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Editorial

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Importance of Sex Differences in Research on Cardiovascular Disease Prevention

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Sex differences in medicine are still in the midst of development; however, one of the areas that recognizes its importance and continues to lead the advancement of evidence is preventive cardiology. Postmenopausal women have a worse prognosis for acute coronary syndrome (ACS) than age-matched men, accounting for the majority of patients after the age of 75. Diabetes mellitus (DM) and smoking have a larger impact on cardiovascular disease (CVD)-related mortality in women than in men, which is widely recognized and utilized in clinical practice. Given that the first women-specific guideline for CVD prevention was published by the American Heart Association in 1999, it has been continuously updated, with the most recent being the 2020 update[1]. It provides evidence on female-specific risk factors, such as preterm birth, hypertensive disorder of pregnancy, gestational DM and other pregnancy-associated conditions, as well as hormonal factors, such as premature menopause. Psychological factors, such as depression, are also reported as stronger associated factors of CVD in women.

With this growing body of research on sex-specific risk factors, CVD and its prevention in young adults has also received much attention[2]. Due to high levels of sex hormone secretions, sex differences are particularly important to consider in younger age groups. Although endogenous estrogens have been proposed to lessen CVD risk, some Western countries have experienced a particular increase in ACS among relatively young women[3], and evidence for sex-specific preventive measures at a young age is becoming increasingly important. In this issue of the Journal of Atherosclerosis and Thrombosis, Kaneko *et al.* retrospectively examined sex differences in the association between lipid abnormalities and later CVD development using a nationwide database of approximately two million Japanese men and women aged 20–49 years without prior history of CVD and lipid-lowering medications[4]. The authors reported a dose-dependent association between lipid abnormalities and CVD development in both men and women, with the association between the number of abnormal lipid profiles and incident myocardial infarction (MI) being more pronounced in men than in women. Although age is a major driver of cardiovascular risk, this study showed that having unfavorable modifiable risk factors, even at a young age, may sharply increase the risk in the coming years, suggesting the significance of proactive intervention even in young adults with abnormal lipid profiles.

Therefore, how rigorous should dyslipidemia management be for young adults? A range of values has been set that require further evaluation and intensive risk factor control for several lipid markers[2]. Current guidelines recommend statin therapy initiation in young adults with severe hypercholesterolemia, including familial hypercholesterolemia, DM, and DM risk factors for primary prevention, regardless of sex. However, women are generally less likely to receive guidelines-recommended statin treatment, and lifestyle risk reduction is often promoted as a priority, especially for premenopausal women. Several factors could be contributing to this current situation. First, there has been a controversy over the role of statin therapy for primary prevention in women, although large meta-analyses conducted over the past decade have demonstrated similar benefits in women and men[5]. In addition, female sex is recognized as a risk factor for statin-associated muscle symptoms[6], and premenopausal women require discontinuation of statins prior to pregnancy. Given the pleiotrophic effects of statins and benefits

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of early statin therapy, which persist after discontinuation, further studies are needed to determine whether any additional groups of young patients will benefit from pharmacotherapy in addition to lifestyle modifications in primary prevention of CVD events. Mild elevation in triglycerides is reported to have several-fold higher risk of premature MI[7], and triglycerides were reported to have a stronger association with premature coronary heart disease than low-density lipoprotein cholesterol (LDL-C) in women[8]. Other lipoproteins and apolipoproteins are also useful in assessing CVD risk, such as lipoprotein (a), small-dense LDL-C, and apolipoprotein B, but few studies have investigated sex differences.

Menopausal transition (MT) is another important sex-specific factor associated with CVD and its risk factors among women of younger age. Early menopause and premature ovarian insufficiency, defined as menopause at age of less than 45 or 40 years, respectively, are associated with 1.5-2-fold increase in CVD risk. Kaneko *et al.* conducted a sensitive analysis with people aged 20–45 years which revealed consistent results. Considering that approximately 15% of the population experiences natural menopause before the age of 45[9] and an additional percentage of women undergo medically-induced menopause, further insights could be obtained on sex differences if these information were included in the study. Meanwhile, detailed mechanisms by which menopause and its transition alter CVD risk, particularly whether they are mediated by changes in lipid profiles, are still not fully understood. Previous reports observed nonlinear changes in LDL-C during MT[10], and whether the degree or slope of change during the MT provides new prognostic value has not been elucidated. The effect of menopausal hormone therapy on CVD risk remains controversial, and current guidelines do not recommend its use for CVD prevention. Recent studies suggest that timing of hormone therapy initiation plays a role in its effect on cardiovascular risk, but the findings have not been consistent and the biological mechanisms underlying them are uncertain.

In summary, although the role of dyslipidemia on CVD development is evident, there is still a lack of evidence on how lipid abnormalities in young people affect later-onset CVD, with consideration of sex differences. The genetic, epigenetic, and hormonal influences of biological sex have a profound impact on one's health, not to mention the social construct of gender, which influences human behavior. Incorporating these differences into research will lead to the advancement of precision medicine that will benefit the health of men and women.

Conflicts of Interest

None.

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