

Are women more susceptible to ischemic heart disease compared to men? A literature overview

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ABSTRACT Ischemic heart disease (IHD) is known as the leading cause of death in both genders. Moreover, significant sex differences were found in cardiac structure, function, pathophysiology, presentation, treatment, and outcome of IHD. The presence of unique risk factors such as exposure to menarche and pregnancy, more anemia, hypertension, and autoimmune disorders in women have recently received attention. Ischemic symptoms are more indefinite and vague in women compared to men as well as a delay in diagnosis, treatment, and worse outcomes compared to men. Women usually receive less evidence-based treatment and intervention, with less concern on preventive health care. Clinical trials primarily recruit male patients and women are underrepresented. Without any correct diagnosis, treatment, and prevention, these problems are accumulated and continue up to older age. Accordingly, with the belief of longer life in women and the increased prevalence of IHD with aging, it will become an important public health problem and concern in the future. This narrative review aimed to provide an overview of some of the differences between the two genders in terms of IHD with paying more attention to practical points.

Ischemic heart disease (IHD) is known as the main cause of death in both genders. Also, there are significant differences in terms of prevalence, etiology, treatment, and outcome of IHD between men and women.^[1-7] These differences may result from the combined expression of different genes and sex hormones. Previously, it was thought that IHD is a similar entity among men and women with a decade of delay. This belief is simplifying and underestimates the importance of sex-specific differences in IHD. As IHD was considered as man's disease, male models (animals and humans) are known as the base of studies, and the women are usually under presented in cardiovascular trials.^[3,5,7-9]

This narrative review of the literature was performed on PubMed and Google Scholar databases through the mentioned keywords. The goal was to consider the sex differences of cardiac anatomy, physiology, aging, cardiovascular risk factors, and sex differences in IHD management and outcome.

SEX DIFFERENCES IN CARDIAC ANATOMY AND PHYSIOLOGY

The biologic differences contribute to different

cardiac structure and function independent of body size in men and women. These differences have effects on cardiovascular risk factors, susceptibility to the development of cardiac disease, and adverse cardiac remodeling.

Under normal conditions and adjusting body size, although women have smaller left ventricle (LV), smaller coronary arteries as well as lower stroke volume, they have similar cardiac output at cost of a higher cardiac rate. Compared to men, women have higher coronary blood flow at rest and similar flow at the stress phase. Women with smaller body size, have shorter arterial length and lower vascular compliance.^[3,5,7,10,11]

Women have a higher pulse rate at rest time, shorter PR interval, and longer QT interval compared to men. Women also have a greater systolic function and less diastolic compliance than men. Women have lower sympathetic and higher parasympathetic activity. Women with lower hemoglobin levels have lower oxygen-carrying capacity.^[5,11,12]

Women also experience an increased pulse rate in response to stress, which results in the increased cardiac output, while the men's response to stress is the increased vascular resistance leading to increased blood pressure.^[10,11]

Myocardial substrate metabolism is not similar between sexes. At the cellular level, there is less uptake of glucose as well as more use of fatty acid and metabolic inefficiency in women compared to men. Also, female mitochondria have a higher resistance to ischemic reperfusion injury, because they produce less reactive oxygen species and have a higher antioxidant capacity.^[10]

Sex Difference in Cardiac Aging

Although the old adaptation is a physiologic process and associated with the increased morbidity and mortality, it seems to be different between sexes. The physiologic changes include an increase in the cardiac extracellular matrix proteins and myocyte hypertrophy, with a decrease in myocyte numbers. At birth, the number of myocytes is similar between both sexes; however, with aging, the number of cardiac myocyte decrease is more significant in men than women. Normally, in the same age, men have a larger LV cavity and women have a higher ejection fraction with less diastolic compliance.^[10,13]

During a normal aging process, arteries lost their elasticity through increase in collagen content and calcification. These changes are lower in premenopausal women than age matched men, but postmenopausal women have more prominent arterial stiffness that leads to increased systolic blood pressure. Although, age-dependent endothelial dysfunction has no sex difference after menopause, microvascular dysfunction and comprised vasodilatory response are more common among women.^[4,10]

Age-related atrial fibrillation more develops in men, but has a worse outcome in women [including more heart failure (HF), thromboembolic stroke, and mortality].

