



Review

Gynecardiology: Distinct patterns of ischemic heart disease in middle-aged women



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ABSTRACT

The past 25 years have revealed that distinct patterns of ischemic heart disease exist in women that are importantly different from the male standard. Premenopausal women have a lower risk factor profile resulting in fewer cardiovascular events at younger age, which reverses at older age. First signs of vascular ageing appear in middle-aged women, with a predominance of functional coronary abnormalities over anatomical obstructions. Over 50% of symptomatic middle-aged women have coronary microvascular dysfunction that is often poorly recognized and treated. This microvascular syndrome has different symptomatic characteristics compared to the classic pattern of angina pectoris related with obstructive coronary disease. Vascular dysfunction is also an important contributor to the occurrence of acute coronary syndromes in relatively young women. Female-specific signs and symptoms related to various stages of life are increasingly helpful tools in identifying women at increased risk. This evolving knowledge in 'gynecardiology' is an important challenge for more interaction between gynecologists and cardiologists to further improve accurate prevention in those women at highest need.

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Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; ESC, European Society of Cardiology; HELLP, hemolysis elevated liver enzymes and low platelets syndrome; HFpEF, heart failure with preserved ejection fraction; HPD, hypertensive pregnancy diseases; IHD, ischemic heart disease; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; PET, positron emission tomography; POI, premature ovarian insufficiency; TTC, Takotsubo cardiomyopathy; VMS, vasomotor menopausal symptoms; WISE, Women's Ischemia Syndrome Evaluation study.

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1. Introduction

Important gender differences exist in the clinical manifestations of ischemic heart disease (IHD), which are closely related to the pathophysiologic changes within various stages of life. Advanced imaging technology over the past 25 years has revealed that the female pattern of IHD is different from the usual male standard. Despite, the female cardiology patient is in general still considered from the male point of view. A greater focus on women-specific aspects of ischemic heart disease, which could be called 'gynecardiology', will lead to a more tailored care for our female cardiac patients. This will reduce the costs of healthcare by inducing more selective diagnostic strategies and implementing timely prevention in those women who are at highest risk.

2. Gender differences in morphology of coronary atherosclerosis

At all ages the total burden of atherosclerosis is lower in women than in men, with a more diffuse, non-obstructive pattern of CAD and relatively more soft plaques rather than calcified lesions in women at middle-age [1,2]. This is strongly related to the premenopausal oestrogen status which has many direct and indirect protective properties on the process of arterial ageing [3]. Below 60 years of age, the chance of having obstructive CAD is over 50% lower in women compared to men. The still relative low chance of having obstructive CAD in the early postmenopausal years is in agreement with the time-frame in which the temporary use of hormone therapy (HT) in women with serious and disabling vasomotor symptoms (VMS) has not been proven to be harmful to the cardiovascular system [4,5]. Although the general pattern of coronary atherosclerosis is more diffuse and less obstructive in women than in men (Table 1), the clinical prognosis is not better [6,7]. The complex interaction between sex-related hormonal status and the extent of atherosclerosis is not only striking at younger age, but persists into old age [8]. Arterial plaque morphology changes throughout menopause transition, with a gradual increase in more vulnerable and calcified plaques after 60 years [9,10].

3. Female-specific aspects of acute coronary syndromes

Of all acute coronary syndromes (ACS) in patients below 65 years, less than 25% occur in females [11]. When having an ACS at younger age, women are lacking twice as often any significant lesion at coronary angiography compared to men [12]. While in men and older women the classical pattern of plaque rupture and subsequent thrombus formation is more common [9,13,14], younger women with ACS have more often plaque erosions and type II ACS. The latter is mainly caused by functional coronary abnormalities, often triggered by cardiovascular risk factors and inflammatory cytokines, that all promote endothelial dysfunction [15,16]. With the use of high sensitive Troponin essays, it is now easier to recognize type II ACS in female patients in clinical practice [17]. A distinctive feature of an ACS, occurring most often in young women, is a spontaneous coronary dissection. This accounts for 10% of all ACS in women <50 years [18] and may occur in women without any risk factors, in women with mixed connective tissue disease or fibromuscular dysplasia, in relation with premature hypertension or during pregnancy/after delivery [19]. While in men vigorous exercise is frequently associated with ACS, severe stress is more often a provoking trigger in females. An extreme example is the Takotsubo cardiomyopathy (TTC), or apical ballooning syndrome, which is an ACS occurring in predominantly 60 plus women after severe emotional stress [20,21]. It is assumed that (a sudden) catecholamine toxicity induces dysfunction in the

