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## **Diabetic Cardiomyopathy: The need for adjusting experimental models to meet clinical reality**

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1 **Diabetic Cardiomyopathy:**

2 **The need for adjusting experimental models to meet clinical reality**

3  
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29

1 **Abstract:**

2 Diabetic cardiomyopathy (CM), occurring in the absence of hypertension, coronary  
3 artery disease and valvular or congenital heart disease, is now recognized as a  
4 distinct, multifactorial disease leading to ventricular hypertrophy and abnormal  
5 myocardial contractility that correlates with an array of complex molecular and  
6 cellular changes.

7 While animal models provide the unique opportunity to investigate mechanistic  
8 aspects of diabetic CM, important caveats exist when extrapolating findings obtained  
9 from preclinical models of diabetes to humans. Indeed, animal models do not  
10 recapitulate the complexity of environmental factors, most notably the duration of the  
11 exposure to insulin resistance that may play a crucial role in the development of  
12 diabetic CM. Also, most preclinical studies are performed in animals with uncontrolled  
13 or poorly controlled diabetes, whereas most patients undergo therapeutic  
14 intervention. Finally, while T2DM is a disease of the elderly in humans, most rodent  
15 models employ juvenile or young adult animals.

16 The aim of this review is to identify the current limitations of rodent models, and to  
17 discuss how future mechanistic and preclinical studies should integrate key  
18 confounding factors to better mimic the diabetic CM phenotype.

19

20 **Key Words:**

21 Diabetic cardiomyopathy; Type 2 diabetes mellitus; Insulin resistance; organ-to-organ  
22 interaction; Heart Failure

23

## 1 **Introduction:**

2           The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide,  
3           afflicting all ages, sexes, and socioeconomic classes, ultimately leading to frailty and  
4           compromising healthy ageing.<sup>1</sup> Cardiovascular (CV) complications are the leading  
5           causes of morbidity and mortality in T2DM patients, accounting for about two-thirds of  
6           overall deaths as evidenced by the Framingham Heart Study.<sup>2</sup> One of the specific CV  
7           complications in T2DM is the onset of diabetic cardiomyopathy (CM), originally  
8           described as an early diastolic dysfunction progressing to systolic dysfunction and  
9           heart failure (HF) in the absence of hypertension, coronary artery disease and  
10          valvular or congenital heart disease.<sup>3</sup> The CARDIA study provided strong evidence  
11          for the diagnosis of diabetic CM,<sup>3</sup> identifying subtle diastolic and/or systolic  
12          myocardial abnormalities preceding the onset of overt CM and HF.<sup>4-6</sup>

13          Diabetic CM is now recognized as a distinct, multifactorial disease leading to  
14          ventricular hypertrophy and abnormal myocardial contractility that correlates with an  
15          array of complex molecular and cellular changes (Figure 1).<sup>7</sup> Both insulin resistance  
16          and chronic hyperglycaemia contribute to impaired cardiac contractility and structure  
17          via reduced Ca<sup>2+</sup> influx through L-type Ca<sup>2+</sup> channels, abnormal PI3K/Akt pathway  
18          signalling, enhanced production of reactive oxygen species (ROS), advanced  
19          glycation end products (AGEs), and toxic fatty acid (FA) metabolites, as well as  
20          potentially involving less well studied mechanisms such as altered autophagy, and  
21          epigenetic control.<sup>8</sup> Asserting the “uniqueness” of diabetic CM will require  
22          determination of the role of the «metabolic exposome», including diet, lifestyle,  
23          glycemic disorders, obesity and sedentary behavior, alongside other confounders  
24          such as systemic hypertension, sex and ageing, which are intertwined in the  
25          pathogenesis of diabetic CM.<sup>9</sup>

1 Moreover, the complex impact of these environmental factors are magnified by other  
2 processes linking the heart to key metabolic organs, i.e., the adipose tissue, liver,  
3 kidney and the gut (microbiota) that may separately exert noxious cardiac effects  
4 through a crosstalk mediated by pro-inflammatory cytokines, pro-fibrotic factors,  
5 microvesicles, miRNAs and immune cells. This endocrine organ-crosstalk evolves  
6 into a paracrine cellular-crosstalk between cardiomyocytes, fibroblasts, endothelial  
7 cells and immune cells in the myocardium (Figure 2).

8 While animal models provide the unique opportunity to investigate mechanistic  
9 aspects of diabetic complications, including diabetic CM, important caveats exist  
10 when extrapolating findings obtained from preclinical models of diabetes to humans.  
11 Indeed, animal models do not recapitulate the complexity of environmental factors,  
12 most notably the duration of the exposure to insulin resistance that may play a crucial  
13 role in the development of diabetic CM. Also, cardiac physiology such as heart rate,  
14 calcium fluxes, sarcomere composition and vessel function is different in rodents  
15 versus humans, and rodent models are less likely to develop micro- and  
16 macrovascular diseases, which are quite prevalent in T2DM patients. Important  
17 differences also exist in the hormonal milieu and the concentrations of various lipid  
18 species. Furthermore, most preclinical studies are performed in animals with  
19 uncontrolled or poorly controlled diabetes, whereas most patients undergo  
20 therapeutic intervention. Finally, while T2DM is a disease of the elderly in humans,  
21 most rodent models employ juvenile or young adult animals.

22  
23 The aim of this review is to identify the current limitations of rodent models, and to  
24 discuss how future mechanistic and preclinical studies should integrate key  
25 confounding factors to better mimic the diabetic CM phenotype.

1 Authors of this review are all partners of the CARDIATEAM consortium, a H2020  
2 Innovative Medicine Initiative (IMI) funded project, aiming to assess the uniqueness  
3 of diabetic CM and develop an innovative approach involving deep clinical  
4 phenotyping for back translation to tailored preclinical models recapitulating human  
5 diabetic CM.

### 6 7 **Investigating diabetic cardiomyopathy in preclinical models: the importance of** 8 **clinical confounding factors:**

9 Most of the molecular mechanisms involved in the pathogenesis of diabetic CM have  
10 been investigated in rodent models of type 1 or type 2 diabetes mellitus (Table 1).  
11 The models consist of animals with defective insulin actions or signalling, altered  
12 cardiac glucose and/or FA utilization, enhanced oxidative stress, and/or cardiac  
13 fibrosis.<sup>10, 11</sup> The most popular animal models include the chemical ablation of the  $\beta$ -  
14 cells of the pancreas by Streptozotocin, genetic interference with leptin signalling  
15 (*ob/ob* and *db/db* mice, ZDF rats), the induction of insulin resistance by exposure to  
16 high fat diet (HFD) and transgenic animals with a cardiac-specific lipotoxicity.<sup>10</sup>  
17 However, important confounding factors contributing to cardiac remodelling and  
18 dysfunction are rarely considered when dissecting the signalling pathways leading to  
19 diabetic CM in rodent models. Experimental approaches that more closely mimic the  
20 clinical scenario in T2DM patients are detailed below:

#### 21 **▪ Ageing**

22 Many of the cardiac abnormalities (i.e., increased wall thickness and interstitial  
23 myocardial fibrosis, cardiomyocyte hypertrophy) found in diabetic CM are analogous  
24 to those induced by ageing.<sup>12, 13</sup> Recent studies suggest that T2DM accelerates the  
25 ageing of the heart and may therefore represent a form of premature senescence

