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Sex Differences of the Diabetic Heart

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Type 2 diabetes is a chronic disease associated with micro- and macro-vascular complications, including myocardial ischemia, and also with a specific and intrinsic cardiac dysfunction called diabetic cardiomyopathy (DCM). Both clinical and animal studies demonstrate significant sex differences in prevalence, pathophysiology, and outcomes of cardiovascular diseases (CVDs), including those associated with diabetes. The increased risk of CVDs with diabetes is higher in women compared to men with 50% higher risk of coronary artery diseases and increased mortality when exposed to acute myocardial infarction. Clinical studies also reveal a sexual dimorphism in the incidence and outcomes of DCM. Based on these clinical findings, growing experimental research was initiated to understand the impact of sex on CVDs associated with diabetes and to identify the molecular mechanisms involved. Endothelial dysfunction, atherosclerosis, coagulation, and fibrosis are mechanisms found to be sex-differentially modulated in the diabetic cardiovascular system. Recently, impairment of energy metabolism also emerged as a determinant of multiple CVDs associated with diabetes. Therefore, future studies should thoroughly analyze the sex-specific metabolic determinants to propose new therapeutic targets. With current medicine tending toward more personalized care of patients, we finally propose to discuss the importance of sex as determinant in the treatment of diabetes-associated cardiac diseases to promote a more systemic inclusion of both males and females in clinical and preclinical studies.

Keywords: type 2 diabetes, cardiovascular diseases, sex differences, gender differences, ischemic heart diseases, personalized care, cardioprotection, diabetic cardiomyopathy

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INTRODUCTION

An alarming report from the International Federation of Diabetes recently highlighted that prevalence of diabetes keeps increasing worldwide, affecting 463 million people in 2019 (International Diabetes Federation, 2019). Cardiovascular (CV) complications remain the predominant causes of morbidity and mortality among diabetic patients with an increased risk of heart failure, coronary artery diseases (CADs), myocardial infarction (MI), diabetic cardiomyopathy (DCM), and stroke (American Diabetes Association, 2015). Despite an estimated prevalence of diabetes slightly lower in women in comparison with men (9 vs. 9.6%) (International Diabetes Federation, 2019), strong evidence suggests worse CV consequences and mortality in diabetic women, independent of age. Consequently, there is a growing

interest for a better understanding of the molecular mechanisms involved in this phenomenon (Kautzky-Willer et al., 2016).

IMPACT OF ESTROGENS ON CARDIOVASCULAR SYSTEM

Multiple studies show that female hormones, particularly estrogens, have a beneficial effect on CV health (Dantas et al., 2012; Kander et al., 2017). Estrogen receptors ERα and ERβ are expressed in endothelial cells, vascular smooth muscle cells, and cardiomyocytes of both sexes (Cid et al., 2002; Iorga et al., 2017). Estrogens can affect lipid metabolism, energy balance, fat distribution, insulin sensitivity, and blood pressure and increase bioavailability of nitric oxide (NO) (Cid et al., 2002; Ventura-Clapier et al., 2017a). Estrogens also positively regulate vascular relaxation factors, such as prostaglandin I2. Therefore, estrogen has the ability to positively regulate CV risk factors, such as obesity, hypertension, and glucose mishandling. Studies on ovariectomized animals demonstrate greater impairment of left ventricular function following an ischemia-reperfusion episode with an implication of apoptosis, pro-inflammatory cytokines, and reactive oxygen species (ROS). Treatment with estrogens resulted in restoration of cardiac function, indicating a potential cardioprotective role of female sex hormones (Lagranha et al., 2010; Yang et al., 2018).

Compared with men, women have a higher percentage of fat mass, primarily accumulating in the subcutaneous area (Power and Schulkin, 2008). Estrogens modulate fat distribution through the expression of their receptors. Of interest, a higher ERα/ERβ ratio has been shown to correlate with lower adiposity, especially at the visceral level (Davis et al., 2013). Importantly, healthy women present lower intracardiac lipid levels than men (Huang et al., 2017), and male sex is a predictor of myocardial steatosis (Kannel and McGee, 1979; Iozzo et al., 2009). Thus, favorable distribution of fat participates in CV health in women. Another important point is the lower blood pressure from adolescence onward, due to 27% less renin system activity (Blenck et al., 2016). Hypertension is a well-known CV risk factor affecting both sexes but with higher incidence and severity in men (Kjeldsen, 2018). Endogenous estrogen maintains vasodilation, contributing to the control of blood pressure in premenopausal women (Garcia et al., 2016).