Also, cardiac remodeling after IHD is more severe in men compared to women. This may explain more prevalence of systolic HF (decreased cardiac contractility) among men. However, in women, there is less apoptosis, inflammation, and fibrosis; with more LV mass preservation compared to men. It was shown that high testosterone level augments myocardial inflammation, and has several adverse effects on myocardial healing. These differences are associated with higher mortality in men, and poor quality of life in women.

In women LV remodeling due to myocardial infarction (MI), aortic stenosis and hypertension pro-

mote concentric hypertrophy, leads to diastolic dysfunction. While in men, eccentric hypertrophy with LV dilation is considered the most common form of LV remodeling, leading to systolic dysfunction. The degree of LV hypertrophy in response to hypertension and obesity is greater in women. Accordingly, these differences may explain different pictures of IHD between men and women with aging. Coronary artery calcium scoring by computed tomography is considered to be more sensitive and specific for the risk of stratification in women. Some observations had also indicated that with similar calcium density, women had fewer lesions and lower calcium volume with larger mean lesion size compared to men.^[2,7,13-15]

ISCHEMIC HEART DISEASE

IHD has different characteristics between sexes according to incidence, age presentation, the pattern of IHD, the importance of risk factors, management, and outcome.

Sex Difference in the Incidence of IHD

IHD, as the leading cause of death in women, has increased from 30% in 1997 to 54% in 2012. Some studies have shown mortality rate in women seems to be sustained since 2010, and it appears to be on the rise since 2015. The incidence of IHD is usually lower among women compared to men except in women aged ≥ 65 years old. After menopause, this gap decreases until elderly women experience a greater incidence of IHD. Delay in the onset of IHD in women may be related to the protective roles of endogenous estrogen and hormonal changes of menopause. Studies suggest the low level of estrogen may be related to the ischemic complications of atherosclerotic plaques.^[4,5,8,11-14,16-18]

Sex Difference in Atheromatous Plaque

Characteristics of the plaque can have differences between men and women. The atherosclerotic plaques are usually calcified, more localized, and obstructive in old men while old women have a more diffuse and less obstructive plaque with more microvascular involvement. In men, plaque rupture is known as the leading cause of thrombus formation in the coronary artery, vessel obstruction, and MI. Women have more plaque erosion, thrombus form-



ation, and embolization to the distal part and microvascular occlusion, which cause focal myocardial necrosis.^[4,6,7,10,12,15,17]

Sex Difference in IHD Presentation

There is an important difference in pain perception between both sexes. Acute coronary syndrome with atypical symptoms (such as abdominal discomfort, anxiety, neck pain, and fatigue) is more common among women. Older women may experience emotional distress rather than physical exercise as a trigger to MI. Different symptoms may lead to delayed diagnosis and even misdiagnosis. Chest pain also is more common in younger women and dyspnea is known as a more frequent symptom of IHD in older women. A higher prevalence of persistent angina may result from more diffuse atherosclerosis and small vessel disease in women.^[1,3-5,7,12,15,17]

Sex Difference in MI with Non-obstructive Coronary Arteries

It is currently well recognized that a normal coronary angiogram is not synonymous with a normal coronary circulation. There is a normal ability to increase the coronary flow 2.5–5 fold in response to stress. Women have a lower flow reserve in response to physiologic or pharmacologic stress. Coronary microvascular dysfunction (CMD) with abnormal epicardial vasomotor or endothelial microvascular dysfunction is known as an important cause of chest pain in women.^[3-7,11,12,14,15,17,19]

The more susceptibility in women may be due to more prevalence of vasomotor, inflammatory disorders, mental stress, autonomic and neuroendocrine dysfunction. CMD is more prevalent in premenopausal than postmenopausal women, while obstructive IHD is more common in older women. In this regard, it is noteworthy that approximately 30%–50% of women with chest pain and even MI have no obstructive IHD in coronary angiography, compared with 17% of men.^[3-5,11-13,15,17]

CMD remains under-diagnosed partly because the diagnosis has been routinely focused on the detection of epicardial coronary stenosis and the cardiac microvascular is too small to be visualized with conventional imaging techniques. Also, clinical suspicion should be high in patients with persistent chest pain, those who have ischemic changes in noninvasive stress testing, and non-obstructive an-

giographic finding. It is diagnosed with coronary reactivity testing, position emission tomography, adenosine cardiac magnetic resonance imaging, and optic coherence tomography.^[3,4,6,13,15,17]