1 leading to premature onset of HF.<sup>14</sup> Indeed, T2DM has a dramatic impact on cellular  
2 senescence of different types of stem cells, including cardiac stem cells and  
3 potentiates the accumulation of senescent cells in the heart.<sup>15</sup>  
4 Senescent cells display a complex phenotype including DNA damage and genomic  
5 instability, endoplasmic reticulum stress, mitochondria dysfunction, impaired  
6 contractile function, hypertrophic growth and change in gene expression involving a  
7 rise of a unique secretory phenotype (senescence-associated secretory phenotype:  
8 SASP) and induction of senescence-associated beta-galactosidase positivity.  
9 Senescent cardiomyocytes secrete growth factors, creating a profibrotic  
10 microenvironment and promoting activation of cardiac fibroblasts, which is harmful to  
11 the myocardium and triggers processes associated with maladaptive cardiac  
12 remodelling.<sup>13, 16</sup> Furthermore, T2DM induces epigenetic alterations, such as  
13 hypermethylation of CpG islands, increased trimethylation of Histone 3 (H3) at lysine  
14 (K)4, H3K9, H3K27, and H4K20, as well as a decreased monomethylation and  
15 acetylation of H3K9. These epigenetic modifications contribute to senescence  
16 through changing the access of transcription factors to promoter/enhancer regions  
17 and are complemented by noncoding RNA regulation by microRNA (i.e., miR 34a)  
18 and long-noncoding RNA.<sup>17</sup>  
19 To underscore the importance of senescence in the pathogenesis of diabetic CM,  
20 senolytic drugs have been shown to alleviate myocardial hypertrophy, fibrosis, and  
21 diastolic dysfunction in db/db obese mice.<sup>18</sup> Such observations have suggested  
22 diabetic CM as a model of premature cardiac aging and that senolytic therapy can  
23 prevent this T2DM-related complication.<sup>19</sup>

24     ▪ **Sex**

1 Women with T2DM, independent of age, are at higher risk of developing CV diseases  
2 (CVD) compared to age-matched men, and tend to manifest a more severe cardiac  
3 remodelling in diabetic CM.<sup>20, 21</sup> Interestingly, this sex-dependent aggravation of  
4 diabetic CM has been successfully recapitulated in several female rodent models.  
5 For instance, ZDF female rats exhibit cardiac hypertrophy with reduced capillary  
6 density and increased myocardial structural damage, even though males develop  
7 more pronounced fibrosis.<sup>22</sup> Increased hypertrophy and endothelial **dysfunction**  
8 have also been shown in female GK rats compared to males.<sup>23</sup> In the db/db mouse  
9 model left ventricular pro-hypertrophic and pro-oxidant gene expression were  
10 exaggerated in female leading to an increased cardiomyocyte size as compared with  
11 males.<sup>24</sup> This difference is probably due to sex hormones and neurohormonal  
12 diversity coupled with gender-specific activation of molecular pathways involved in  
13 cardiac metabolism/remodelling.<sup>25, 26</sup> For instance, sex differences have been  
14 demonstrated in terms of a dichotomous fatty acid handling pattern: differential FA  
15 activation together with acylcarnitine (AC) and triglyceride (TG) metabolism has been  
16 reported in the GK rat model, with increased accumulation of AC species and  
17 reduced TG in female compared to male rats, thus providing enhanced production of  
18 ROS in cardiomyocytes.<sup>27</sup>

19 Therefore, exploring both sexes in preclinical models of CVD is recommended.<sup>26, 28</sup>

#### 20 ▪ **Obesity / adiposity**

21 Adipose tissue represents an intersection of pathways involved in longevity, genesis  
22 of age-related chronic diseases, metabolic dysfunction, and low-grade inflammation.  
23 Obesity and adiposity are causally linked to the development of T2DM and strongly  
24 contribute to diabetic CM.<sup>29</sup> The cardiac risk of obesity per se, without diabetes and  
25 other co-morbid conditions, is underscored by its close association with structural,



1 functional, metabolic, and haemodynamic changes in the heart, leading to a condition  
2 clinically termed as obesity CM.<sup>30</sup> Cardiac alterations related to obesity include  
3 progressive increase in left ventricular (LV) mass, LV remodelling with interstitial  
4 fibrosis and systolic dysfunction that may lead to HF in both patients and rodent  
5 models<sup>31, 32</sup> and less energetic efficiency with reduced ATP delivery in obese CM  
6 hearts.<sup>33</sup> Several wild type high fat diet (HFD) or genetically modified rodent models  
7 have shown to partially recapitulate features of human obesity CM (Table 1).  
8 Although conflicting data exists as per the ability of HFD to induce myocardial  
9 dysfunction these are likely explained by differences in mouse strains, the duration  
10 and timing of dietary intervention, and composition of diet.<sup>33, 34</sup> Overall, the  
11 mechanisms by which adiposity contributes to cardiac alterations largely overlap with  
12 those reported for diabetic CM and include oxidative stress, inflammation, apoptosis,  
13 dysregulated autophagy, hypertrophy, interstitial fibrosis, lipotoxicity and metabolic  
14 defects. It seems that not only the degree of adiposity counts but the location of body  
15 fat accumulation influences the risk of cardiac dysfunction: ectopic adiposity (visceral,  
16 pericardial and epicardial) carries a higher risk than subcutaneous fat<sup>35, 36</sup> through the  
17 release of pro-inflammatory and pro-fibrotic factors.<sup>37, 38</sup> Interestingly, the effects of  
18 HFD on cardiac remodelling are reversible, as a switch from HFD to standard diet for  
19 8 weeks reduced lipid accumulation, myocardial hypertrophy, and fibrosis, and  
20 improved myocardial function in 16-week HFD mice.<sup>39</sup> These preclinical data are in  
21 line with clinical intervention studies, such as gastric bypass, caloric restriction or  
22 exercise, intended to reduce myocardial structural and functional consequences of  
23 diabetes or obesity.<sup>40, 41</sup>

24     ▪ **Sedentary life/exercise**

1 Physical exercise is an important non-pharmacological treatment in T2DM, with high  
2 efficacy in delaying or preventing diabetic CM.<sup>42</sup> Preclinical studies have identified  
3 some mechanisms underlying the exercise-related benefits. Exercise inhibits the  
4 pathological processes of myocardial apoptosis, fibrosis, and microvascular  
5 alterations through improving myocardial metabolism (improved glucose oxidation  
6 and reduced FA oxidation), restoring the physiological regulation of Ca<sup>2+</sup> (normalizing  
7 depressed expression and function of SERCA2a in HFD + streptozotocin rats) and  
8 protecting mitochondrial function.<sup>43</sup> Beneficial cardiac effects of exercise are also  
9 mediated by a decrease in adipose tissue senescence and its related pro-fibrotic  
10 secretome, independently of improvement in metabolic status in HFD mice.<sup>44</sup>

