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CONTEMPORARY REVIEW

Sex-Related Differences in Genetic Cardiomyopathies

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ABSTRACT: Cardiomyopathies are a heterogeneous collection of diseases that have in common primary functional and structural abnormalities of the heart muscle, often genetically determined. The most effective categorization of cardiomyopathies is based on the presenting phenotype, with hypertrophic, dilated, arrhythmogenic, and restrictive cardiomyopathy as the prototypes. Sex modulates the prevalence, morpho-functional manifestations and clinical course of cardiomyopathies. Aspects as diverse as ion channel expression and left ventricular remodeling differ in male and female patients with myocardial disease, although the reasons for this are poorly understood. Moreover, clinical differences may also result from complex societal/environmental discrepancies between sexes that may disadvantage women. This review provides a state-of-the-art appraisal of the influence of sex on cardiomyopathies, highlighting the many gaps in knowledge and open research questions.

Key Words: cardiomyopathies ■ heart disease in women ■ heart failure

Sex has a diverse impact on the cardiovascular system in physiology and disease, reflecting true biological variation as well as complex societal/environmental discrepancies. Sexual hormones have been shown to exert various effects on the myocardium, modulating systolic and diastolic function, left ventricular (LV) remodeling and fibrotic response to injury.[1] To date, however, the influence of sex on the morpho-functional and clinical manifestations of myocardial disease is largely unresolved. While knowledge has advanced thanks to ex vivo, in vitro, and in silico studies, several fundamental research questions in the field are still in search of an answer (Table 1). Cardiomyopathies are a spectrum of diseases involving primary abnormalities of the myocardium, often genetically determined. The phenotypes encountered in clinical practice encompass hypertrophic (HCM), dilated (familial DCM), arrhythmogenic, and restrictive cardiomyopathy. Among these, rare X-linked variants of hypertrophic heart disease, such as Fabry disease and Danon disease (DD), and DCM, such as Duchenne and Becker muscular dystrophy, best epitomize sex-related differences, for obvious reasons. Included in the cardiomyopathy spectrum is also a variety of acquired conditions, generally manifesting with a DCM phenotype, caused by noxious stimuli such as inflammation and autoimmunity. This review aims to appraise the impact of sex on the clinical expression and outcome of myocardial diseases, highlighting the limited certainties versus the many residual gaps in knowledge, each potentially relevant to personalized management of these complex conditions (Table 2).

DILATED CARDIOMYOPATHY

Epidemiologic studies suggest a lower population burden of DCM in women. In Olmsted County, the prevalence of DCM was 19.4 versus 58.0 per 100 000 patients for women and men, respectively.[2] Similarly, among 16 091 patients with DCM undergoing cardiac transplantation,[3] and in a contemporary DCM registry,[4] women constituted only 31% and 33% of the respective cohorts. However, pediatric DCM cases do not appear to demonstrate a sex bias.[5] Collectively,

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Nonstandard Abbreviations and Acronyms

AL	light chain amyloidosis
ATTRwt	wild-type transthyretin cardiac amyloidosis
DCM	dilated cardiomyopathy
DD	Danon disease
HCM	hypertrophic cardiomyopathy

these observations may illustrate differences in access to care in adult women and true sex-based biological differences in the manifestations of DCM in children versus adults. Other examples of the complex interplay between biology and environment are seen in acquired DCM. Alcoholic cardiomyopathy is more prevalent in men related to their greater alcohol consumption. Women, however, are more vulnerable to the detrimental effects of alcohol and develop alcoholic cardiomyopathy at lower levels of consumption than men.[6] Myocarditis results in hospitalization for twice as many men as women, but once hospitalized, the mortality rate in women is double that in men.[7]

DCM is familial or determined to have a genetic etiology in ≈40% of cases. Studies investigating family screening of probands with DCM have indicated that women and men are equally likely be diagnosed with DCM.[8] Although X-linked, recessive, and matrilineal (from variation in mitochondrial genes) inheritance occur, autosomal dominant is most common. Over 50 putative DCM-linked disease genes have been reported, but after applying rigorous standards, 19 genes play the most prominent role and account for the majority of DCM cases.[9,10] Among DCM probands, the yield of genetic testing is ≈30% and does not vary by sex in adults[11] or children.[5] The impact of sex on the expression of pathogenic variants has not been fully elucidated, but several observations are described below.

Titin truncating variants represent the most common identifiable cause of DCM, found in ≈20% of patients.[12] Higher penetrance and younger age at presentation have been demonstrated in men, who tend to exhibit worse systolic function and higher rates of atrial fibrillation (Figure 1).[13] This may be partly explained by greater alcohol abuse in men.[14] Women carrying titin truncating variants appear to be at greater risk of peripartum DCM, further corroborating an interplay between genetic and sex-related features.[15] Mutations in the sarcomere genes *MYH7*, *TNNT2*, *TPM1*, and *TNNC1* account for ≈6% of genetic DCM. Unlike DCM caused by titin truncating variants, which is an adult illness, DCM caused by these other sarcomeric genes may present across a broad spectrum of ages, from infancy to late adulthood, but without obvious sex-based differences in penetrance or expression.[16,17] Pathogenic variants in *LMNA*, encoding the nuclear lamina proteins lamin A and C, are present in 4% to 8% of adults with DCM and present with skeletal myopathy, conduction disease, severe and progressive LV dysfunction, and a heavy burden of atrial and ventricular arrhythmias. Because women with *LMNA* heart disease are at ≈45% lower risk for life-threatening ventricular arrhythmias,[18] male sex is used along with other risk factors to identify high-risk patients who may benefit from primary prevention implantable cardioverter-defibrillator placement.[19] In contrast, progression to end-stage heart failure (HF) in *LMNA* DCM does not appear to vary by sex.[20,21]