INCREASED RISK IN CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETIC WOMEN

Several parameters linked to sexual dimorphism could contribute to higher CV risk in type 2 diabetic (T2D) women in comparison to T2D men (**Table 1**).

A role of estrogen and its receptors has been evocated to explain the higher CV risk found in T2D women. Increased expression of ERβ compared with ERα is associated with increased oxidative stress, inflammation, and atheromatous plaque formation (Xing et al., 2009), leading to the development of type 2 diabetes and CV complications. Diabetic women present higher insulin resistance (Flanagan et al., 2006; Reichelt et al., 2013) and are more likely to be glucose intolerant, and diabetic men have elevated fasting blood glucose levels (Rydén et al., 2007). Estrogen supplementation in postmenopausal women decreases fasting blood glucose and, thus, improves glucose tolerance (Huang et al., 2017). Ovariectomized Sprague–Dawley

TABLE 1 | Sexual dimorphism in cardiovascular risk factors in absence or presence of diabetes.

	Male	Female	References
Absence of diabetes			
Lifestyle			
Food intake and energy expenditure	↑	↓	Kautzky-Willer et al., 2016
Risk of T2D with consumption of sugary drinks	–	↑	Eshak et al., 2013
Physical activity and MI risk	↓	↑	Kriska et al., 2006
Smoking and CADs risk	↓	↑	Thomas, 2017
Smoking and diabetes risk	=	=	Willi et al., 2007
Fat distribution			
Fat percent	↓	↑	Power and Schulkin, 2008
Preferential localization	Visceral	Subcutaneous	Power and Schulkin, 2008; Blüher, 2013
Ectopic cardiac fat	↑	↓	Kannel and McGee, 1979; Iozzo et al., 2009
Blood pressure			
Basal systolic and diastolic blood pressure	↑	↓	Blenck et al., 2016; Kjeldsen, 2018
Incidence and severity of HT	↑	↓	Anand et al., 2008
Cardiac adaptation to HT	Eccentric hypertrophy	Concentric hypertrophy	Krumholz et al., 1993; Santos and Shah, 2014
HF failure risk	↓	↑	Beale et al., 2018
Glucose metabolism			
Basal insulin level	↓	↑	Flanagan et al., 2006; Reichelt et al., 2013
Risk of diabetes	↑	↓	International Diabetes Federation, 2019
Presence of diabetes			
Fat distribution			
Preferential localization	Visceral	Visceral	Power and Schulkin, 2008
Risk of CADs with obesity	↓	↑	Elffers et al., 2017; Lind et al., 2017
Cardiac lipid level	↓	↑	Iozzo et al., 2009
Blood pressure			
Incidence and severity of HT	↓	↑	Anand et al., 2008
Glucose metabolism			
Manifestation	Impaired fasting blood glucose	Impaired glucose tolerance	Rydén et al., 2007
Insulin resistance	↓	↑	Flanagan et al., 2006; Reichelt et al., 2013
CV risk with prediabetes	–	↑	Levitzky et al., 2008

Arrows in the "male" column indicate differences in comparison to female; and arrows in the "female" column indicate differences in comparison to male. CV, cardiovascular; CADs, Coronary artery diseases; HF, heart failure; HT, hypertension.

females had poorer glucose tolerance than non-ovariectomized animals (Saengsirisuwan et al., 2009). Importantly, prediabetes (fasting blood glucose: 100–125 mg/dL) is predictive of CVDs only in women (Levitzky et al., 2008). The greater insulin resistance found in women, coupled with endothelial dysfunction, may explain the high risk of CV complications in T2D (Rutter et al., 2003).

Importantly, obesity increases the relative risk of CADs by 64% in women as opposed to 46% in men (Elffers et al., 2017; Lind et al., 2017). Besides this, visceral adipose tissue is the source of ectopic deposition of fat in the heart (Tchernof and Despres, 2013), participating in the development of DCM through lipotoxicity (Listenberger et al., 2001; Bugger and Abel, 2014). T2D women have a more pronounced increase in intracardiac lipid content than T2D men (Iozzo et al., 2009). The ERβ receptor prevalence results in an adipogenic and diabetogenic profile (Blüher, 2013; Davis et al., 2013), probably explaining this difference.