11 **▪ Left ventricular pressure overload**

12 Left ventricular pressure overload occurs in a variety of conditions such as advanced  
13 age, hypertension, valvular heart disease, often in association with obesity, and  
14 diabetes. Its deleterious consequences, i.e., myocardial fibrosis and hypertrophy, are  
15 mediated by neuro-hormonal factors involving the sympathetic nervous system and  
16 the renin–angiotensin–aldosterone system (RAAS). The sympathetic nervous system  
17 provides the most powerful, but also deleterious, stimulation of cardiac function, via  
18 catecholamines and their post-synaptic  $\beta$ -adrenergic receptors ( $\beta$ -AR) including  $\beta$ 1-  
19 AR,  $\beta$ 2-AR, and  $\beta$ 3-AR subtypes.<sup>45</sup> Interestingly, diabetic CM, similar to other forms  
20 of HF, displays alterations of autonomic control with reduction of parasympathetic  
21 activity and an increase of sympathetic nervous system activity, which promotes  
22 decreased  $\beta$ -AR responsiveness.<sup>46</sup> The latter increases heart rate, stroke volume  
23 and peripheral vascular resistance, and stimulates the RAAS, exacerbating left  
24 ventricular dysfunction. At the molecular level, elevated sympathetic drive enhances  
25  $\beta$ 1-AR signalling, which promotes hypertrophy, interstitial fibrosis, cardiomyocyte

1 apoptosis and impairs energy metabolism and myocardial function.<sup>45</sup> Additional  
2 mechanistic studies suggested that a canonical downstream effector of  $\beta$ -AR, the  
3 cyclic AMP-dependent protein kinase A (PKA) may be involved in the deficient  
4 ventricular performance and metabolism in the mouse diabetic heart,<sup>47</sup> potentially  
5 giving way to other cAMP effectors, such as the Epac proteins.<sup>48</sup> Interestingly, the  
6 relationship between insulin resistance and  $\beta$ -AR signalling is emerging as an  
7 important focal node in the pathogenesis of diabetic CM since hyperinsulinemia may  
8 play a role in desensitization of  $\beta$ -AR signalling in T2DM. This is well illustrated in a  
9 study showing that in a diabetic CM murine model induced by HFD, myocardial injury  
10 and dysfunction could be reversed by pharmacologically inhibition of  $\beta$ 2-AR or G  
11 protein-coupled receptor kinase 2 (GRK2) activity.<sup>49</sup> In contrast to cardiac  $\beta$ 1- and  
12  $\beta$ 2-AR, the role of the  $\beta$ 3-AR in the diabetic heart has been minimally investigated. It  
13 was reported that a  $\beta$ 3-adrenoceptor-mediated negative inotropic effect contributes to  
14 the altered positive inotropic response induced by  $\beta$ -adrenoceptor activation in  
15 diabetic rat heart.<sup>50</sup>

#### 16     ▪ **Intermittent hypoxia**

17 Prevalence and severity of obstructive sleep apnoea (OSA) is higher among diabetic  
18 individuals compared to non-diabetic subjects.<sup>51</sup> OSA is associated with metabolic  
19 and CV co-morbidities including hypertension, arrhythmia, stroke, coronary heart  
20 disease, which supports OSA as a major health burden. Mechanistic studies in  
21 rodents subjected to chronic intermittent hypoxia (the pathophysiologic basis of OSA)  
22 found that OSA-induced CV dysfunction (vascular remodelling, endothelial  
23 dysfunction, early atherosclerosis and increased arterial blood pressure) depends on  
24 oxidative stress- and HIF1 $\alpha$ -driven sympathetic overactivity. Specifically, increased  
25 levels of ROS and HIF $\alpha$  activate chemoreflex and suppress baroreflex, thereby

1 stimulating the sympathetic nervous system, increasing LV afterload, and contributing  
2 to insulin resistance and T2DM.<sup>52</sup>

3

4

## 5 **Crosstalk between metabolic organs and the heart beyond cardiac glucose** 6 **toxicity:**

7 There is need to consider each major organ, heart, liver, adipose tissue, skeletal  
8 muscle, lung and kidney operating as an integrated network within the human body in  
9 response to dysregulated metabolism. In particular, T2DM is associated with  
10 progressive microvascular disorders and systemic inflammatory processes, inducing  
11 fibrosis in several organs, including CV system, liver, adipose tissue, and skeletal  
12 muscle. During the progression of these fibro-inflammatory processes, there are  
13 significant haemodynamic and metabolic interactions between these organs, which  
14 need to be assessed to predict health trajectories in T2DM patients<sup>53</sup> and more  
15 specifically the progression towards diabetic CM and HF with preserved ejection  
16 fraction (HFpEF).<sup>54, 55</sup> Indeed, dysregulation of both the immune system and  
17 microcirculation through endothelial cell dysfunction and procoagulant changes  
18 contributes to diabetic CM beyond hyperglycaemia, insulin resistance, and metabolic  
19 derangements.<sup>8, 53</sup> Importantly, the microcirculation impacts on insulin sensitivity by  
20 affecting the delivery of insulin and glucose to skeletal muscle. Thus, endothelial  
21 dysfunction and extracellular matrix remodelling promote the progression from  
22 prediabetes to diabetes and the development of diabetic CM and other T2DM  
23 complications, including HFpEF and chronic kidney disease (CKD).<sup>56, 57</sup> Thus, whilst  
24 HFpEF was initially considered as a disorder characterized by hypertension, cardiac

1 hypertrophy and diastolic dysfunction, the pandemics of obesity and T2DM have  
2 modified the HFpEF syndrome. As a result, HFpEF is now recognized as a  
3 multisystem disorder involving the heart, lungs, kidneys, skeletal muscle, adipose  
4 tissue, vascular system, and immune and inflammatory signalling.<sup>54, 58</sup>

5 How inter organ crosstalk during T2DM specifically contributes to diabetic CM  
6 requires further exploration. Animal models of T2DM represent a unique approach to  
7 test the mechanisms of such organ interactions and to assess how the pathological  
8 state developing in one organ, can lead to deleterious functional and structural  
9 consequences in the heart.

#### 10     ▪ **Kidney**

11 T2DM is directly related to both CKD and CVD. Patients with diabetes and CVD are  
12 twice as likely to develop CKD than those without CVD.<sup>56-59</sup> Furthermore, the co-  
13 incidence of HFpEF and CKD is very strong since approximately 50% of the patients  
14 with HFpEF also suffer from CKD.<sup>55, 60</sup> To further underscore a pathophysiological  
15 crosstalk, activated inflammatory cascades and endothelial dysfunction in renal injury  
16 promote features of HFpEF, such as cardiomyocyte stiffening and myocardial  
17 fibrosis.<sup>55</sup> Beside clinical evidence, a causal relationship between CKD and HFpEF  
18 came from an experimental rat model of CKD induced by nephrectomy, which  
19 resulted in a cardiac HFpEF-like phenotype, with left ventricular hypertrophy and  
20 diastolic dysfunction.<sup>61</sup> The kidney-heart relationship is also achieved by complex  
21 interactions involving neuro-hormonal pathways.<sup>62</sup> This is well illustrated with the  
22 RAAS system, which is overactivated during CKD and causes a cascade of events  
23 leading to vasoconstriction, increased sodium retention, and reduced water excretion.  
24 All of which increase blood volume expansion and restore perfusion pressure and  
25 therefore may contribute to the development of HFpEF.<sup>62</sup> Besides its renal effects,

1 aldosterone directly promotes cardiac fibrosis, left ventricular hypertrophy, and  
2 coronary microvascular dysfunction.<sup>58</sup> Additional renal factors such as uremic toxins  
3 and galectin 3 may also have a direct impact on the heart and/or coronary  
4 microvasculature and therefore may play a role in the pathogenesis of HFpEF.<sup>63, 64</sup>  
5 These important interactions between T2DM, renal dysfunction and diabetic CM  
6 induce a downward spiral of deleterious events, whose interruption represents a  
7 novel therapeutic opportunity.<sup>65</sup>