Truncating variants in the desmosome gene desmoplakin and the cytoskeletal gene filamin C cause DCM with an increased burden of ventricular tachyarrhythmias. The penetrance of desmoplakin gene seems higher in women.[22] However, disease severity and the expression of associated cutaneous abnormalities associated with desmoplakin gene variants (curly hair, palmar-plantar keratoderma) do not appear to differ by sex. In filamin C gene cardiomyopathy, there was a trend toward a lower risk of major cardiovascular events in women in one multicenter study.[23] Variants in the X-chromosome gene dystrophin cause Becker and Duchenne muscular dystrophy in men. While female

Table 1. Unanswered Questions in Sex- and Sex-Specific Differences in Cardiomyopathies

Should sex-specific cutoff values for cardiac mass and dimensions normalized to body size in cardiomyopathies be developed?
More studies are needed to identify sex-specific diagnostic cutoffs for LV dimensions in cardiomyopathies
Are there differences in molecular, proteomic, and metabolic signatures of female vs male myocardium?
Implementation of basic science studies is pivotal to evaluate differences between sexes and potential therapeutic targets.
Do structural and functional characteristics differ in male and female hiPSC-derived cardiomyocytes?
Sex-specific hiPSCs are useful models to evaluate cardiomyocyte characteristics. Through this technique a deeper insight into pathophysiology and eventually drug development may be feasible.
What is the impact of sex on the expression of pathogenic genetic variants?
A wider use of genetic testing and further association studies between female sex and clinical outcomes are warranted.
How can awareness be raised for sarcomeric HCM and phenocopies that are frequently misdiagnosed or delayed in diagnosis in women?
Educational and sensibilization initiatives for cardiologists may be useful to raise awareness.
How do socioenvironmental factors impact disease progression and outcomes in women with cardiomyopathies?
More studies are needed to evaluate the impact of socioenvironmental factors in cardiomyopathies.

HCM indicates hypertrophic cardiomyopathy; hiPSC, human induced pluripotent stem cell; and LV, left ventricular.

Table 2. Clinical Characteristics and Sex-Related Differences in Cardiomyopathies

Pathology	Transmission and genes	Pathophysiology and clinical features	Clinical characteristics by sex
DCM	Acquired familial: Autosomal dominant (TTNtv, MYH7, MYBPC3, LMNA)	LV or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment Clinical manifestations: HF, atrial and ventricular arrhythmias	Women compared with men present: 1. ↓ prevalence in epidemiologic studies 2. ↓ representation among patients undergoing cardiac transplantation Acquired DCM: 1. Alcoholic cardiomyopathy: more prevalent in men but women more vulnerable to alcohol-related damage 2. Men are more hospitalized for myocarditis, although hospitalized women present higher mortality rate. Familial DCM: 1. Women and men are equally likely be diagnosed with DCM 2. Yield of genetic testing is similar between sexes 3. Clinical characteristics are influenced by sex and mutation
Sarcomeric HCM	Autosomal dominant sarcomeric genes (MYH7, MYBPC3)	LVH ≥15mm unexplained by abnormal loading conditions. LVH ≥13mm in familial HCM Patients may: - remain asymptomatic, - develop HF symptoms attributable to LVOTO or diastolic dysfunction - develop a restrictive or hypokinetic phenotype (minority) - present a higher risk of atrial and ventricular arrhythmias variable according to clinical characteristics	Women compared with men are: 1. Underrepresented in HCM cohorts 2. Older at diagnosis 3. ↑ rate of HF progression and all-cause mortality 4. ↑ symptom burden and ↓ exercise capacity regardless of LVOTO. 5. ↑ prevalence of pulmonary hypertension 6. ↑ diastolic dysfunction, smaller LV cavities. 7. ↑sarcomere variant carriers
Fabry disease	X-linked GLA	Reduced or undetectable GLA enzyme activity and progressive accumulation of glycosphingolipids in cells Multisystemic disease: gastrointestinal symptoms, peripheral neuropathy, juvenile stroke febrile crisis, angiokeratomas, hypohidrosis, cornea verticillata, chronic kidney disease Cardiac manifestations: concentric LVH, HF, arrhythmias	Hemizygous men: 1. Early-onset multisystemic disease associated with truncating mutations and absent residual enzyme activity (neurological, gastrointestinal, cutaneous, ophthalmological, cardiac manifestations) 2. Late-onset forms attributable to missense mutations and preserved residual enzyme activity (cardiac, renal, neurological manifestations) Heterozygous women: various degrees of disease severity depending on the inactivation level of the wild-type X chromosome.
Danon disease	X-linked LAMP2	LAMP2 deficiency leads to failure to complete the final step of the autophagic process with cellular formation of vacuoles with undigested glycogen Cardiomyopathy, myopathy, and cognitive impairment Cardiac manifestations: Rapidly progressive LVH, HF, arrhythmias	Hemizygous men: adolescence onset with rapid progression to HF Heterozygous women: 1. Often unrecognized because of later onset and slower progression 2. DCM presentation more frequent among women 3. ↓ extracardiac manifestations
Cardiac amyloidosis	ATTRwt (senescent transthyretin) ATTRv (mutated transthyretin) AL	Extracellular deposition of fibrils that originate from misfolded amyloidogenic proteins in the heart Clinical manifestation: HF with preserved ejection fraction and reduced ejection fraction in end stage, atrial arrhythmias	ATTRwt: men 90% of the population → women are older and with more advanced heart disease ATTRv: male predominance has been reported for Val30Met, Ile68Leu and Val122Ile. No differences in clinical presentation have been seen 1. AL: men and women have similar prevalence of the disease with no differences in clinical presentation
Arrhythmogenic cardiomyopathy	AD (DSC2, DSG2, DSP, JUP, PKP2)	fibro-fatty replacement of the myocardium → electrical instability and dysfunction of the right or the left ventricle or both Clinical characteristics: Ventricular arrhythmias	Men have ↑ prevalence and worse outcome compared with women → the role of sex hormones and exercise has been called into play

AL indicates light chain amyloidosis; ATTRv, hereditary transthyretin cardiac amyloidosis; ATTRwt, wild type transthyretin cardiac amyloidosis; DCM, dilated cardiomyopathy; DSC2, Desmocollin-2; DSG2, Desmoglein-2; DSP, desmoplakin; GLA, α-galactosidase A; HCM, hypertrophic cardiomyopathy; HF, heart failure; JUP, junctional plakoglobin; LAMP2, lysosomal associated membrane protein 2; LMNA, lamin A/C; LV, left ventricular; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MYBPC3, myosin-binding protein C; MYH7, myosin heavy chain 7; PKP2, plakophilin-2; and TTNtv, titin truncating variant.

