

Received: 23/11/2014

Accepted: 17/01/2015

Published: 15/03/2015

EJCM 2015; 03 (1): 1-6

Doi: 10.15511/ejcm.16.00301

Feminine heart puzzle in 2015

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Abstract

In order to decrease the cardiovascular morbidity and mortality special attention should be given to the feminine heart. The first step is to evaluate the major differences in the pathophysiology, symptom onset and clinical outcomes of ischemic heart disease between the genders. Next is to find the best imaging modality that will lead to appropriate treatment.

Keywords: Heart disease, coronary artery, female

Please cite this article as: Keser N, Feminine heart puzzle 2015. EJCM 2015; 03 (1): 1-6. DOI: 10.15511/ejcm.16.00301

Heart disease has been stated to be number one killer in women^[1] and in 2015 nothing much seems to have changed. It is still the leading killer of women at all ages affecting more women under the ages of 55 years than breast cancer.^[2-5]

In order to solve this global problem, special attention should be given to gender differences in the etiology, pathophysiology, clinical presentation, prognosis and treatment of ischemic heart disease (IHD) which has been accepted as a more inclusive term to define the pathology in women.^[6]

Clinical presentation

The onset of clinical manifestations of coronary artery disease (CAD) in women has been stated to lag behind men by about 10 years.^[1] Following menopause the symptoms become more manifest in women. However instead of typical symptoms, atypical symptoms defined as dyspnea and fatigue may be more prominent in women.^[7] Moreover in almost 60% of women with IHD the initial presentation can be acute myocardial infarction (AMI) or sudden cardiac death^[3,4,8-11] and up to 50% of women presenting with an AMI may not report any prior chest pain symptoms.^[2,12]

This gender difference in clinical presentation carries utmost importance as it may lead to underdiagnosis of IHD in women.

Moreover, even with the clinical diagnosis of angina and traditional risk factors in women there may not be any evidence of CAD at angiography which was first demonstrated by The Coronary Artery Surgery Study (CASS).^[7,13,14]

Almost 50% of women with chest pain suggestive of angina pectoris will have normal or insignificant CAD as compared to 17% of men and 20% of these women will still have evidence for myocardial ischemia.^[15,16]

In such cases coronary microvascular dysfunction involving endothelial and nonendothelial pathways^[7,17] can be identified as reported by Reis et al.^[18]

However ischemia in the setting of vascular dysfunction is not so innocent^[8] and coronary endothelial dysfunction is reported to be associated with adverse

cardiovascular outcomes regardless of CAD severity in the WISE study.^[7,19]

The underlying difference in pathophysiology including smaller arterial size, more prominent positive remodeling and greater role of the microvasculature as demonstrated by various noninvasive imaging modalities has been claimed to carry a greater prognostic weight in women.^[8,20-27]

Risk factors

As stated before, the CASS study was one of the first landmark studies evaluating the cardiac risk factors in women which showed that the use of traditional risk factor assessment was limited in the prediction of CAD in women.^[7,13,14]

The WISE study further revealed that the CV events were independently predicted by coronary vascular endothelial function independent of risk factors and extent of CAD.^[15,19]

This study also showed prominent gender differences in the impact of CV risk factors such as not obesity but metabolic syndrome was reported to be a better predictor for the underlying severity of CAD and event-free survival in women.^[15,28,29]

Moreover waist circumference has been reported to be a stronger risk factor in women^[30] and DAS1 was reported to be strongly correlated with the occurrence of CAD and adverse events.^[31]

Bairey Merz CN et al.^[32] added new insights to risk factor analysis in women and showed that disruption of ovulatory cycling resulting in hypoestrogenemia in premenopausal women appeared to be associated with increased risk of obstructive CAD which claims that hypoestrogenemia might be the underlying reason for obstructive CAD during the postmenopausal years.