Rutter et al. (2003) show that the increase in left ventricular mass and wall thickness correlating to glucose intolerance is more important in women than in men, largely accounted for by obesity and pressure overload. Hypertension is more pronounced in T2D women than in T2D men, and sex appears to influence morphological cardiac adaptation to hypertension (Santos and Shah, 2014). Women tend to develop concentric hypertrophy compared with men who tend to develop eccentric hypertrophy (Krumholz et al., 1993). This is confirmed in animal models (Olsson et al., 2001). A decrease in peroxisome proliferator-activated receptor-α (PPARα) signaling is found in hypertrophic males but not in females (Harrington et al., 2017), and acute inhibition of PPARα blocks the sex difference in hypertrophy development. Accordingly, in humans suffering from aortic stenosis, Kararigas et al. (2014) reveal that cardiac hypertrophy is related to increased activation of profibrotic and inflammatory markers in men compared with women.

SEXUAL DIMORPHISM IN ISCHEMIC HEART DISEASES ASSOCIATED WITH DIABETES

In the general population, incidence of MI remains higher in men than in women. CVDs appear on average 10 years earlier in men than in women (Kannel and McGee, 1979; Thom et al., 2006; Anand et al., 2008; Dantas et al., 2012). Interestingly, women seem to lose this sex-related protection in the presence of T2D (Murphy, 2011). This could be primarily due to differences in diagnosis and treatment of MI itself. Symptoms experienced by women are, in 50% of cases, different from the classic symptoms recognized in men, such as feelings of exhaustion, digestive disorders, and shortness of breath (Mehta et al., 2016), resulting in delayed treatment (Bugiardini et al., 2017). When considering CADs, women have a 50% higher risk than men, presenting increased mortality when exposed to acute MI (Kannel, 1987; Toedebusch et al., 2018) with a strong impact of long-standing diabetes in women (Natarajan et al., 2005). Several studies show a higher risk of CADs at lower glucose levels in women (Koro et al., 2008; Levitzky et al., 2008). The Framingham study also demonstrated that risk of MI is increased by five in T2D women compared with non-diabetic women, and this risk is only multiplied by two in T2D men (Kannel et al., 1974; Wannamethee et al., 2012). Moreover, 38% of women die within 1 year of their first MI although only 25% of men do so (Thom et al., 2006).

Concomitant development of atherosclerosis, endothelial dysfunction, and impairment of the coagulation profile could explain, in part, why diabetic women present a higher risk of ischemic heart diseases (IHDs). Clinical studies reveal a more severe atherogenic dyslipidemia in diabetic women, particularly through an increase in triglycerides and lipoprotein cholesterol concentrations (Walden et al., 1984). Accumulation of oxidized low-density lipoprotein within arteries is a mechanism contributing to the development of atherosclerotic plaques. In particular, Chen et al. (2002) show that its receptor, the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), has an important role in atherosclerosis development. Interestingly, sex differences in LOX-1 are reported with a particularly high expression in diabetic and obese women (Brinkley et al., 2008), making it an interesting pathway related to sex differences in diabetes and IHDs.

Atherosclerosis is an important factor contributing to the development of endothelial dysfunction. Diabetic women are also characterized by greater endothelium impairment in comparison to diabetic men. Clinical studies particularly show endothelium-dependent vasodilation alteration, which is confirmed in different animal models of T2D (Alameddine et al., 2015; Ranucci et al., 2019). A decrease in endothelium-dependent and -independent vascular response is observed in female Goto-Kakizaki rats with lower coronary flow and reduced upregulation of the NO pathway (Desrois et al., 2017; Palee et al., 2017). Zhang et al. reveal a predisposition of females to vascular lesions after induction of diabetes in both mesenteric arteries and the aorta (Zhang et al., 2012; Hunter et al., 2017). Regulation of the protein kinase B pathway may also contribute to vascular endothelial dysfunction and myocardial sensitivity to an ischemia-reperfusion episode (Desrois et al., 2004), especially in females (Reichelt et al., 2013). Goel et al. (2008) suggest that estrogen causes gender-specific endothelial dysfunction in hyperglycemic conditions by increasing the expression of PKCβ and increasing O_2^- production in females. Hyperglycemia also alters the balance of estrogen receptors and increases both oxidative stress and the level of vasoconstrictors (Donahue et al., 2007; Wannamethee et al., 2012; Hunter et al., 2017).