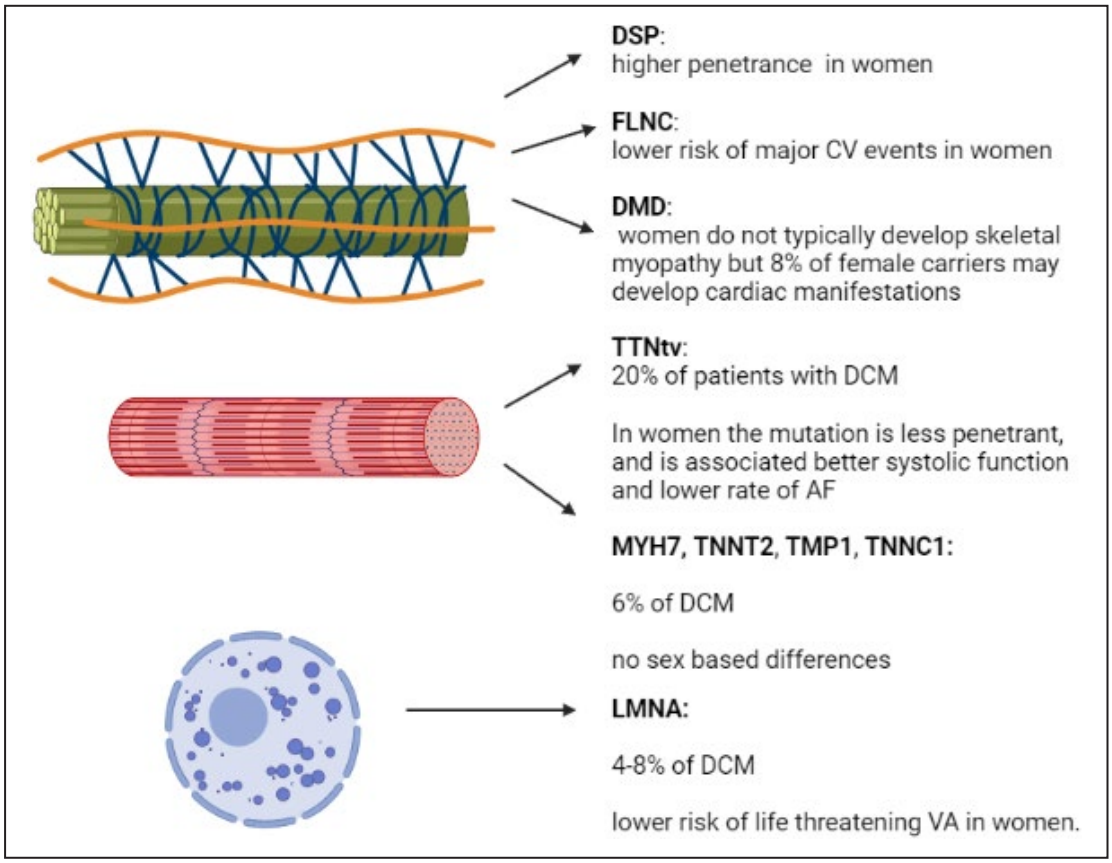

Figure 1. Clinical characteristics of pathogenic variants in women compared with men with dilated cardiomyopathy.
AF indicates atrial fibrillation; CV, cardiovascular; DCM, dilated cardiomyopathy; DMD, dystrophin; DSP, desmoplakin; FLNC, filamin C; LMNA, lamin A/C; MYH7, myosin heavy chain 7; TNNC1, troponin C1; TNNT2, troponin T2; TPM1, tropomyosin alpha-1 chain; TTNtv, titin truncating variants; and VA, ventricular arrhythmia.

carriers of pathogenic dystrophin gene variants do not typically develop skeletal myopathy, ≈8% will develop cardiac manifestations, including DCM, and longitudinal clinical surveillance is appropriate. Women with dystrophin gene–associated DCM may present late in adulthood, but most are diagnosed during adolescence.[24]

Overall, few consistent sex-related trends in the development of DCM have been identified to date. The complicated and oftentimes confounding interactions between biological and societal/environmental influences to disease pathogenesis further challenge study. However, with greater use of genetic testing, new and more consistent genotype-phenotype correlations are emerging, improving management and risk prediction. Continued development of genotyped registries will be critical to gain additional insights regarding the impact of sex and genetic background on disease expression.

HYPERTROPHIC CARDIOMYOPATHY

A number of large single-center and multicenter studies, including collectively >17 000 patients and spanning >15 years, have documented sex differences in the presentation, phenotype, symptom burden, and clinical outcomes in patients with HCM. Women are consistently underrepresented, comprising 35% to 45% of total patient cohorts.[25–28] Additionally, women are 6 to 9 years older at the time of diagnosis or first visit, and more symptomatic at presentation than their male counterparts.[25–29] (Table 2 and Figure 2). Among candidates for myectomy or alcohol septal ablation, female patients present more frequently as New York Heart Association class III/IV compared with men,[26,28] but the proportion of women with more advanced symptoms is consistently higher across all studies, regardless of LV outflow tract obstruction. Consistently, women have lower objective exercise capacity compared with men,[26,30] even after controlling for age and sex, and increased E/E′ and right ventricular systolic pressure values, reflecting a greater magnitude of diastolic dysfunction and pulmonary hypertension.
Pulmonary hypertension is reported in >80% of patients with obstructive HCM and severe HF. This is attributable to a combination of increased LV cavitary pressure, diastolic dysfunction, and mitral regurgitation, all contributing to HF symptoms.[31] However, a minority of