#### 8     ▪   **Adipose tissue**

9     A growing body of evidence supports the existence of a two-way adipose-myocardial  
10    axis in which products released from fat affect myocardial metabolism and function,  
11    whilst peptides secreted from the heart affect FA disposal. Accumulation of ectopic  
12    fat in various organs, e.g., in heart, liver, pancreas and kidney has been identified as  
13    an important marker in the pathogenesis of T2DM in both human and animal  
14    studies.<sup>66-68</sup> Although the causal relationship between the pathophysiological status  
15    of white adipose tissue and cardiac lipotoxicity remains elusive, elevated lipolytic rate  
16    in adipose tissue has been demonstrated to contribute to the overall augmentation of  
17    plasma lipid levels, as observed in the majority of patients suffering from HF.  
18    Excessive release of FA from adipose tissue contributes to myocardial insulin  
19    resistance with subsequent metabolic inflexibility characterised by a shift in cardiac  
20    energy expenditure towards a near-exclusive and less oxygen-efficient FA oxidation.  
21    The perpetuation of this metabolic deregulation leads to the development of cardiac  
22    lipotoxicity.<sup>69, 70</sup> Cardiac lipid overload promotes the formation of cytotoxic  
23    intermediates (diacyl-glycerols and ceramides) and enhances ROS generation  
24    through exacerbated peroxisomal and mitochondria FA oxidation. Both intermediate

1 lipotoxic species and ROS affect mitochondrial function and Ca<sup>2+</sup> handling proteins  
2 promoting cardiac dysfunction.<sup>71, 72</sup>

3 Adipose tissue is an important source of inflammatory mediators (TNF- $\alpha$ , IL6, IL-8,  
4 MCP-1) and adipokines (leptin, resistin, and omentin), which may act in an autocrine,  
5 paracrine, and endocrine manner ultimately furthering cardiac injury.<sup>38, 73</sup> In contrast,  
6 the anti-inflammatory adipokine, adiponectin, has been found to be inversely  
7 correlated with myocardial adiposity. Whilst visceral adipose tissue contributes to a  
8 low-level and sustained systemic inflammation, pericardial and epicardial fat can  
9 directly affect the underlying myocardium by local diffusion of secreted inflammatory  
10 mediators.<sup>74-76</sup> Another ectopic fat source known to influence the heart is the  
11 perivascular adipose tissue (PVAT) surrounding the vasculature, which volume  
12 increases proportionally to elevated visceral adipose tissue.<sup>77</sup> In obesity, PVAT has  
13 been shown to shift from an anti-inflammatory and vasodilatory profile towards a  
14 proinflammatory and impaired vasodilation status favouring the progression of  
15 vascular disease.<sup>78, 79</sup>

16 Finally, a prominent role for atrial and B-type natriuretic peptides (ANP and BNP,  
17 respectively) has been proposed in the crosstalk between the heart and the adipose  
18 tissue.<sup>80</sup> As such, the induction of lipolysis by natriuretic peptides secreted by the  
19 damaged heart has been suggested to counteract obesity, with a disproportionately  
20 greater role in reducing visceral adipose tissue than subcutaneous adipose tissue.<sup>81</sup>

21 On the other hand, increased release of adipocyte FA may contribute to cardiac  
22 steatosis and cardiac cachexia.<sup>82</sup>

23 Further analysis of the crosstalk between adipose tissue and the heart may identify  
24 new treatment options such as targeting lipolysis and cardiac lipid metabolism in  
25 diabetic CM to avoid its progression towards HFpEF.

## 1     ▪   **Liver**

2   Several studies support the bidirectional crosstalk between the heart and liver and  
3   the consequences of simultaneous development of hepatic metabolic diseases,  
4   diabetic CM, and HF. A better understanding of this hepato-cardiac axis is required to  
5   ensure an effective management of T2DM patients with heart or liver diseases in  
6   order to improve overall prognosis.

7   Whilst T2DM and metabolic diseases (obesity and non-alcoholic fatty liver disease)  
8   are important risk factors to induce cardiac dysfunction,<sup>31, 83</sup> a growing body of  
9   evidence suggests that the dysfunctional heart per se could affect both systemic  
10   metabolism and liver function, and thus, create a vicious injurious cycle between  
11   heart and liver. The close association among cardiac and metabolic diseases  
12   suggests a common pathophysiological basis. Notably, in metabolic diseases, the  
13   heart and liver share similar intracellular defects such as mitochondria dysfunction,  
14   ER stress, lipotoxicity and disrupted calcium homeostasis. Interestingly, mitochondria  
15   and endoplasmic reticulum interact at contact sites called mitochondria-associated  
16   membranes (MAMs) to exchange phospholipid and calcium and regulate metabolic  
17   homeostasis and signalling.<sup>84</sup> Of note, reduction of ER-mitochondria communication  
18   was observed in both heart<sup>39</sup> and liver<sup>85</sup> of HFD mice. In the heart, decreased ER-  
19   mitochondria communication caused mitochondrial dysfunction leading to diabetic  
20   CM, whereas in the liver, disrupted ER-mitochondria interactions alters hepatic  
21   metabolic flexibility and insulin sensitivity. Therefore, targeting MAMs could be a new  
22   strategy to concomitantly improve both heart and liver function in T2DM.

23   In addition, the heart secretes proteins referred to as cardiokines, which go beyond  
24   local cardiac effects, and mediate changes in extracardiac tissues, including liver  
25   function. For example, the cardiac atrial natriuretic peptide attenuates glycolysis and



1 increases gluconeogenesis in rat liver.<sup>86</sup> Other studies showed that the heart controls  
2 systemic metabolism via the cardiac-specific microRNA-208a and the mediator  
3 complex subunit 13 (MED13) signalling in rodent cardiomyocytes.<sup>87</sup> Overexpression  
4 of MED13 or inhibition of miR-208a in cardiac tissue of transgenic mice enhanced  
5 lipid uptake,  $\beta$ -oxidation, mitochondrial content, and other genes involved in FA  
6 utilization in adipose tissue and liver,<sup>88</sup> thus supporting the existence of a functionally  
7 relevant, metabolic crosstalk between the heart and liver.