Interaction between endothelial impairment and platelet aggregation is also implicated in atherosclerosis pathogenesis. Diabetic women present elevation of fibrinolytic/thrombotic factors during the transition from normoglycemia to diabetes (Steinberg et al., 2000; Donahue et al., 2007, 2011), leading to a prothrombotic coagulation profile (Steinberg et al., 2000; Donahue et al., 2007). Meigs et al. report an increase in circulating levels of thrombosis-promoting factors (Plasminogen activator inhibitor-1, von Willebrand factor) and adhesion molecules (vascular cell adhesion molecule 1, intercellular adhesion molecule 1) associated with atherosclerosis and microvascular diseases (Meigs et al., 2006; Madhu, 2010). In addition, women

with T2D are more sensitive to changes in coagulation and inflammation than men, which could be explained by the fact that women have a larger platelet count as well as higher platelet reactivity than men (Ranucci et al., 2019). Together, concomitant development of atherosclerosis, endothelial dysfunction, and impairment of the coagulation profile lead to a favorable environment for IHD development in diabetic women (**Figure 1**).

Mechanisms involved in increased mortality following myocardial infarction in diabetic women are not fully understood. Nevertheless, energy metabolism has recently emerged to explain this sex difference (**Figure 1**). A strong decrease in ATP and phosphocreatine cardiac content has been observed following ischemia-reperfusion injury in prediabetic female rats fed with a high-fat, high-sucrose diet and in diabetic GK female rats (Fourny et al., 2019a,b). Importantly a previous study reports no difference in high-energy compounds following ischemia-reperfusion injury in male GK (Desrois et al., 2010), suggesting the important role of mitochondria and particularly the energy production pathway in female sensitivity to IHDs.

SEXUAL DIMORPHISM IN HEART FAILURE ASSOCIATED WITH DIABETES

Heart failure is driven by CADs but also by aging, hypertension, diabetes, and obesity (Ho et al., 2016; Beale et al., 2018; Seferović et al., 2018). The excess risk of HF associated with diabetes is significantly greater in women with diabetes than in diabetic men (Ohkuma et al., 2019), increasing HF risk fivefold in women compared to 2.4-fold in men (Beale et al., 2018). Kim et al. (2019) also show that the impact of diabetes on long-term mortality and HF readmission seems to be greater in females than in males. Women represent ∼60% of patients having HF with preserved ejection fraction (HFpEF) whether they present with diabetes or not, but T2D women are younger, more obese, have worse renal function, lower prevalence of atrial fibrillation, and decreased hemoglobin levels (Lejeune et al., 2021). Importantly, HFpEF is more prevalent in women than in men, who preferentially exert HF with reduced ejection fraction (Beale et al., 2019; Dewan et al., 2019). In line, Weinberg et al. (1999) show sex-related differences in genes regulating calcium handling and contractile function. Males have higher beta-myosin heavy chain and atrial natriuretic factor, and lower SERCA-2 mRNAs in comparison with females despite a similar left ventricular hypertrophy and systolic overload (Weinberg et al., 1999).

Besides CADs and hypertension, the diabetic heart is characterized by alterations of its structure and mass as well as of its diastolic and systolic function, leading to the concept of DCM (Boudina and Abel, 2010). Interestingly, DCM prevalence is higher in women in comparison to men. In particular, Kiencke et al. (2010) show that female gender is an independent risk factor for DCM, characterized by greater structural and functional impairment (Kiencke et al., 2010; Toedebusch et al., 2018; **Figure 1**).

Myocardial remodeling occurs during DCM development with an increase in fibrosis and collagen I and III deposits, leading to myocardial rigidity (Murphy et al., 2017). Studies show greater myocardial remodeling and fibrosis in women with HF compared with men (Li et al., 2017). Women with T2D have greater cardiac hypertrophy, myocardial wall thickening, and an increase in left ventricular mass. Greater hypertrophy is also observed in female GK rats compared with males (Desrois et al., 2004). Estrogen receptor ERβ is shown to play an important role in the regulation of collagen levels (Schuster et al., 2016). Schuster et al. (2016) reveal that overexpression of ERβ in mice reduced myocardial fibrosis and collagen I/III deposits, improving cardiac function. Inversely, Skavdahl et al. (2005) detect basal cardiac hypertrophy in female mice deficient for ERβ, confirming the important role of this receptor for cardiac hypertrophy development in females. Moreover, imbalance between ERα and ERβ is reported in diabetic women and may explain the loss of estrogen cardioprotection regarding myocardial hypertrophy and fibrosis in DCM (Wells et al., 2005).