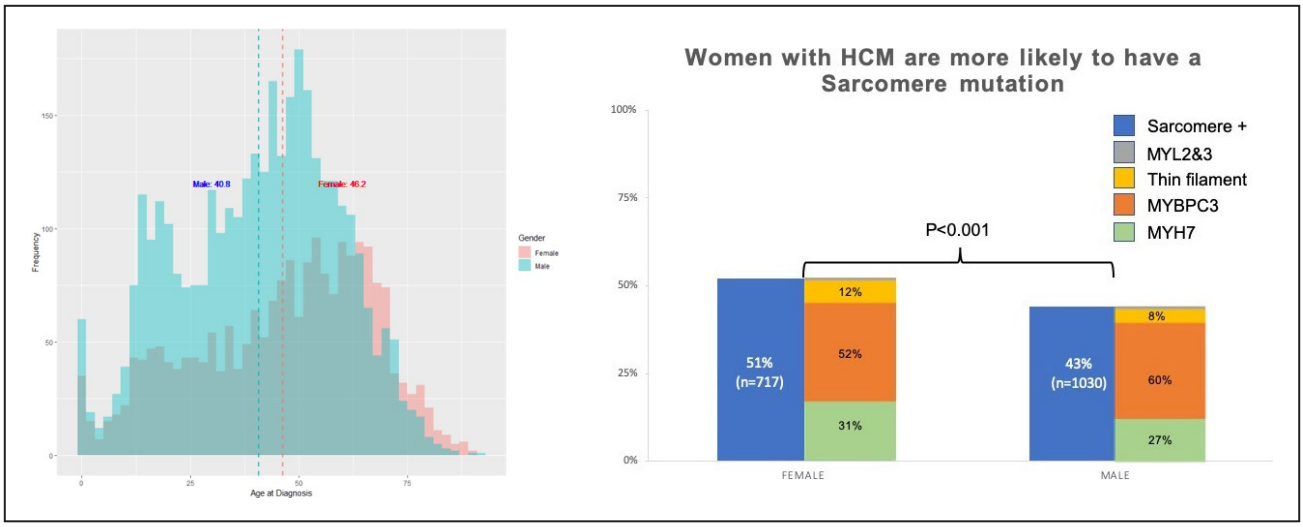

Figure 2. Women are older than men at the time of hypertrophic cardiomyopathy (HCM) diagnosis and were more likely to have a sarcomere mutation.

Left: Age at HCM diagnosis for all women (shaded pink) and men (shaded blue), irrespective of sarcomere variant status. Where age of diagnosis overlaps, the frequency of female patients is represented by the darker color. Mean age of diagnosis labeled and indicated by line. Right: Frequency of pathogenic/likely-pathogenic sarcomere variants in patients who had undergone genetic testing, excluding patients with multiple variants.[10] MYBPC3 indicates myosin-binding protein C; MYH7, beta-myosin heavy chain; and MYL2&3, myosin regulatory light chains 2 and 3.

patients, of whom almost 60% were women, showed normal pulmonary capillary wedge pressure, raising the possibility of coexistent precapillary pulmonary hypertension. Indeed, women with HF with preserved ejection fraction show differences in pulmonary vascular reactivity with higher pulmonary vascular resistance and blunted compliance compared with men.[32] Although the underlying pathophysiology is still unresolved, women have a 4 times greater prevalence of idiopathic pulmonary arterial hypertension compared with men.[33] This may suggest that there are intrinsic sex differences in pulmonary vascular function and remodeling, contributing to exercise intolerance independent of pulmonary capillary wedge pressure.

On average, women with HCM have smaller LV cavities than men, with a greater proportion manifesting LV outflow tract obstruction, and increased relative use of alcohol septal ablation or septal myectomy.[25–29] Of patients referred for septal myectomy at Mayo Clinic, women had higher resting LV outflow tract obstruction gradients and more severe mitral regurgitation compared with men but comparably excellent results.[34] Notably, while the rate of HF progression and risk of stroke[25] and atrial fibrillation[29] seem greater in women than in men, the incidence of sudden cardiac death is similar.[25–28] In most studies, women also have higher all-cause mortality, with hazard ratios from 1.13 to 1.5 after adjustment for factors such as older age, New York Heart Association class, comorbidities, genetic status, LV ejection fraction, and left atrial diameter.[25,26,29]

Despite similarities in the referral and uptake of genetic testing, a greater percentage of women are sarcomere gene variant carriers compared with men (Figure 2).[25,28] Women with variants in *MYBPC3* and thin-filament genes present at older ages, while those with variants in *MYH7* present at similar ages to their male counterparts. Indeed, the penetrance of sarcomere gene variants has been reported as ≈3-fold higher in men than women.[35,36] However, sex seems to act as a phenotype modifier to a greater extent for *MYBPC3* and thin-filament gene variants compared with *MYH7* variants.

Increased penetrance of sarcomere gene variants in men compared with women suggests that underlying biological mechanisms, if anything, would favor a worse prognosis for men. The later age of presentation and greater symptomatic burden in women therefore supports the premise that suspicion for HCM is reduced in women, resulting in more frequent misdiagnosis or delayed diagnosis. Men are more likely to have cardiovascular screening tests, and HCM may be detected earlier as an incidental finding more frequently.[27] Together, these differences highlight the need for a higher index of diagnostic suspicion and lower threshold for referral for specialized care to improve the outcomes and survival of women living with HCM.[37,38]

HYPERTROPHIC HEART DISEASE CAUSED BY X-LINKED GENETIC VARIANTS

DD is a rare, X-linked dominant, and highly penetrant vacuolar myopathy caused by pathogenic variants in the lysosomal-associated membrane protein 2 gene[39,40] (Table 2). The

lysosomal-associated membrane protein 2 is integral to the final step of the autophagic process, and its absence or reduced expression results in marked accumulation of late autophagic vacuoles in cardiac and skeletal muscle cells.[40] DD is believed to represent 5% of all pediatric HCM patients and 17% to 30% of HCM patients with preexcitation on the ECG.[41–44] Historically, DD has been described as having a triad of clinical manifestations including cardiomyopathy, skeletal myopathy, and cognitive impairment. However, because of its X-linked nature and the hemizygous male status, DD arises 1 to 2 decades earlier in men, with onset typically by adolescence.[45–47] Women have far less common extracardiac manifestations than men, making the clinical diagnosis challenging and often delayed in the absence of family history or genetic testing.[45,47,48] DD cardiomyopathy is typically rapidly progressive. A DCM phenotype has been described, more frequently among women, but occurs rarely. Cardiac conduction abnormalities are common and independent of sex, including atrioventricular block and ventricular preexcitation.[45–48] Following the onset of cardiac disease, progression toward advanced HF is rapid in men, resulting in death or heart transplantation before the age of 30 years. In women, progression is slower, with death or transplant occurring in the fourth or fifth decade.[48]