macro- and/or microvascular coronary arteries, leading to a temporary severe "stunning" of the myocardium. One reason for the higher susceptibility for TTC in elderly females, is their enhanced sympathetic activity after menopause [22].

In the elderly (>75 years) ACS becomes more prevalent in women than in men. This apparent paradox is closely related to a higher risk factor burden after menopause and to the fact that women have a longer life expectancy than men.

4. Coronary microvascular dysfunction

In the Women's Ischemia Syndrome Evaluation (WISE)-study, it has been found that in more than 50% of middle-aged women with symptoms of chest pain, these are related to vascular dysfunction in the epicardial and microvascular coronary vessels and not with obstructive CAD [1,23,24]. In contrast to what was previously thought, these women have an unfavorable cardiovascular prognosis with an annual rate of major cardiovascular events of 3.4% [25]. Despite, many symptomatic women remain undiagnosed and undertreated for their risk factors. This often results in recurrent hospitalizations, second opinions, uncertain diagnoses, high treatment costs, diminished quality of life and lost productivity [26–28]. Clinicians have been puzzled for years by this condition and often refer to it as 'cardiac syndrome X'. The coronary microcirculation consists of a lattice of very small pre-arterioles and arterioles comprising about 90% of the coronary circulation. Its principal task is to regulate vascular resistance and thereby myocardial blood flow. Coronary microvascular dysfunction (CMD) is considered an early manifestation of a mismatch of myocardial blood flow and myocardial metabolic demand. Although CMD is a type of IHD, myocardial ischemia is not apparent in all CMD patients but occurs with longer duration of exposure to this mismatch [1]. When no other structural cardiac disease is present, as in the majority of middle-aged women, this is called type 1 CMD [29,30]. Although the exact pathophysiologic mechanisms underlying CMD are still elusive, it is associated with risk factors for atherosclerosis. Both endothelial and non-endothelial dependent impaired vasoreactivity plays an important role.

Diagnosing CMD is still a challenge: the gold standard is invasive coronary reactivity testing, a burdensome and specialized test reserved to cardiac intervention centers. Detection of CMD with non-invasive methods such as PET scanning, cardiac MRI and echocardiography are under development [31]. As pivotal as diagnosing CMD is to treat women with CMD who are at increased cardiovascular risk. However, optimal therapeutic strategies for CMD are unknown yet and still under investigation [32–34]. Since CMD is related to cardiovascular risk factors, aggressive risk reduction seems warranted in affected women. Moreover, lifestyle modifications such as smoking cessation, weight-loss, and exercise training improve CMD [32]. Currently, appropriately powered, randomized clinical trials testing the effect of multi-modality management strategies on cardiovascular outcome in CMD patients are very much awaited.

4.1. Cardiac symptoms due to endothelial ageing/dysfunction

Undetermined symptoms of chest pain and dyspnea are common in middle-aged females and these are often labeled as "stress" or complaints secondary to menopause. However, these symptoms may be related to age-related structural changes of the vascular endothelium [10,35]. Vascular endothelial dysfunction is the first manifestation of arterial ageing and is characterized by an imbalance in vasodilatation and vasoconstriction that may lead to first manifestations of chest pain and dyspnea, mostly at exertion. As women who are diagnosed with 'undetermined' chest

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