Gender Specificity and Interpretation of Functional Cardiac Imaging: Let's Talk about Sex

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Introduction

In their present study, Fiechter et al report from nuclear medicine that for women, a strong association exists between inflammation, as measured by vertebral bone marrow metabolism, and impaired myocardial function and perfusion, as assessed by single photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI).[1] Among a total of 294 patients (28.6% women, mean age 67 years old) who underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography and ^{99}Tc-tetrofosmin SPECT-MPI, a significant increase in ^{18}F-FDG bone marrow uptake was observed in women with impaired myocardial perfusion as compared with normal myocardial perfusion (standardized uptake 2.2 ± 1.2 vs. 1.7 ± 1.2, $p = 0.013$), while no differences were found in men (1.6 ± 0.8 vs. 1.6 ± 0.4, $p = 0.372$). In addition, a significant inverse correlation between left ventricular ejection fraction and bone marrow metabolism was seen in women ($r = -0.229$, $p = 0.037$), but not in men ($r = -0.075$, $p = 0.289$). The present findings are relevant, interesting, and novel as no previous study has applied two different nuclear medicine imaging modalities simultaneously to investigate the degree of inflammation and the amount of myocardial ischemia perfusion in the same patient. In particular, a major difference between genders was found, suggesting the importance of the gender specificity when interpreting cardiac functional test.

Gender Specificities in Cardiovascular Epidemiology

It is well known that inflammation plays a fundamental role in mediating all phases of atherosclerosis, both in men and women.[2] Cardiovascular (CV) disease is still the leading cause of mortality for women globally, although the trend over the last years clearly shows a reduction of mortality both for men and women.[3] Women are characterized by stronger immune responses and have a higher prevalence of inflammatory rheumatologic conditions compared with men.[4] For instance, elevated high-sensitive C-reactive protein values were associated with a greater risk of stroke and hypertension among women compared with men.[5] The recent guidelines highlighted the consideration of women-specific risk factors in the history, including gestational diabetes and hypertension, preeclampsia, eclampsia, autoimmune disorders, obstructive sleep apnea, and radiation-induced myocardial injury.[6] The 2016 European Society of Cardiology guidelines for prevention recommend starting systematic CV risk assessment in women from the age of 50 years or after menopause even in case of no known CV risk factor. Women are generally considered at a lower CV risk than men, with a gap of the estimated risk to be approximately 10 years (e.g., the risk of a 60-year-old woman is similar to that of a 50-year-old man).[7] However, the period following menopause is characterized by an increase of the CV risk profile and it is estimated that new coronary calcification occurs at a rate of 6% per year, as detected with the calcium score.[8]

The need to define a prevention strategy tailored to address the women's CV risk associated with inflammation is becoming all the more pressing given the increased prevalence of active smoking and the additional detrimental effect of passive smoking in women compared with men.[9] In addition, among middle-aged and older women, the prevalence of physical inactivity and obesity is substantially higher compared with men and associated with higher levels of inflammatory markers.[10] Some strategies have shown to be more promising in women. For example, the measurement of the intima-media thickness, a subclinical marker of CV disease, seems to be more predictive of clinical CV events in women than in men.[11] Also, efforts to prevent CV disease in women should probably start before the onset of the

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menopause to be more beneficial. Overall, several health care interventions specifically adapted to women have already proved to be successful.[6]

Gender Specificities in Coronary Artery Disease

Women with established coronary artery disease (CAD) also have relevant specificities that need to be emphasized.[6] Plaque anatomy and characteristics can differ between men and women, with a greater role of microvascular disease in the pathophysiology of coronary events among women (►**Fig. 1**).[6] At the time of manifestation of CV disease, women tend to be older, and with a greater risk factor profile and symptom burden of angina with positive ischemia on stress testing.[6] However, positive ischemia on stress testing does not preclude having a higher prevalence of nontreatable lesions. Previous reports have suggested that women have paradoxically less obstructive coronary disease than men at the angiography exam.[12] Along these lines, the clinical prognosis of symptomatic women with ischemia and nonobstructive CAD is worse than asymptomatic women.[13] Therefore, the role of additional noninvasive evaluation in women with chest pain, including cardiac magnetic resonance stress testing for subendocardial ischemia or cardiac myocardial perfusion nuclear imaging for coronary flow reserve, are determinant to detect abnormalities due to microvascular ischemia.[14]

Another striking point is, unfortunately, the persisting disparity in clinical outcomes that still prevails between women and men known to have CAD.[3,15] Observational data suggest that women admitted with myocardial infarction tend to receive reperfusion therapy and other evidence-based treatments less frequently and/or in a delayed manner compared with men.[16,17] The presence of atypical symptoms is still more frequent in women, and the absence of chest pain is not a protective factor of CAD severity.[18] Furthermore, evidence still points to the unfavorable outcomes associated with gender after myocardial infarction.[3,19] Elevated residual inflammation predicts poor health status, and young women with acute myocardial infarction are known to have higher levels of inflammation compared with young men.[20] In addition to inflammation, higher levels of lipoprotein(a) have also been observed in women with CAD.[21,22] Furthermore, quality of life is significantly impaired in women with CAD compared with men.[23]

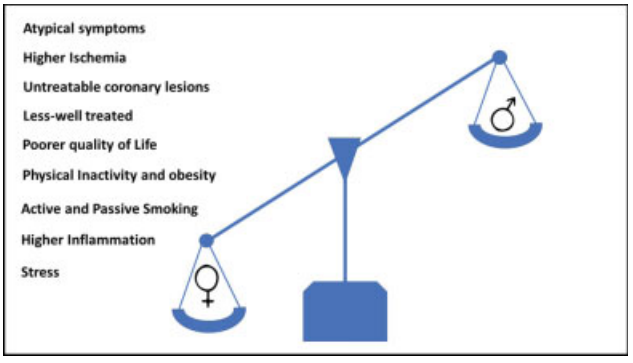

Fig. 1 Gender specificities for the prevention of cardiovascular disease.

Conclusion

The current study concurs with other evidence from the literature highlighting substantial gender disparities in several areas of CV imaging interpretation, prevention, and treatment. These gender disparities in the physiopathology mechanisms of atherosclerosis translate into higher CV mortality rates in women compared with men. Imaging modalities are appropriate screening and diagnostic tools to detect inflammation to improve CV prevention. This analysis is, to our knowledge, the first to combine two imaging diagnostic methods and show a relationship between increased vertebral bone marrow metabolic activity and impaired cardiac function and perfusion in women. These findings strengthen the role of inflammation in CAD and ischemic cardiomyopathy and the potential of imaging methods using the inflammatory process to improve prediction of CAD in women.

Future studies in the form of randomized controlled trials should clarify whether nuclear medicine can add prognostic value in medical decision-making and improve the prognosis of CAD in asymptomatic women. The sex differences in various CVD states have been well recognized.[24] Integrating gender specificities in scientific statements, medical investigations, and practical guidelines will be determinant in improving women's health care.[25,26]

Conflict of Interest
None declared.

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