#### 8     ▪   **Skeletal muscle**

9 Sarcopenia is characterized by a loss of skeletal muscle strength due to reduction in  
10 the quality and quantity of muscle mass, replacement of muscle fibres with fat,  
11 changes in muscle metabolism, oxidative stress, degeneration of neuromuscular  
12 junctions and increased fibrosis. Whilst sarcopenia has been described in elderly  
13 individuals, mounting evidence suggests a higher prevalence in T2DM patients.  
14 Sarcopenia in T2DM patients may be caused by different mechanisms, such as  
15 impaired insulin sensitivity, chronic hyperglycaemia, advanced glycosylation end  
16 products, subclinical inflammation, microvascular and macrovascular complications.<sup>89</sup>  
17 It seems that the opposite also applies; patients with sarcopenia are at increased risk  
18 to develop T2DM.<sup>89, 90</sup> In addition, sarcopenia is associated with CVD<sup>91, 92</sup> and both  
19 share common risk factors, such as altered glucose metabolism, insulin resistance,  
20 inflammation, and metabolic syndrome.<sup>93</sup> For instance, T2DM patients with chronic  
21 HF exhibit severe skeletal muscle fibre atrophy, capillary remodelling and impaired  
22 mitochondrial function, characterized by mitochondrial complex I dysfunction, lower  
23 transcript levels of complex I and ROS overproduction.<sup>94</sup>

#### 24     ▪   **Brain**

1 Recent studies shed light on the relationship between the brain and CV system, and  
2 how the brain-heart axis regulates T2DM.<sup>95</sup> Cohort studies highlight the link between  
3 Alzheimer's disease and T2DM,<sup>96</sup> whilst drugs that are currently approved for the  
4 treatment of T2DM, such as metformin, have shown promising results in improving  
5 cognitive function, and even preventing the development of Alzheimer's disease in  
6 diabetic patients.<sup>97</sup>

### 7 **Investigating diabetic cardiomyopathy in preclinical models: the role of cellular** 8 **crosstalk within the heart:**

9 The same inter organ signalling also works in a paracrine and autocrine fashion,  
10 where a given cell type can detrimentally affect neighbouring cells, leading to a  
11 vicious cycle and subsequent cardiac dysfunction. In addition to its signature  
12 parenchymal cells, the contracting cardiomyocytes, the heart contains many other  
13 cells, including fibroblasts, smooth muscle cells, endothelial cells, and resident  
14 macrophages. Crosstalk between these different cells ensures myocardial  
15 homeostasis but a pathologically altered cell-cell communication may initiate and  
16 propagate adverse cardiac remodelling and play a crucial role in the development of  
17 diabetic CM.<sup>58, 98</sup>

#### 18 **▪ Fibroblasts / cardiomyocytes**

19 Cardiac fibroblasts play a crucial role in extracellular matrix (ECM) turnover, as they  
20 are involved in both synthesis and degradation of ECM components through matrix  
21 metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).  
22 Fibroblasts adhere to ECM proteins through integrins that are critical mediators of cell  
23 attachment, adhesive signalling, and remodelling of collagen fibrils. Excessive  
24 cardiac ECM deposition is a key feature of the remodelling response in diabetic CM

1 and promotes myocardial stiffness and cardiac dysfunction in experimental rodent  
2 models of diabetes.<sup>99</sup> Experimentally, high glucose levels induce cardiac fibroblasts  
3 into a state of increased proliferation,<sup>100</sup> with increased DNA and collagen synthesis  
4 as well as fibronectin and TGF-beta-1 gene expression.<sup>101, 102</sup> Genetic inhibition of  
5  $\alpha 11\beta 1$  integrin in STZ diabetic mice prevents the progression of fibrosis and  
6 abnormal cardiomyocyte growth, indicating that this specific integrin plays a critical  
7 role in modifying fibroblast-cardiomyocyte-ECM interactions.<sup>103</sup> Crosstalk between  
8 cardiomyocytes and fibroblasts is also associated with cardiomyocyte switching to a  
9 fibrogenic phenotype, characterized by increased synthesis and release of cytokines  
10 that induce fibroblast proliferation and activation, as well as proinflammatory  
11 molecules that trigger fibrosis through activation of immune cells.<sup>99</sup>

#### 12 ▪ **Endothelial cells**

13 Diabetic CM is associated with coronary microvascular dysfunction, which impairs  
14 coronary blood flow and myocardial perfusion.<sup>104</sup> Abnormalities in the coronary  
15 microcirculation result from endothelial cell dysfunction, which is considered a central  
16 mechanism in HFpEF pathophysiology.<sup>7, 79</sup> Indeed, endothelial cells have altered  
17 paracrine signalling to cardiomyocytes by reducing the bioavailable vasodilator  
18 molecules, nitric oxide (NO) and endothelium-derived hyperpolarising factors  
19 (EDHFs), thereby limiting blood flow and promoting leukocyte infiltration in the  
20 myocardium.<sup>105</sup> The latter leads to activation of myofibroblasts and interstitial  
21 collagen deposition. As part of T2DM-associated glucotoxicity and lipotoxicity,  
22 endothelial cells generate ROS and reactive nitrogen species (RNS) that uncouple  
23 endothelial NO synthase (eNOS) activity (by oxidising eNOS cofactor  
24 tetrahydrobiopterin) leading to decreased NO bioavailability.<sup>106</sup> This effect together  
25 with insulin resistance converges on and minimizes the activity of guanylate cyclase

1 and cyclic guanosine monophosphate (cGMP)- protein kinase G (PKG) signalling that  
2 results in deranged titin phosphorylation and increased cardiomyocyte hypertrophy  
3 and stiffness in diabetic hearts.<sup>107</sup> Endothelial cells can also contribute to the  
4 development of cardiac fibrosis through endothelial-to-mesenchymal transition to  
5 myofibroblasts.<sup>108</sup>

6     ▪   **Immune cells**

7 Numerous experimental and clinical studies have reported a role of adaptive  
8 immunity in diabetic CM pathogenesis.<sup>109-111</sup> T2DM is associated with chronic  
9 systemic inflammation, which leads to leukocyte activation and recruitment to various  
10 organs, further aggravating inflammatory cardiac tissue remodelling over time.<sup>110</sup> This  
11 results in cardiac fibrosis as resident fibroblasts become activated in response to  
12 pathophysiologic conditions, which for the heart, leads to wall stiffening and  
13 decreased contractility.<sup>99</sup> Although the role of B-cells is still unclear, T-cell derived  
14 immune response has shown to contribute to the progression of diabetic CM.<sup>111</sup> As  
15 such, in STZ-induced rodent models of diabetic CM, increased infiltration of T  
16 lymphocytes into the myocardium is positively correlated with increased collagen  
17 deposition and wall stiffness,<sup>110</sup> whilst genetic depletion of CD4+ T cells protects  
18 against cardiac fibrosis and impairment in LV function.<sup>111, 112</sup> Yet, recent studies have  
19 further delineated the contribution of each T-lymphocyte subset in the context of  
20 diabetic CM. Pro-inflammatory T helper cells Th1, Th17 and Th22 subtypes are  
21 increased in diabetic CM,<sup>113</sup> whereas the activation of anti-inflammatory Th2 and  
22 Foxp3+ Treg subtypes is delayed or impaired,<sup>114</sup> overall promoting chronic  
23 inflammatory tissue damage. Increased neutrophil/lymphocyte ratio (an indicator of  
24 systemic inflammation) is associated with the occurrence of subclinical diabetic  
25 CM.<sup>115</sup> As per potential mechanisms involved, the sphingosine-1-phosphate

1 (S1P)/S1P-receptor signalling axis has been shown to regulate T-cell trafficking,  
2 activation, and polarization.<sup>116</sup> Indeed, targeted deletion of T-cell S1P-R or  
3 administration of fingolimod (an analogue of S1P) both reduce myocardial fibrosis  
4 and improve cardiac function in STZ-induced diabetic CM mice.<sup>117</sup>