Fabry disease is an X-linked lysosomal storage disorder caused by pathogenic variants in the alpha-galactosidase A gene resulting in deficiency of alpha-galactosidase A enzyme activity and accumulation of glycosphingolipids in a wide range of cell types, resulting in multisystem disease including cardiac, renal, and cerebrovascular manifestations (Table 2).[49] The spectrum of clinical involvement is variable from severe disease in "classical" hemizygous male patients to predominant cardiac and renal involvement in "cardiac variants" and "renal variants," respectively. The cardiac phenotype is slowly progressive and may be difficult to distinguish from classic sarcomeric HCM by cardiac imaging alone and in the absence of extracardiac red flags. Heterozygous women have long been considered clinically unaffected "gene carriers." However, this is a misconception, as heterozygous women often have clinical manifestations and may develop severe phenotypes similar to men[50–52] because of unfavorable X-chromosome inactivation.[53] As a general rule, however, signs and symptoms of Fabry disease at any given age are milder in women, and typical cardiac, cerebrovascular, and renal disease present ≥1 decades later than in men.[50,51] The frequency and severity of cardiac manifestations increase with age in both sexes,[54] with cardiovascular disease being the main cause of death among patients with Fabry disease.[55]

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis is characterized by the extracellular deposition of amyloid fibrils in the heart. The amyloidogenic proteins in the majority of cases are senescent or mutated transthyretin in wild-type transthyretin cardiac amyloidosis (ATTRwt) and hereditary transthyretin cardiac amyloidosis, or monoclonal immunoglobulin light chains in light chain amyloidosis (AL).

Men represent 90% of all patients with ATTRwt,[56] and sex hormones may influence transthyretin levels. In fact, in animal models, 5α-dihydrotestosterone was more effective than estradiol in raising transthyretin expression. Furthermore, women present overall a reduced concentration of sex hormones compared with men in older age.[57] In a recent work, women with ATTRwt were older at diagnosis and showed more advanced disease compared with men with higher NT-proBNP (N-terminal pro-B-type natriuretic peptide), greater concentric hypertrophy, higher LV filling pressures, and worse right ventricular systolic function.[58] The older age of presentation and the more severe presentation may be related to diagnostic delay. The latter, in its turn, may be attributable to a milder disease progression,[59] the lack of sex-specific diagnostic cutoffs for LV hypertrophy, and the lower clinical suspicion of cardiologists that are used to seeing mostly male patients with ATTRwt.

A male predominance has been reported also in hereditary transthyretin cardiac amyloidosis, in particular in patients with late-onset transthyretin cardiac amyloidosis Val30Met in Japan[60] and Sweden,[61] as well as in Ile68Leu and Val122Ile mutation.[58,62]

In the previous study, including mostly patients with Ile68Leu and Val122Ile mutation, men presented higher normalized mass compared with women, which may suggest a greater myocardial involvement. This behavior might be explained by fibril composition. In a Swedish cohort with late-onset Val30Met amyloidosis, women with type A fibrils (a mixture of truncated and full-length transthyretin cardiac amyloidosis fibrils) had lesser concentric remodeling compared with men, while no difference between sexes was reported in patients with type B fibrils (full length).[63]

AL frequency seem less influenced by sex, and men have a slightly higher incidence of AL than women.[64] Women with hereditary transthyretin cardiac amyloidosis and AL do not present relevant clinical differences compared with men at baseline.[58,62] Eventually, no differences in all-cause mortality have been reported between sexes in AL, ATTRwt, and hereditary transthyretin cardiac amyloidosis.[58,62]

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy is characterized by fibro-fatty replacement of the myocardium and

subsequent electrical instability and dysfunction of the right, or the left ventricle or both.[65] The pattern of inheritance is autosomal dominant, and pathogenic variants are mainly found in genes encoding desmosomal proteins. The disease is characterized by variable disease penetrance and expressivity and a high risk of life-threatening ventricular arrhythmias.[66] There is higher disease prevalence and worse outcomes among men as compared with women.[67,68] In particular, men more frequently have abnormal ECGs and late potentials, worse biventricular cardiac function with a higher risk for ventricular arrhythmias compared with women.[68,69] To explain this phenomenon, a role of sex hormones has been postulated. In an induced pluripotent stem cell–derived arrhythmogenic cardiomyopathy cardiomyocyte model, elevated testosterone levels worsened, whereas normal estradiol levels decreased cardiomyocyte apoptosis and lipogenesis.[70] Furthermore, data suggest an association with vigorous-intensity exercise training and arrhythmias and cardiomyopathy progression in arrhythmogenic cardiomyopathy. The historically higher proportion of men participating in competitive sports as compared with women may thus also influence the observed sex-based prevalence and natural history of the disease.[71] A mechanistic insight into this phenomenon has been recently provided through an animal model. In mice, plakophilin-2 loss and training synergically worsened cardiac function because of a reduced reserve of desmosomal proteins.[72] Although in a limited sample, when adjusted for exercise, odds of proband status and ventricular arrhythmias did not differ between sexes, and, after introduction of exercise restrictions, disease progression did not differ between sexes.[69]