A fined-tuned regulation of metabolism and energy production is essential for heart function (Horman et al., 2012; Bertrand et al., 2020). Female cardiomyocytes contain

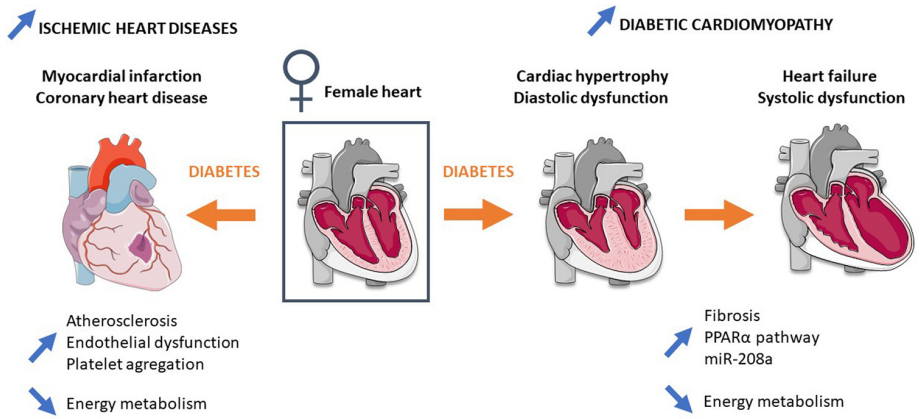

FIGURE 1 | Mechanisms involved in the higher risk and mortality of type 2 diabetic women in ischemic heart diseases and diabetic cardiomyopathy. Detailed information is provided in the main text. Blue arrows represent differences in comparison to diabetic men.

less mitochondria, but they are more efficient than in male cardiomyocytes. Female hearts use fatty acids for energy production in greater proportion than males (Djouadi et al., 1998; Ventura-Clapier et al., 2017b). They also produce fewer ROS, have a lower calcium uptake rate, and a greater calcium retention capacity (Ventura-Clapier et al., 2017b). This sexual dimorphism does not lead to a difference in respiration and mitochondrial efficiency in the basal state but could play a role in pathological situations such as DCM. Of interest, a mitochondrial localization of estrogen receptors is reported, inducing direct effects of estrogen on mitochondrial respiration and antioxidant defenses (Gupte et al., 2015). Billimoria et al. (2006) show a greater mitochondrial respiration in female streptozotocin-treated (STZ) rats in comparison with corresponding males. Lagranha et al. (2010) show that the phosphorylation level of mitochondrial proteins is more important in females compared with males. This is particularly the case for the aldehyde dehydrogenase 2, leading to a decrease in ROS production (Lagranha et al., 2010; Tchernof and Despres, 2013).

Metabolic inflexibility is commonly noticed in the diabetic heart, which mainly relies on fatty acid oxidation for energy production (Vallerie and Bornfeldt, 2015). The increase in fatty acid oxidation in the diabetic heart is associated with an increase in PPARα, which plays a key role in the development of cardiac hypertrophy and dysfunction in DCM (Madrazo and Kelly, 2008; Bayeva et al., 2013). Interestingly, estrogen is involved in the signaling pathway of lipid metabolism and may explain the differences in mitochondrial metabolism observed between diabetic males and females. Indeed, Djouadi et al. (1998) show, in PPARα$^{-/-}$ mice, that the subsequent inhibition of cellular fatty acid metabolism caused massive accumulation of hepatic and cardiac lipids, hypoglycemia, and death in 100% of males but only 25% of females. The treatment with β-estradiol decreased the mortality in males, demonstrating the role of female sex hormones in lipid homeostasis mediated by PPARα (Djouadi et al., 1998). In the last decade, micro-RNAs emerged as biomarkers of DCM and targets for new treatment. Yin et al. (2019) show that miR-30c protects cardiac metabolism and function in diabetes through PPARα modulation and its downstream effector, the co-activator Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α). The miR-208a, whose overexpression induced spontaneous cardiac hypertrophy (Callis et al., 2009), is another miR playing a role in DCM. Recently, Lum-Naihe et al. (2017) highlighted higher miR-208a expression in female diabetic hearts than in male counterparts.