The non-obstructive coronary artery disease is not necessarily considered as a benign condition, as some studies have shown that without treatment, symptoms would be persistent and associated with the increased risk of cardiovascular events including death. Women should also be considered at a higher risk for future events, rather than labeling them as having a false-positive test. Treatment remains empiric due to limited data on this field as well as focusing on symptoms alleviation and general preventive strategies. Two distinct studies showed that less than one-fourth of these patients receive conventional anti-ischemic medications at hospital discharge compared to obstructive IHD.^[3-6,9,14,15,17]

Sex Difference in Young IHD Patients

Although statistics showed a decreased incidence of IHD in both sexes in recent years, it is accelerating in younger women. A surveillance study performed on the incidence and management of MI between 1995 and 2014, showed a significant increase in the annual incidence of hospitalized MI among young women (35–54 years old), with the decreased incidence rate among men in the same age.

Numerous studies have shown younger women with premature IHD exhibit a higher prevalence of cardiovascular risk factors.^[4,12,16-18]

Premenopausal women have more plaque erosion and less calcification and inflammatory components compared with plaque rupture in postmenopausal women and men. In this regard, MI in the absence of a significant atherosclerotic lesion is more common among younger women. In young patients with IHD, atypical and non-cardiac chest pain is reported to be as common as typical angina. The absence of chest pain is more commonly described in younger women.^[12,17,18]

Furthermore, young women are less likely to receive evidence-based treatment compared to men. The IHD death rate in young women continues to increase while it has the decreasing trend in men.^[2,4,5,9,11,12,16-18]

The period of 45–65 years is recognized as the transition phase from low risk for IHD in young women to high risk at the postmenopausal stage. During these times, women could experience non-



classic symptoms of IHD, and their complaints are often attributed to menopause and emotional stress erroneously. Plenty of studies showed a delay in diagnosis, under treatment, and less referral to angiography with worse baseline risk factors in young women. So these problems are accumulated and continue up to older age.^[7,15,20]

Sex Differences in Awareness of IHD

Awareness of IHD, as the primary cause of mortality in women, has been gradually increasing. Although developing breast cancer is a more annoying subject for women, more women die from IHD. Studies continue to report that many women frequently attribute symptoms to non-cardiac reasons, do not recognize the typical risk factors for IHD and also minimize the importance of symptoms or put other responsibilities ahead of their seeking medical attention for themselves. Insufficient awareness leads to higher rates of missed or delayed management. Indeed, women are less likely to receive the routine cardiovascular risk assessment as a part of routine screening. In a recent survey, 74% of women reported having one or more risk factors, who had modest levels of IHD awareness.^[3,7-9,11,14,15,19]

Insufficient awareness exists among physicians, as well. Previous studies demonstrated physicians are more likely to underestimate the probability of IHD in women compared to the risk-matched male patients. Only half of the cardiologists and primary care physicians utilized IHD risk assessment for their female patients.^[2,5,8,14]

Sex Differences in IHD Outcomes

There is a different outcome despite similar current treatment in both genders. Numerous studies performed in different countries confirm less awareness on seeking medical care, less aggressive treatment in women in the setting of older age, and higher comorbidities that cause less favorable clinical outcomes with higher mortality and lower health-related quality of life.^[2-4,6-9,11-18,20]

Several studies have reported the trend to decrease IHD incidence and mortality among men significantly, with a slower rate and more stagnant in women. After adjustment for many clinical variables, women still had a higher risk of death compared to men. Sex and age are also clinically im-

portant prognostic factors for MI and subsequent outcome.^[1-4,6,9,11,12,15,18,20]

SEX DIFFERENCES IN IHD RISK FACTORS

Although there are some classic risk factors for IHD, the significance and relative weighting of these factors are different in men and women.