5 Macrophages also play a key role in regulating inflammatory responses and  
6 homeostatic maintenance of the myocardium. Normally in injured tissue, efferocytosis  
7 allows macrophages to engulf apoptotic cells and cellular debris to reduce  
8 inflammation.<sup>118</sup> Efferocytosis is regulated by many processes in the context of high  
9 glucose. In particular, the metalloproteinase disintegrin and metalloproteinase  
10 domain-containing protein 9 (ADAM-9) were shown to be upregulated in  
11 macrophages, secondary to a downregulation of miR-126, which increased MER  
12 proto-oncogene, tyrosine kinase (MerTK) cleavage with a net effect of reduced  
13 efferocytosis.<sup>119</sup> Interestingly, human diabetic hearts display the same molecular  
14 signatures in terms of miR-126, ADAM9, and cleaved MerTK expression, suggesting  
15 that this chain of events may be involved in regulating human diabetic CM  
16 progression. Recently, cardiac-resident MHCII-high macrophages showed a  
17 pathogenic role in cardiac remodelling through production of IL-10. The profibrotic  
18 effect of IL-10 autocrine loop promotes macrophages to secrete osteopontin and  
19 TGF $\beta$ , which activate cardiac fibroblasts to produce collagen that results in cardiac  
20 fibrosis and increased cardiac stiffness.<sup>120</sup> Therefore, a new understanding of  
21 communication between cardiac resident macrophages and fibroblasts could lead to  
22 novel therapeutic strategies for diabetic CM and its progression towards HF.

23

24 **Investigating diabetic cardiomyopathy in preclinical models: identifying new**  
25 **biomarkers and therapeutic targets**

## ▪ **Biomarkers**

Since T2DM patients at high risk of developing HF display altered metabolism in cardiomyocytes, with underlying changes in protein and metabolite profiles related to hyperglycaemia, lipotoxicity and oxidative stress, a systems biology approach may identify a specific signature of diabetic CM. To reduce disease burden, it is imperative to develop non-invasive biomarkers to detect and characterize diabetic CM processes at their early and possibly reversible stages in order to reveal new therapeutic targets and to follow disease progression. These last years, new methods have emerged, which offer a great potential to identify such biomarkers. Big datasets derived from in silico predictive models, imaging, and omics technologies (metabolomics, lipidomics, transcriptomics, proteomics) may be used for developing multiparametric datasets to assist improved diagnostic and therapeutic decisions.

Metabolic alterations and insulin resistance are early signs of future cardiac dysfunction and have a causative role in the development of the diabetic CM.<sup>121</sup> Metabolomics using different analytical techniques such as magnetic resonance spectroscopy, mass spectrometry and chromatography<sup>122</sup> are powerful approaches to follow simultaneous changes in multiple metabolite levels occurring in the diabetic heart. Indeed, cardiac energetic metabolism assessed by the PCr/ATP ratio, is reduced in some studies,<sup>123</sup> although some discrepancies exist depending on the models.<sup>124, 125</sup> In parallel, lipid metabolism is altered with increased FA oxidation and lipid accumulation.<sup>66</sup>

In silico predictive methods have the potential to reveal or to confirm effective biomarkers. Using this approach and exploiting meta-analysis of transcriptomic datasets, differential expression levels of lysyl oxidase like 2 (LOXL2) and electron transfer flavoprotein beta subunit (ETF $\beta$ ) in serum and heart tissue of 6–16-week-old

1 db/db mice correlated closely with a reduced LV diastolic dysfunction, supporting the  
2 use of LOXL2 and ETF $\beta$  as early predictive biomarkers for diabetic CM.<sup>126</sup>

3 Moreover, systematic multiorgan biobanking of porcine models of diabetes and  
4 obesity subjected to molecular profiling by transcriptomics, proteomics and  
5 metabolomics has been proposed to better understand tissue specific pathogenic  
6 mechanisms and organ crosstalk with the prospect of revealing novel molecular  
7 targets.<sup>127</sup>

8 In the field of imaging technologies, the development of machine learning algorithms  
9 aims to provide more accurate biomarkers.<sup>128</sup> Thus, combining imaging, radiomics  
10 and multi-omics data with machine learning will provide large datasets of parameters  
11 to find pertinent biomarkers for early diagnosis of diabetic CM and predict its  
12 progression.

### 13 **▪ New therapeutic targets**

14 Drug development is time consuming and costly, urging the use of precision medicine  
15 to replace the 'one size fits all' paradigm with more patient tailoring approaches.  
16 Understanding T2DM-specific mechanisms shall lead to opportunities of developing  
17 better therapies. Mechanistic studies have demonstrated dramatic glucotoxicity in the  
18 heart, and linked it to accelerated sugar-related protein modifications, such as O-  
19 GlcNAcylation<sup>129</sup> and AGE formation,<sup>130</sup> as well as from increased ROS formation.<sup>131</sup>  
20 Yet, most interventional studies have focused on the reduction of plasma glucose in  
21 T2DM patients and studies with DPP4 inhibitors and GLP-1 peptides produced  
22 modest effects in terms of improving HF outcomes,<sup>132</sup> whilst the recent benefits  
23 obtained with SGLT2 inhibitor (SGLT2i) treatment for HF and CKD are partly  
24 independent of their hypoglycaemic effects. Many potential mechanisms have been  
25 proposed for SGLT2i.<sup>133-135</sup> For example, studies suggest that natriuresis, diuresis

1 and decreased blood volume that reduced preload and afterload are possible  
2 mechanisms. Reduced cardiac oxidative stress and fibrosis have also been observed  
3 with SGLT2i treatment.<sup>136</sup> Occurrence of ketoacidosis prompted suggestions that  
4 plasma ketone bodies serve as an alternative and efficient source of cardiac fuel.<sup>137</sup> It  
5 has also been proposed that SGLT2 inhibitors have off-target pharmacology by  
6 directly inhibiting cardiac NHE1 activity and protect the myocardium under ischemic  
7 conditions.<sup>138</sup> Nevertheless, confirmation of specific SGLT-2 inhibitor cardioprotective  
8 mechanisms remains elusive to date.

9 Research efforts need therefore to focus on finding therapeutic strategies to inhibit  
10 these pathophysiological pathways, and thereby reduce the risk of diabetic CM. In  
11 addition, the understanding of diabetic CM pathophysiology should generate  
12 awareness regarding its multiorgan nature. Thus, holistic approaches taking the  
13 complexity of myocardial damage induced by T2DM along with the functional  
14 interplay between different key organs into account will advance our knowledge of  
15 diabetic CM. This type of multidimensional approach will increase the likelihood of  
16 early diagnosis and the translational success of new drugs in development. Currently,  
17 there are no specific therapies for diabetic CM. Further refinement of diabetic CM  
18 molecular signatures derived from improved preclinical models should provide new  
19 mechanistic insights leading to specific targets, drugs, biomarkers, and effective  
20 patient management in the future.

21

## 22 **Future Perspectives**

23 The lack of experimental models that reproduce all structural, functional, and  
24 molecular alterations of human diabetic CM is one of the barriers to advance patient



1 care. Animal models have provided information about the initiation and progression of  
2 diabetic CM. They have decoded a few molecular mechanisms of diabetic CM. In  
3 addition, they are useful for testing new treatments, and identifying possible side-  
4 effects.