Clear differences also exist regarding the impact of lipid parameters such as Manolio et al.^[2,33] reported that HDL cholesterol inversely predicted CAD in younger women and men as well as older (>65 years) women; whereas the relative risks for IHD in women and men as related to total and LDL-cholesterol were found to be similar.^[2-4,10]

As for the triglyceride levels a meta-analysis of 17 studies revealed that hypertriglyceridemia increased the CAD relative risk by 32% in men and 76% in women^[2,34] and diabetes was also reported to be a stronger risk factor for IHD in women.^[2,35]

Smoking also deserves special attention in women. As it is complicated by hormonal variables, it has a larger detrimental impact in female hearts and especially in young women smoking is the most important risk factor for sudden cardiac death.^[36] A recent meta-analysis demonstrated a 25 % higher relative risk of heart disease in women smokers compared to men.^[37]

Specific conditions during pregnancy also need emphasis^[35] such as preeclampsia doubles the risk for subsequent IHD^[38] and gestational diabetes increases the risk of development of diabetes and thereby IHD.^[39]

Prognosis

As mentioned before 50% of women referred for the evaluation of suspected myocardial ischemia were found to have no obstructive CAD and the prognosis of future adverse cardiac events was reported to be intermediate for these women.^[7]

After an acute coronary syndrome(ACS) women and especially younger women with less obstructive CAD will also have a poorer prognosis.^[35,40,41]

It should also be remembered that although the total number of sudden cardiac deaths is higher in men^[42], 52% of women are more likely to die of a cardiac arrest before hospital arrival as compared to 42% for men.^[2,4,42,43]

Sex differences in cardiac catheterization and revascularization use and timing which are associated with poorer outcomes in women after an ACS^[35,44-46] cause a dilemma in treating the feminine heart.

Although stent usage is similar in women and men^[19,47] they tend to be treated less often with platelet glycoprotein IIb/IIIa receptor antagonists, possibly due to the increased incidence of bleeding which also may limit the effectiveness of the therapy.

Coronary artery Bypass Surgery(CABG) is also

troublesome in women. Following CABG the operative mortality is 4.0% for women and 3.2% for men^[48], in part due to excessive rates of congestive heart failure.^[8,48-51]

In addition, women have a higher incidence of bleeding complications^[1,19] and a more difficult recovery after CABG^[8,52] which may prolong the duration of hospital stay.

Diagnostic tests

Due to pathophysiological differences in IHD traditional tests for diagnosis that focus on identifying obstructive CAD work suboptimal in women.^[8]

Thus a need for an alternative strategy that would rely upon the estimation of the “culprit patient” or prognosis instead of culprit” obstructive coronary lesions has been proposed in women.^[8]

In order to choose the best noninvasive imaging modality the American Heart Association (AHA) has proposed to include the pretest risk stratification as low, intermediate and high risk before diagnostic testing referral^[53] which added a valuable insight for diagnosis.

We also agree with Lerman et al.^[7] who emphasize strongly that nonobstructive coronary angiograms in women should not be ignored and till new imaging modalities that will clearly diagnose ischemia due to vascular dysfunction are utilised, careful attention should be paid to the clear evidences of ischemia such as a positive troponin or an abnormal stress perfusion test in the absence of coronary artery obstruction.

Treatment

The necessity of earlier and aggressive primary prevention in women has been clearly reported.^[1] Prudent treatment directed at improving endothelial function, atherosclerosis and established risk factors in women including lipid-lowering, angiotensin-converting enzyme inhibitors and aspirin is well established.^[7]

However there is still a necessity for the FDA to monitor inclusion of proportional amount of women in all stages of drug research and as offered by Wenger et al.^[1]

further evaluation of the possible sex-based differences in drug metabolism is required before choosing the optimal management strategy for the female heart.

Till the feminine heart puzzle is completely solved

there is a compelling need to drive sustained attention to the female heart and remind the physicians to be more more aware of the basic differences between the 2 genders.

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Received: 23/11/2014

Accepted: 17/01/2015

Published: 15/03/2015

Disclosure and conflicts of interest:

Conflicts of interest were not reported.

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