SEX-SPECIFIC PATHOMECHANISMS AND CARDIAC REMODELING

LV Remodeling and Adaptation

LV mass and dimensions indexed for body size are significantly lower in women compared with men.[73,74] These differences should be taken into consideration to avoid underestimation of disease-mediated remodeling in women, and imply that we need sex-specific thresholds to diagnose cardiac remodeling in cardiomyopathies (Figure 3). At the time of cardiomyopathy phenotype development, both structural and ultrastructural changes occur and start to progress, generally at a slow rate, over the years. These are influenced by sex. For example, in the specific setting of obstructive HCM, indexed septal thickness and atrial dimensions are significantly greater in women at the time of myectomy or alcohol septal ablation.[75,76] Furthermore, women with HCM exhibit worse diastolic dysfunction, subtended by more advanced fibrosis, lower capillary density, and, at the molecular level, more evident changes in HF-associated proteins (eg, SERCA2a and titin).[75,77] Thus, women seem to develop a worse structural and functional adaptation to obstruction in HCM, and this might contribute to their worse prognosis.[27]

Electrophysiological Remodeling

Electrophysiological remodeling is a hallmark of cardiomyopathies. Sex differences in cellular cardiac electrophysiology exist, which may be either increased or attenuated by disease. Reports on sex-dependent arrhythmic burden vary considerably: women with DCM caused by truncating variants in the giant sarcomere gene titin appear to have longer event-free survival than men,[13,78] whereas women with HCM, irrespective of genotype, show a similar prevalence of ventricular arrhythmias compared with men.[25]

From a translational perspective, regardless of the underlying defect, cardiomyocyte adaption to contractile or metabolic impairment generally leads to prolongation of action potential duration attributable to reduced expression and function of potassium channels and altered intracellular calcium handling. Both mechanisms are markedly arrhythmogenic, exposing to early and delayed afterdepolarizations. In a human ventricular cardiomyocyte model, female cells showed longer action potential duration with limited repolarization reserve and increased propensity to drug-induced arrhythmias caused by QT interval prolongation.[79,80] Indeed, sex hormones, and in particular 17β-estradiol, seem to modulate the hERG/KCNH2 channel[79,81] eventually reducing its activity and prolonging the QT interval in both human and guinea pig cells (Figure 4).[82] Paradoxically, however, increased plasma 17β-estradiol levels in healthy women treated for infertility correlated with acceleration of cardiac repolarization, the in vitro mechanism being enhanced KCNH2 membrane trafficking.[83]

Studies in cardiomyocytes from explanted human hearts point to L-type calcium current enhancement as a potential mechanism for longer action potential duration in women in various conditions.[80] Greater expression of the L-type cardiac calcium channel Cav1.2α and the sodium-calcium exchanger NCX1 have been detected in epicardial LV cardiomyocytes derived from postmortem human LV tissue samples of fertile women compared with postmenopausal women or to men. These differences were partially reproduced in female cardiomyocytes from human induced pluripotent stem cells exposed to 17β-estradiol, while electrophysiological properties of male cardiomyocytes were slightly or not affected.[84] A recent in silico model