5 From the results of the CARDIATEAM study involving cohorts of diabetic patients  
6 with and without overt diabetic CM and control subjects, it is anticipated that many  
7 pathways specifically involved in diabetic CM will be discovered by employing  
8 unsupervised analysis and disease modelling of imaging and “omics” data. By  
9 backtranslation of these clinical results, the aim of CARDIATEAM consortium is to  
10 develop a preclinical model that recapitulates human diabetic CM. We postulate this  
11 will prove a powerful approach in improving the diagnosis and treatment of diabetic  
12 CM.

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4

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1

2 **Table 1. Rodent models that recapitulate diabetic cardiomyopathy features**  
 3 **found in humans.**

		<b>Animal model</b>	<b>Cardiac functional and structural alterations</b>	<b>Ref.</b>	
<b>Mice</b>	<b>HFD</b>	<i>C57/BL6 mice</i>	Early onset of metabolic alterations and cardiac LV dysfunction (5 weeks after starting HFD) and defects in glucose handling.	32, 139	
		<i>Old female C/57BL/6J mice + HFD + angiotensin II infusion.</i>	Model of HFpEF (LV hypertrophy and LV diastolic dysfunction; no change in LVEF)	140	
		<i>ob/ob Mouse Model</i>	LV diastolic dysfunction and features of lipotoxicity.	141, 142	
		<i>C57BL/6N mice + HFD+L-NAME administration (p.o)</i>	Model of HFpEF (Hypertrophic response, diastolic dysfunction, pulmonary congestion, reduction in contraction velocity and impaired relaxation)	143	
	<b>Models of lipotoxicity</b>		<i>Alteration in myosin heavy chain acyl-CoA synthetase (MHC-ACS mice)</i>	Lipotoxicity, abnormal cardiac metabolism, cardiac hypertrophy, LV dysfunction and premature death	144
			<i>GPI-anchored human lipoprotein lipase transgenic mice (hLpLGPI mice)</i>	Lipotoxicity, cardiac hypertrophy, abnormal cardiac metabolism, LV dysfunction, and cardiac fibrosis.	145
			<i>Myosin heavy chain-peroxisome proliferator-activated receptor <math>\alpha</math> mice (MHC-PPAR<math>\alpha</math> mice)</i>	Lipotoxicity, cardiac hypertrophy, abnormal cardiac metabolism, LV dysfunction, and cardiac fibrosis.	146
			<i>Myosin heavy chain fatty acid transport protein mice (MHC-FATP mice)</i>	Lipotoxicity, LV diastolic dysfunction and prolonged QTc intervals.	147, 148
			<i>Adipose TG lipase knockout mice</i>	Lipotoxicity. LV dysfunction and premature death	149
<b>T2DM</b>		<i>Streptozotocin</i>	Reduction in heart rate, amplitude of contraction and of ventricular pressure, and prolongation on the rate of ventricular myocyte contraction and relaxation	150-156	
		- <i>Intraperitoneal route</i> - <i>Intravenous route</i>			
<b>T1DM</b>		<i>db/db Mouse Model</i>	Decreased systolic function, abnormal diastolic filling, and electrophysiological alterations	157	

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		<b>Animal model</b>	<b>Cardiac functional and structural alterations that recapitulate human features of Diabetic Cardiomyopathy</b>	<b>Ref.</b>
<b>Rat</b>	<b>HFD</b>	<i>Sprague-Dawley rats</i>	Lipotoxicity, cardiac fibrosis and hypertrophy	158, 159
	<b>Obesity</b>	<i>Obese Zucker rat (fa/fa)</i>	Lipotoxicity and increased LV end-diastolic volume and stroke volume	160
		<i>DahlS.Z-Lepr(fa)/Lepr(fa) (DS/obese) rat</i>	LV diastolic dysfunction, LV hypertrophy, and cardiac fibrosis.	161
	<b>T1DM</b>	<i>Streptozotocin</i>	LV systolic and diastolic dysfunction and fibrosis.	162-
		- <i>Intraperitoneal route</i>		164
		- <i>Intravenous route</i>		165-167
	<b>T2DM</b>	<i>Zucker diabetic fatty rat (ZDF)</i>	Increased heart and LV weights, presence of fibrosis, depressed RV and LV systolic function	168, 169
<i>Goto-Kakizaki rat (GK)</i>		Cardiac hypertrophy, increased extracellular matrix deposition and increased heart size	170, 171	

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2 Abbreviations: HFD: high fat diet. LV: left ventricle; LVEF: left ventricle ejection fraction; T1DM: Type 1

3 diabetes mellitus; T2DM: Type 2 diabetes mellitus

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## 2 **Figures Legends**

3 **Figure 1: Mechanisms contributing to cardiomyocyte dysfunction in diabetic**  
4 **cardiomyopathy.** Hormonal and metabolic alterations may result in hyperglycemia,  
5 insulin resistance and lipid overload which cause through specific signalling pathways  
6 subcellular component abnormalities. This includes mitochondrial dysfunction,  
7 impaired metabolic flexibility, Ca<sup>2+</sup> dysregulation and activation of gene transcription  
8 program involved in cardiac remodelling and senescence. These molecular and  
9 cellular events contribute to diastolic and systolic dysfunction. GPCR, G protein-  
10 coupled receptor; IR, insulin receptor; ROS, reactive oxygen species; RyR, ryanodine  
11 receptor.

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13 **Figure 2:** Diabetic heart is at the cross-road of environmental factors, organ-crosstalk  
14 and paracrine cellular-crosstalk between cardiomyocytes, fibroblasts, endothelial  
15 cells and immune cells in the myocardium.

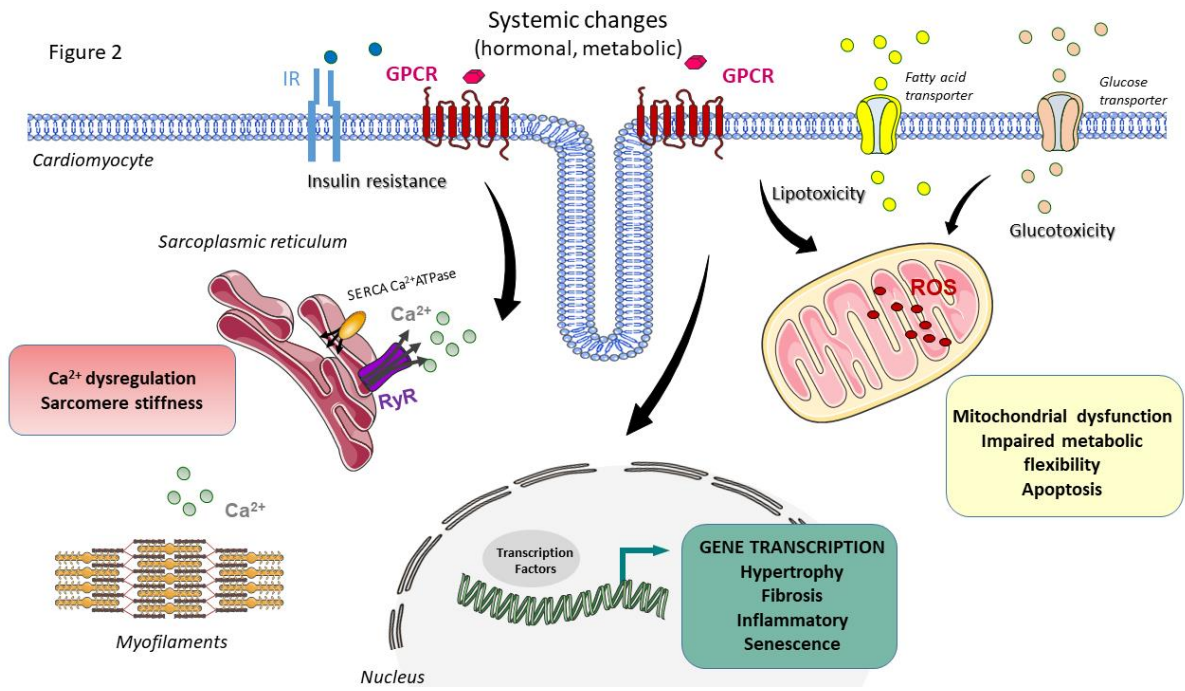
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17 **Graphical Abstract: Rodent models should recapitulate the clinical phenotype**  
18 **to better mimic the progression of diabetic cardiomyopathy towards heart**  
19 **failure**