Sex Difference in Age of IHD

The incidence of IHD is increasing with aging in a log-linear model for both women and men worldwide. Its prevalence is generally lower in women compared to men in all age groups until menopause. At advanced age, the gap shrinks, in a way that women outnumber men, so the absolute number of female patients is greater. Also, the increased life expectancy and in turn the growing number of older adults in the population, provide more chance of exposure to the cardiac risk factors in women.^[1,4,8,11,12,14-17,20]

Sex-related Cardiovascular Risk Factors

While men and women have similar risk factors for IHD, additional sex-based risk factors have been shown to play an important role in women. These unique factors are early menarche, pregnancy-induced complications such as hypertension, preeclampsia, gestational diabetes, the increased parity and miscarriage, small for gestational age, primary ovarian insufficiency, contraceptive drugs, chemotherapy and chest wall radiation for breast cancer, spontaneous menopause before the age of 40 years old. In this regard, these disorders can accelerate the development of cardiovascular disease at a younger age.^[2,5,7,13,15,20]

The beneficial effect of estrogen and the detrimental effect of androgen on cardiac function have been documented. Estrogen promotes vasodilation by nitric oxide and prostacyclin production, stabilization of atherosclerotic plaque through anti-inflammatory mechanisms, and preservation of endothelial function in premenopausal women. Besides, endogenous estrogen deficiency 7-fold increases the risk of IHD in young women. In WISE study, premenopausal women with IHD had significantly lower levels of estradiol and follicle stimulating hormone, compared to those women with no documented IHD. Recently, the measurement of endogenous sex hormones in postmenopausal women confirmed the association of a higher testoster-



one/estradiol ratio with increased risk of cardiovascular disease and HF events.^[2,5,7,11,14]

After menopause, estrogen withdrawal, change body fat distribution, endothelial dysfunction, and increased sympathetic tone would increase the risk of developing IHD in women as twice as men. There is no cardiovascular benefit of exogenous estrogen treatment and in fact, it may be harmful.^[1,5,7,11,14]

Sex Difference in Obesity

Increased adiposity contributes to cardiovascular risk; associated with systemic inflammation, microvascular dysfunction, and diastolic HF. Obesity has a greater impact on the development of IHD in women. Also, women have more percentage of body fat and sedentary behavior compared to men. It was indicated that abdominal obesity is associated with a higher incidence of IHD than excess fat in the lower body. There is a weight gain and abdominal obesity after menopause, which highlight the impact of the reduced estrogen on metabolic profile and fat redistribution.^[1,2,10-12,15,16]

Sex Difference in Diabetes

Although the prevalence of diabetes is less in women, robust evidence exists for a greater excess risk of developing IHD among diabetic women than men with an earlier occurrence of MI, greater adverse LV remodeling, and a higher risk of mortality.^[1-3,7,11-15,17,18,20]

The more increased risk of IHD in diabetic women compared to diabetic men may be due to more involvement of inflammatory factors, greater prevalence of risk factors, diffuse atherosclerosis, small vessel disease, and greater endothelial dysfunction.

There is a higher prevalence of diabetes in young women with IHD compared to age-matched men, which represents an obligation of aggressive IHD prevention strategies. Indeed, diabetes overcomes the benefits of estrogen in young women. The coronary revascularization rate is lower in diabetic women than in diabetic men. Diabetic women are less likely to be treated aggressively and have less response to treatment.^[2-4,7,14-16,20]

Sex Differences in Dyslipidemia

Among IHD risk factors, dyslipidemia is the greatest population attributable risk among women. Premenopausal women tend more to have a lower low-density lipoprotein (LDL) and a higher high-

density lipoprotein (HDL) than men. The LDL is more likely to increase the risk of IHD in men, while HDL levels mainly act in women. The low HDL increases risk of coronary events more significantly in women than men.^[5,15,18,20]

Menopause is associated with a worsening lipid profile in women. The LDL level increases and this increase is larger than that observed in age-matched men.