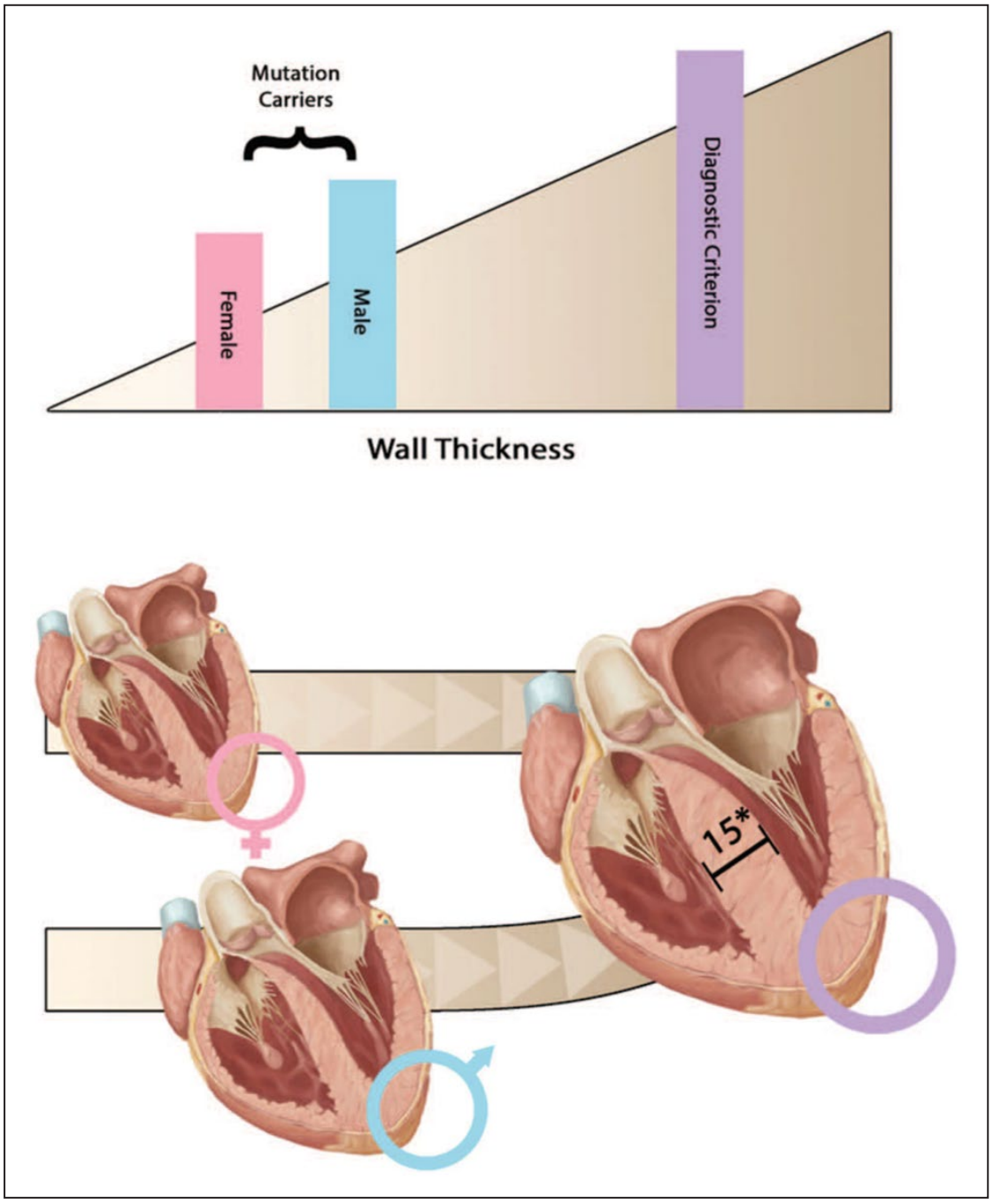

Figure 3. Women show lower left ventricular (LV) mass and dimensions indexed to BSA compared with men.
As a consequence, a relatively greater degree of hypertrophy is needed in women to reach the diagnostic criteria for hypertrophic cardiomyopathy (HCM); this might contribute to a delay in diagnosis and treatment. Reproduced with permission from van Driel et al. [74]©2019 Wolters Kluwer Health, Inc.

of "healthy" human ventricular action potential, based on updated electrophysiological properties of isolated cardiomyocytes, could not reproduce action potential duration prolongation in women compared with men, but only a slightly slower calcium transient decay.[85] Finally, in ventricular cardiomyocytes of male patients with compensated myocardial hypertrophy, a higher frequency of calcium sparks and sarcoplasmic reticulum leakage has been shown, compared with women, although this did not result in increased arrhythmogenic propensity or greater diastolic impairment in vitro.[86] Consistently, cardiomyocytes from patients with

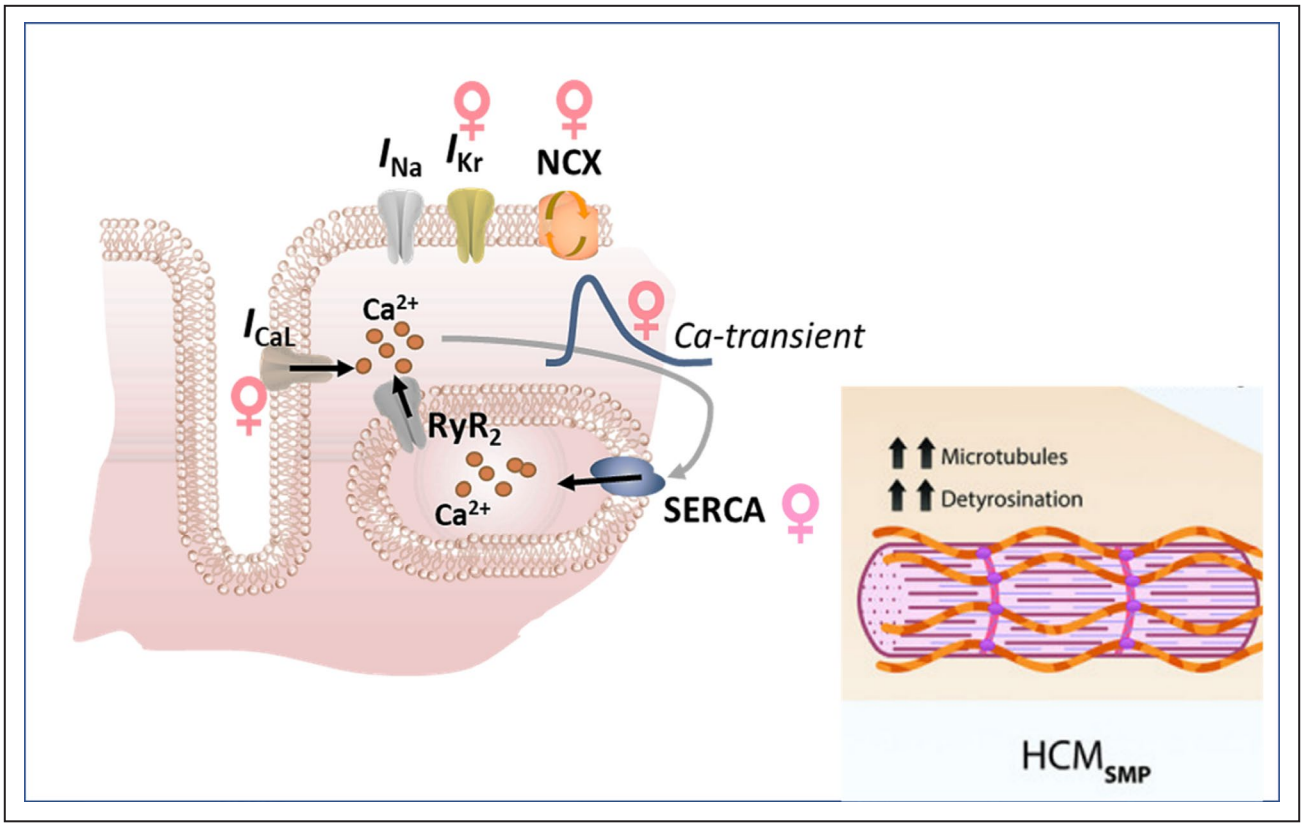

Figure 4. Channels and pumps as targets of 17β-estradiol in human cardiomyocytes.
The rapidly activating component of the delayed rectifier K^+ current (IKr), coded by KCNH2, is modulated by sex hormones. A greater expression of L-type cardiac calcium channel, sodium-calcium exchanger NCX1 and a slower decay of the calcium transient have been detected in women compared with men. A higher frequency of calcium sparks and sarcoplasmic reticulum leakage has been described in men compared with women. Increased levels of detyrosinated microtubules may contribute to the worse diastolic function in women with hypertrophic cardiomyopathy. HCM_{SMP} indicates hypertrophic cardiomyopathy sarcomere mutation-positive.

