothesize that a long-term and low-dose combination of estrogen and testosterone could be an effective prevention for the disease in men.

Sexes and CAD

Multiple conditions such as lipid abnormalities, hypertension, obesity, smoking, family history, and genetic disposition have been linked with an increased risk of CAD [3–12]. However, gender difference of the disease is perhaps the most remarkable risk factor [13–19]. A recent report released from American Heart Association [20] demonstrates not only a higher prevalence of CAD in men than in women, but also a similar pattern of difference measured by the incidence rate, a better indicator of the occurrence of the disease. The fact that the gender difference of CAD is age-dependent and the highest incidence rate ratio of men versus women is observed in adults before 45 years, the age of menopause for most women (CHD and myocardial infarction (MI): <45 years: 3:1; 45–64 years: 2.5:1; >65 years: 1.5:1, approximately), strongly suggests a favorable effect from female hormones and different profiles of sex hormones on the risk of CAD between sexes.

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Female hormones and CAD in postmenopausal women

The age and gender-dependent variation in the risk of CAD leads to the general belief that female hormones can protect postmenopausal women from CAD. Indeed, the decrease of estrogen in circulation resulting from menopause has been found to unfavorably affect LDL-C, HDL-C, and triglycerides, the three well-characterized biomarkers of atherosclerosis [21,22]. In contrast, the supplementation of female hormones in postmenopausal women has been shown to be able to reduce the risk of CAD [23,24]. In addition, a decreased risk of CAD in women administrated with HRT has been detected measuring by emerging risk factors such as C-reactive protein, homocysteine, and lipoprotein (a) [25–28]. However, several recent large cohort studies as well as randomized control trials failed to show a protective effect of estrogen on CAD [29–31]. Therefore, it is not clear at this point whether exogenous female hormones can protect women against CAD to the extent as previously believed.

Sex hormones for prevention of CAD in men?

While female hormones have been used in preventing CAD in postmenopausal women for several decades, such a practice has not been adequately tested in men. Early studies in the Coronary Drug Project back in 1960's showed that the administration of a 5.0 mg/day estrogen in men with MI history failed to protect patients from recurrent MI and a 2.5 mg/day estrogen group was discontinued because of the trends of adverse cardiovascular events such as pulmonary embolism and thromboembolism [32,33]. However, since MI is the end stage of CAD and there is a difference in CAD risk between men with and without MI history, it is understandable that estrogen might not be able to prevent MI, especially the recurrent MI. The application of estrogen in a population at a high risk of but not developed CAD might produce a different outcome.

In contrast to female hormones that have been suggested to be anti-atherogenic, male hormones are perceived to be the cause of greater risk of CAD in men. Although the fact that a higher level in total cholesterol and LDL was linked to androgen administration and an increased extent of atherosclerosis was associated with testosterone appears to indicate an atherogenic effect of male hormones, recent studies demonstrated that the aging associated low endogenous testosterone level in elderly men in fact increased the risk of cardiovascular mortality [34–36]. An inverse correlation between plasma free testosterone levels and the degree of CAD was also reported [37,38]. As more studies are undergoing, researchers start to call for testing testosterone in the prevention of CAD in men [39].

One important mechanism in hormone metabolism is the conversion of testosterone into estrogen catalyzed by aromatase. Although testosterone could be promising in preventing CAD in men, the fact is that the anti-atherogenic effect of the supplementation of testosterone is due to this conversion and such beneficial effect was not observed when co-administrated with aromatase inhibitors which block the conversion [40]. It is likely that it is estrogen that eventually exerts the protective effect on CAD. Therefore, it appears necessary to re-open the investigation on the use of estrogen in the prevention of CAD in men while urging the test of testosterone supplementation.

Based on recent progress in the study of sex hormones on CAD, it is reasonable to be optimistic that both estrogen and testosterone might have favorable effects. However, it is likely that the use of exogenous testosterone or estrogen alone would only benefit people who are either in testosterone deficiency or in a lipid abnormality, and thus, a high risk of atherogenesis which could be inhibited by estrogen regardless of sexes. For the rest of aging male population, it is important to maintain the testosterone level as well as a proper testosterone:estrogen ratio that has been demonstrated to be a critical predictor of the risk of CAD in postmenopausal women and is likely also true in men [41]. Therefore, a combination of estrogen and testosterone could be synergic, and thus, more efficient in protecting men against CAD and in reducing the adverse effects caused by using estrogen alone as seen in the Coronary Drug Project [32,33]. Once an appropriate dose for a long-term application of the combination is identified, it is possible to reduce the early development of CAD in men who are at a high risk of the disease.

Conclusion

Supplementation of hormones has been a clinical practice for many medical conditions. Estrogen is particularly a common application in preventing and/or treatment of aging associated diseases in postmenopausal women. Evidence from recent studies not only challenge the concept that male hormones are the cause of increased risk of CAD in men, but show that estrogen is the downstream factor that leads to a protective effect of the administration of testosterone on CAD and it is the sex hormone ratio changes rather than individual hormones that predict the risk of CAD. Therefore, while the use of estrogen or testosterone alone in men could be an effective prevention against CAD, the combination of these two might restore a proper estrogen:testosterone balance and thus are more applicable and beneficial to general aging male population. Nevertheless, the adverse effects associated with estrogen use in men such as feminization and thromboembolism are concerns and the timing of administration of the hormones is critical. Optimizing dosage and co-administrating other medications when necessary would be keys to the success of such an application in men. Monitoring sex hormones could help in predicting the risk of CAD and in determining the intervention strategy for each individual. It is possible that an appropriate low-dose and long-term application of estrogen plus testosterone can act like aspirin or better for men who are at a high risk of but not developed CAD. Thus, this hypothesis deserves a full investigation and, if confirmed, a new strategy for prevention of CAD could be established in the near future.

Conflicts of Interest

None declared.

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