Women are less likely to receive statin therapy after MI. However, atheroma regression and LDL lowering may be even greater among women on a statin, with a greater likelihood of the development of diabetes and myalgia in women.^[2,14,15]

Sex Difference in Smoking Effect

Smoking has a disproportionately large effect on the IHD risk in women compared to men. Also, at younger age smoking puts women at a greater risk to contribute to premature IHD.^[1,2,6,7,11,13-15,17,20]

Sex Difference in Hypertension

Hypertension is known as the most prevalent risk factor of cardiovascular disease. The prevalence of hypertension differs between men and women across the life span. Hypertension is more in young men compared to young women, which is maybe due to the vasodilatory effect of endogenous estrogen. A more rapid increase in the prevalence of hypertension was displayed in menopause women as well as exceed in men. A survey showed less than 30% of women older than 70 years have adequate blood pressure.^[2,6,10-12,14,15,19,20]

Hypertension is associated with the more increased risk of IHD and MI in women compared to men. It is considered as the cause of more LV hypertrophy and HF with preserved cardiac contractility in women. Women are less likely to achieve adequate blood pressure control than men. LV hypertrophy after hypertension also has less response to medical treatment in women.^[2,6,9,10,12,19]

Sex Difference in Immune Response

The inflammatory disorders accelerate atherosclerosis disease. Women have a higher level of inflammatory markers, especially at postmenopausal. The severe inflammatory response and autoimmune disorders are more prevalent in women.^[10,11,14,15,18]

Sex Differences in Psychosocial Effects

Exposure to psychological stress and lack of so-

cial relationships are associated with the increased cardiovascular risk. It may be through the increased inflammation, chronic autonomic dysregulation, endothelial dysfunction, and hypercoagulable state. Also, the inflammatory response in IHD may be augmented in a depressive mood. Notably, that depression is associated with the increased risk of heart disease and worse quality of life up to 70%.^[1,2,5,11,13,15-18]

Psychosocial factors have significant sex differences. Depression and post-traumatic stress disorder also are more prevalent in women. Moreover, acute stress can more induce myocardial ischemia in women compared to men. It was shown half of the young women (≤ 55 years old) with MI had a history of major depression. Indeed, it may potentiate the chance of other cardiovascular risk factors two times.^[2,7,17]

The low socioeconomic status is considered as a coronary risk, which imposes a higher risk on women compared to men. Additionally, women are more likely to live at the poverty level. The association of IHD and lower education state was found to be more in women. It was shown that young and middle-aged women with MI, had lower socioeconomic status, higher emotional stress, and lower quality of life compared to men.^[4,7,8,12,13,15,19]

Sex Differences in Physical Activity

The prevalence of physical inactivity and sedentary lifestyle behaviors are higher among middle-aged and older women with less experience in team activities and group exercise. Achievement of the recommended physical activity is an essential component of management. Studies have shown although the cardio-protective benefit of exercise is more in women than men, the proportion of women with IHD not meeting the recommended physical activity is high and on the rise.^[11,15,17]

Other Sex Differences in IHD Risk Factors

There is growing evidence on the association of gut microbiome and IHD and hypertension, and it is different between men and women.^[7,16]

Women are more sensitive to noise, and sensitivity to noise and noise pollution is a known risk factor for mortality in patients with IHD. Its mechanism may be through the over-activation of the autonomic system.^[11]

Notably, in the setting of air pollution, women are more susceptible to IHD.^[11,16]

Sleep disorders are now recognized as an important cardiac risk factor and reported to be more underdiagnosed and undertreated in women.^[2]

SEX DIFFERENCES IN IHD MANAGEMENT

The recommended treatment for IHD between men and women is similar. Numerous surveys performed in different countries have shown that women are less likely to receive the recommended guideline-based treatment, despite the higher baseline risk profile and comorbidities at the time of presentation of MI.^[1,4,5,9,11,12,14,17]

The diagnosis of IHD in women is more challenging and often delayed as women are presented with more atypical symptoms, especially the younger ones. The beginning of treatment in women is associated with more delay by both patients and care providers. Women usually wait longer to seek medical attention. The data analysis of Thoracic Pain in Community cohort study has explained the lower quality of care in women may be due to a lower 2.5 times the chance of referring to a cardiologist for chest pain.^[7,8,13] Numerous studies support the lower rate of coronary angiography and intervention in women despite higher angina class, owing to the underestimation of IHD.^[3,4,8,9,11,12,14,16,17]

Sex Differences in Pharmacologic Management

The efficacy of aspirin, statin, and beta-blockers for secondary prevention are equally established in both men and women by guidelines. Some surveys have shown that women with stable angina and documented IHD are less likely to receive evidence-based medicine.^[4,9,11-15,17]