20

1

2 **Figure 1:**



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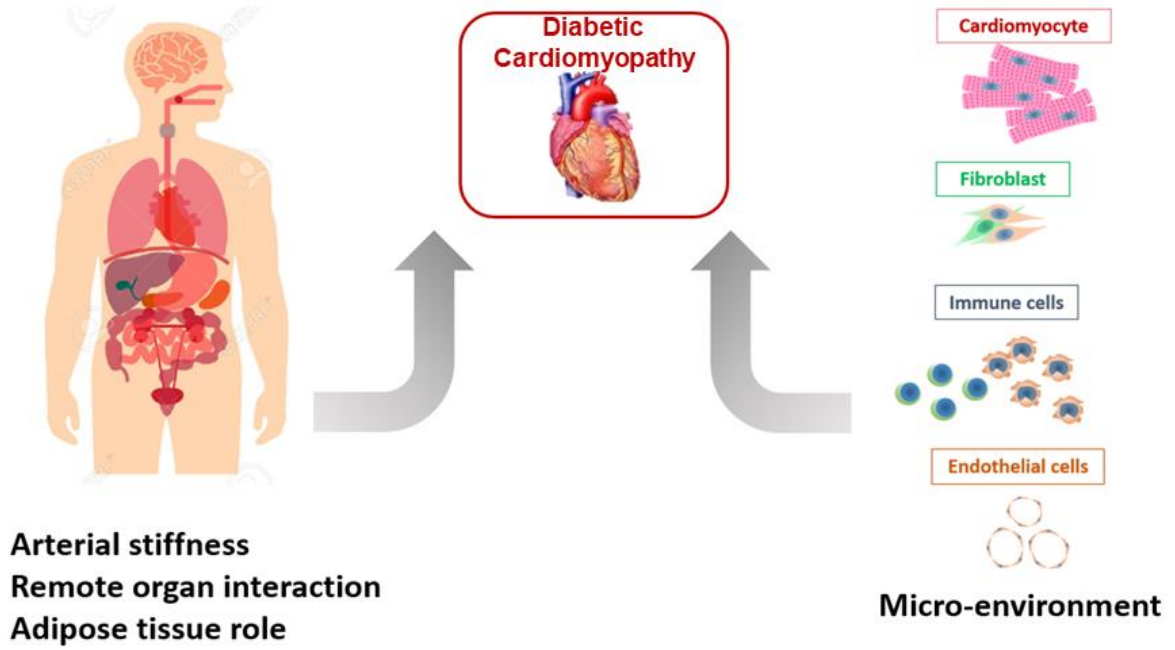
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2 **Figure 2:**

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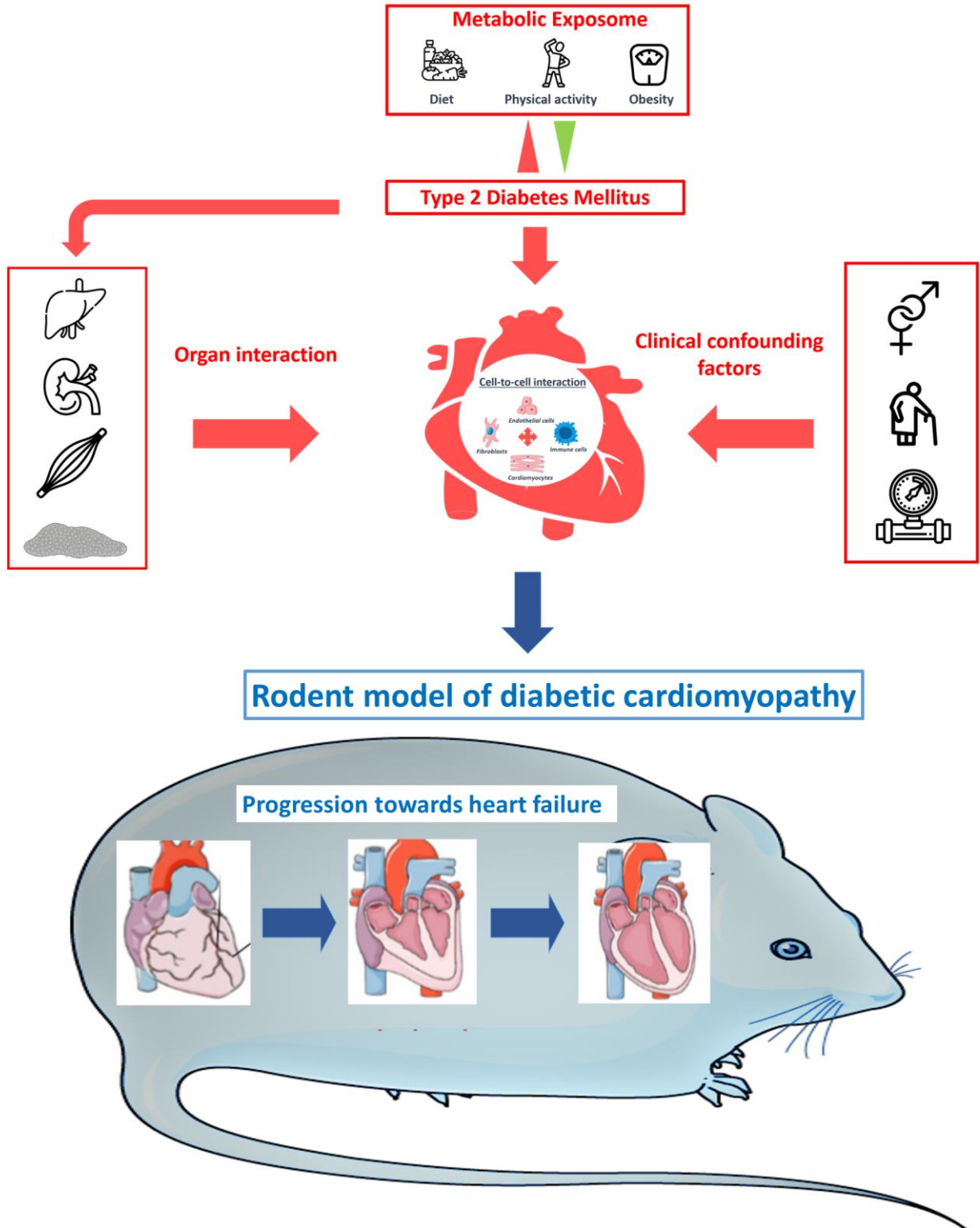
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2 **Graphical abstract:**

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