PERSONALIZED CARE OF DIABETIC PATIENTS

Involvement of female hormones in various physiological and pathophysiological processes has led the scientific community to focus their research on the male sex. However, we currently know that women have a different clinical presentation and drug response in multiple pathologies, including CVDs and T2D (Mathieu et al., 2018; Fourny et al., 2019b). First, clinical trials demonstrated sex differences in lifestyle intervention in diabetic patients. Moderate-intensity resistance exercise training is a more favorable approach for hypertensive women because of greater decreases in diastolic blood pressure and significant increases in flow-mediated dilation compared with their male counterparts (Collier et al., 2011). Weight loss with intensive lifestyle modification led to greater decreases in glucose/insulin concentration, insulin resistance, triglyceride, and glycated hemoglobin HbA1c levels in men than in women, indicating that women should particularly pay attention to risk factors, such as obesity (Perreault et al., 2008). This was confirmed in animal models in which diet change is most effective to reduce inflammation in male mice (Griffin et al., 2019).

Sex differences are also reported in regard to the response to antidiabetic drugs. In young patients, metformin plus rosiglitazone was more effective in girls than in boys (Zeitler et al., 2012). In adults, women had a higher reduction of body weight after treatment with metformin or sulfonylurea, whereas men displayed higher HbA1c reduction after treatment with metformin only (Schütt et al., 2015). Sex differences were also reported for incretins with a better glycemic control in men (Anichini et al., 2013) while others showed greater weight loss, reductions of fasting glucose, and blood pressure levels in women (Pencek et al., 2012). The LEADER study highlighted a greater CV benefit in men than in women with liraglutide treatment (Verma et al., 2018). Recently, Raparelli et al. (2020) demonstrated greater CV effectiveness of GLP-1 receptor agonist in women. However, "the real-world experience" study showed that men achieved target glycemic response in higher proportions than women after 1 year of exenatide (Anichini et al., 2013). A greater glycemic response and HbA1c reduction was found with sulfonylureas than with thiazolidinediones in men, whereas female sex was associated with greater HbA1c reduction but a weight gain and edema risk with thiazolidinediones (Dennis et al., 2018). Interestingly, Zinman et al. (2015) reported no sex difference in the EMPA-REG OUTCOME trial in effects of a sodium-glucose cotransporter 2 inhibitor. However, subgroup analysis showed a significant CV benefit in males only (Kautzky-Willer and Harreiter, 2017). In 2020, an important study showed no differences for vascular efficacy outcomes or death with major protection against major adverse CV events, HF, vascular death, and total mortality in both men and women (Rådholm et al., 2020). Taken together, these studies clearly show that sex should be considered in the choice of antidiabetic treatment to move toward "precision medicine," which aims to treat patients with accurate care that is more personalized and including individual variability (Currie and Delles, 2018; Prasad and Groop, 2019). However, mechanisms involved in these differences are not yet understood, and disparity of antidiabetic treatments used, alone or in combination, makes comparison difficult.

The choice of the animal model to be employed is also delicate for the efficient transfer of results to humans, particularly when comparing males and females. Indeed, studying females is not always possible in animal T2D models. For example, the female TallyHo mouse does not show hyperglycemia unlike males (Kim et al., 2005) and the female Nagoya-Shibata-Yasuda mouse has a low incidence of type 2 diabetes compared with

males (Ueda et al., 1995). Besides this, enriched diets are also commonly used in the literature, but their diversity and duration make comparison difficult. Thus, each diet-induced and energetic diabetic model should be well characterized to ensure good interpretation of the results obtained in both sexes.

CONCLUSION

In conclusion, clinical and animal studies clearly indicate that there are sex differences in T2D-associated CV complications. However, the precise molecular mechanisms responsible for these differences are still largely blurred. Recent studies have particularly emphasized the link between energy metabolism and miRs. Thus, future studies should particularly pay attention to the metabolic dysfunctions that are involved in both IHDs and DCM development. This could provide new targets for the treatment of the diabetic heart. In addition, the antidiabetic drug response also differs significantly according to sex. Therefore, the scientific community must include both sexes in future clinical trials and animal studies to improve quality of care and bring a more personalized treatment to each patient.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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