Men and women have differences in absorption, distribution, metabolism, and exertion of drugs, so they may differently respond to cardiovascular drugs. Women have higher body fat, lower body weight, plasma volume, and blood flow; therefore, the faster onset, higher volume of distribution, and longer effect of lipophilic drugs with more adverse drug effects can be explained in women.^[15,17,19]

Normally, women have a longer QT interval, so fatal ventricular tachycardia, as a complication of



some antiarrhythmics, antidepressive and anti-allergic medications are more seen in the female sex.^[11,19]

In HF medications, some trials showed angiotensin-converting enzyme inhibitor can significantly reduce the risk of death in men, rather than women; and angiotensin-receptor blocker can significantly reduce the risk of death in women, rather than men. Some trials reported the increased mortality in women with digoxin, maybe due to higher drug levels and lower clearance rates. In a similar dose, women are better at responding to diuretics, angiotensin-converting enzyme inhibitor, beta-blockers, but with more side effects, which may contribute to lower adherence rates.^[17,19] The side effects of statins are often reported by women, which may disrupt the adequate dosage. While some data suggest that statin therapy in women results in greater coronary atheroma regression and greater benefit in cardiovascular outcomes.^[3,14]

Sex Differences in Percutaneous Coronary Intervention

The benefit from percutaneous coronary intervention (PCI) is similar in both sexes in the current guideline; however, women are less likely to be treated with a reperfusion strategy.^[4,12-14,17]

Numerous studies have shown female gender can be considered as the independent predictor of the worse outcomes in terms of periprocedural MI and the increased risk of in-hospital events. This finding could be explained by women with older age during PCI, greater prevalence of cardiovascular risk factors, small size vessel, and delays in reperfusion. A few studies have also suggested that after performing multivariable analysis and adjustment for cardiovascular risk factors, major adverse cardiovascular events and mortality were not greater in women following PCI.^[4,9,17,19]

The importance of early revascularization is well established on both survival and clinical outcomes in MI. Different registries in different countries have shown more delay in symptoms-to-door and door-to-balloon in women. Comparing data obtained in 2006 and a decade later showed significant disparities persist in the timeliness of revascularization.^[9,14,17]

Women, due to functional coronary abnormality and more diffuse patterns of atherosclerosis, have shown more residual symptoms after PCI with a

higher rate of functional disability. Also, restenosis after the intervention and need of revascularization and access site complication, still are more in women.^[13,19]

Sex Differences in Coronary Artery Bypass Graft

Women comprise a minority in both observational and randomized coronary artery bypass graft (CABG) trials. In addition, women are less likely to be referred for revascularization, are older, and have more comorbidities. Several earlier studies have shown the poorer quality of life after CABG in women, more post and perioperative complications, and longer recovery times with higher mortality. As shown, women after CABG have less symptomatic relief and less functional improvement than men due to a more diffuse pattern of atherosclerosis and less complete revascularization. There are conflicting results in studies on the role of the female sex, as an independent risk factor after CABG.^[4,9,12,17,19]

Sex Differences in Cardiac Rehabilitation

Cardiac rehabilitation programs remain a cornerstone therapy for the prevention of recurrent cardiovascular events as well as a significant reduction in mortality rates. It results in achieving optimal physical exercise and a healthy lifestyle with control of cardiac risk factors level.^[14]

Despite a worse prognosis after IHD, women are less involved in the primary and secondary prevention treatment and have less access to the rehabilitation programs. Even after referring, they have a very low attendance rate and significantly lower finish the program compared with the man after CABG. Data suggested that women enjoy a greater benefit than men concerning mortality reduction.^[4,9,11,14,15]

CONCLUSIONS

This paper reviewed the important well-established differences between men and women in terms of the different aspects of IHD. Sex-specific data focused on cardiovascular disease has been steadily increasing, but they were not put into practice. Understanding the differences is important, but more importantly, is how we should deal with these differences. All these recent articles and reviews showed and confirmed one clear message as follows: women's cardiovascular health, need sex-specific re-



search, and need to improve cardiac care in women must be paid more attention. Since women live longer than men on average, and advanced age provides longer exposure to risk factors, it is reasonable to assume that IHD among older women in terms of disease prevention will become an important public health challenge in the future.

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