HCM[87,88] do not exhibit sex-dependent differences in calcium transient kinetics.[85]

RNA Sequencing and the Role of Inflammation

To identify whether sex-specific changes in the human heart contribute to differences in disease progression and drug response, extensive multiomics analyses, stratified by sex, are warranted. An RNA sequencing study in 46 control hearts revealed sex-specific differential expression of autosomal genes involved in inflammation, which are key in cardiac remodeling.[89] These included a variety of chemokines and, importantly, vascular cell adhesion molecule 1, which regulates endothelial cell adhesion of immune cells.[89] An age-dependent shift toward a proinflammatory state was observed exclusively in female cardiac samples, including downregulation of Sirt1 and Sirt3, NAD^+-dependent deacetylase sirtuins, which are involved in anti-inflammatory responses and mitochondrial biogenesis and function[90] and of superoxide dismutase 2, a key mitochondrial antioxidative enzyme.

Sex Differences in Proteomics

Recent studies also suggest differences in the proteome of male and female cardiomyopathic hearts at early and advanced disease stages.[91,92] For example, proteomics and functional studies have identified tubulins as potential treatment targets for HCM.[93–95] It has been hypothesized that the higher tubulin levels found in female patients may contribute to their more advanced diastolic dysfunction compared with men.[75,76]

SOCIOECONOMIC DETERMINANTS OF HEALTH IN WOMEN

It is well known that differences in incidence and outcomes of cardiovascular diseases in women may be influenced by socioenvironmental factors. Overall, lower income, living in rural areas, belonging to a racial minority, lower social support, and lower levels of education have been associated with higher risk of cardiovascular events, all factors that disproportionately

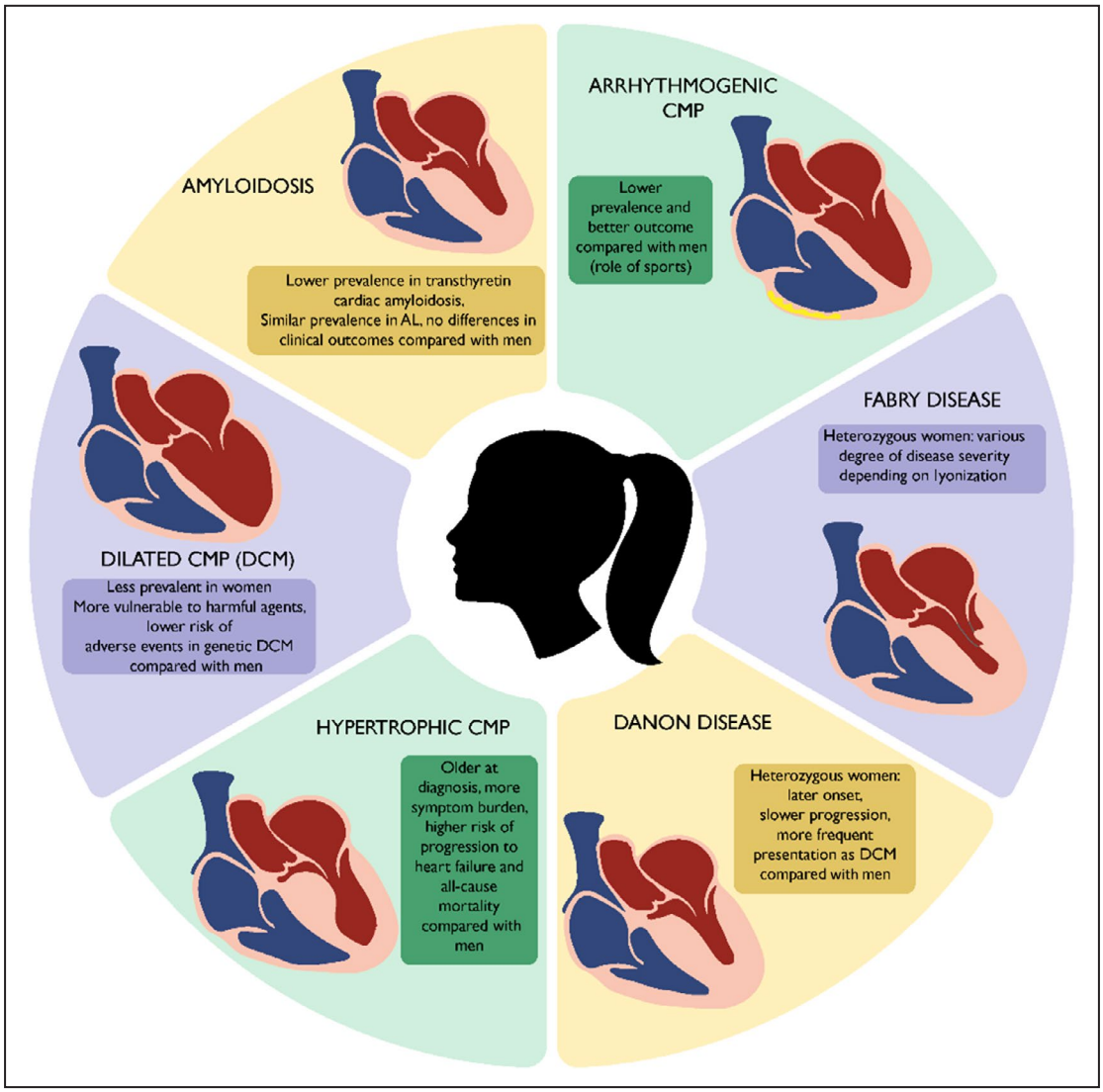

Figure 5. Sex-related differences in cardiomyopathies.
"Sex" refers to the biological differences between men and women. AL indicates light chain amyloidosis; CMP, cardiomyopathy, and DCM, dilated cardiomyopathy.

affect women.[96] Further studies to evaluate the impact of socioeconomic factors on outcomes of patients with cardiomyopathies are warranted.

SUMMARY

Phenotypic expression of cardiomyopathies may differ profoundly between sexes (Figure 5). This phenomenon is the result of a complex interaction among true biological differences and socioenvironmental factors. To date, our understanding of both aspects remains poor, and while genetic and molecular diversity deserves a comprehensive, translational approach to the core mechanisms of disease, the abolition of social discrepancies and discriminations should be pursued equally aggressively in the health care community.

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Disclosures

None.

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