Role of inflammation in diabetic cardiomyopathy

Pranav Ramesh, Jian L. Yeo, Emer M. Brady and Gerry P. McCann

Abstract: The prevalence of type 2 diabetes (T2D) has reached a pandemic scale. Systemic chronic inflammation dominates the diabetes pathophysiology and has been implicated as a causal factor for the development of vascular complications. Heart failure (HF) is regarded as the most common cardiovascular complication of T2D and the diabetic diagnosis is an independent risk factor for HF development. Key molecular mechanisms pivotal to the development of diabetic cardiomyopathy include the NF-κB pathway and renin–angiotensin–aldosterone system, in addition to advanced glycation end product accumulation and inflammatory interleukin overexpression. Chronic myocardial inflammation in T2D mediates structural and metabolic changes, including cardiomyocyte apoptosis, impaired calcium handling, myocardial hypertrophy and fibrosis, all of which contribute to the diabetic HF phenotype. Advanced cardiovascular magnetic resonance imaging (CMR) has emerged as a gold standard non-invasive tool to delineate myocardial structural and functional changes. This review explores the role of chronic inflammation in diabetic cardiomyopathy and the ability of CMR to identify inflammation-mediated myocardial sequelae, such as oedema and diffuse fibrosis.

Keywords: cardiovascular magnetic resonance imaging, diabetic cardiomyopathy, heart failure, inflammation, type 2 diabetes

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Introduction

The prevalence of type 2 diabetes (T2D) has reached a pandemic scale. T2D is characterised by reduced insulin secretion and insulin resistance. Inflammation has emerged as a key component in the pathophysiology of T2D, with damage to the pancreatic islets resulting from pro-inflammatory processes. This stress to the pancreatic islets is linked with elevated glucose and free fatty acids (FFA) levels seen in states of nutritional excess and obesity. The 2017–2018 National Diabetes Audit in England and Wales collated data from 2.9 million individuals with T2D and reported heart failure (HF) to be the most common cardiovascular complication with a prevalence of 3.4% (Figure 1). Hyperglycaemia is a key prerequisite for the induction of chemokines, cytokines and leukocyte adhesion molecules which in turn result in myocardial inflammation. Myocardial inflammation is a heterogeneous process with multiple pathways implicated in the development of diabetic cardiomyopathy (DC). Chronic low-grade inflammation partially mediates structural and metabolic changes in the diabetic heart, including left ventricular hypertrophy (LVH), myocardial fibrosis and abnormalities in calcium handling. This review explores the role of inflammation in the pathophysiology of DC and highlights the potential use of cardiac magnetic resonance imaging (CMR) in identifying myocardial inflammation.

Diabetic cardiomyopathy

The term DC was first coined in 1972 by Rubler et al., who demonstrated evidence of cardiomegaly and congestive cardiac failure on post-mortem of four diabetic individuals with coexistent...
All four of the deceased had signs of LVH and myocardial fibrosis. This finding was expanded on by the landmark Framingham Heart Study which showed the risk of HF was increased by up to five times in people with T2D. Clinical classification stages for DC have been proposed by Maisch et al., with semblance to other widely used clinical staging systems, most notably the American College of Cardiology (ACC) classification of HF. Up to 37% of asymptomatic individuals in Stage 1 DC progress to develop HF symptoms, while Stage 2 of DC results in annual mortality rates of up to 20%. Progression of other factors, such as hypertension and coronary artery disease (CAD), contribute to the development of HF symptoms in Stages 3–4, with greater morbidity and mortality.

Inflammation in DC

T2D is characterised by a systemic inflammatory state. Numerous cytokines and chemokines work in conjunction with each other (Figure 2), which makes evaluating the contribution of specific mediators to the phenotypes seen in DC difficult. Most notable markers of inflammation include tumour necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8, IL-1β and C-reactive protein (CRP). Certain mediators result in downstream release of other mediators; hence, there is ambiguity in determining which of these cytokines result in direct adverse myocardial changes. However, it has been shown that inflammation in diabetes seems to result in a common endpoint, nuclear factor kappa-B (NF-κB) activation. Expression of this transcription factor results in cytokine-mediated myocardial and vascular damage. Table 1 summarises the predictive value of specific serum biomarkers in identifying cardiovascular disease (CVD) within a cohort of T2D.

NF-κB – a common inflammatory signalling pathway

Hyperglycaemia promotes cytokine and chemokine release, which in turn activates a common signalling pathway involving a transcription factor, known as NF-κB, postulated in the pathophysiology of DC. Activation of NF-κB via toll-like receptor (TLR) 4 results in downstream pro-inflammatory cytokine release involving mediators, such as TNF-α, IL-6, IL-1β, IL-8 and monocyte chemoattractant protein (MCP)-1. Cytokines and chemokines released via this mechanism cause reactive oxygen species (ROS) stress to the myocardium, with remodelling, fibrosis and eventual myocardial diastolic dysfunction.

Hallmark myocardial changes associated with DC and the role of inflammatory mediators

Diastolic dysfunction

Diastolic dysfunction is an early hallmark of DC. Myocardial stiffening occurs through impaired myocardial calcium handling, diffuse fibrosis and hypo-phosphorylation of myocardial titin, a
cytoskeletal protein, all of which contribute to impaired relaxation of the diabetic heart. Indeed, multiple observational studies have concluded that the rates of diastolic dysfunction were up to five times higher in people with T2D. Furthermore, diastolic dysfunction persisted in those with adequate control of metabolic risk factors.

Another major pathway implicated in the development of diastolic dysfunction includes renin–angiotensin–aldosterone system (RAAS) pathway. RAAS activity is upregulated in T2D, and evidence suggests that angiotensin-2 mediates myocardial inflammation through NF-κB activation, leading to myocardial stiffening. In T2D, elevated levels of FFAs result in stress on the endoplasmic reticulum causing the activation of the NLRP3 inflammasome which, in turn, induces the release of IL-1β through caspase-1 mediated interactions (Figure 2). IL-1β, a NF-κB dependent cytokine, results in impaired myocardial contractility through beta-adrenergic receptor inhibition in a population of healthy, non-diabetic mice. Angiotensin 1–7, a physiological inhibitor of RAAS, when administered to diabetic mice, reduced LV hypertrophy, myocardial triglyceride content and fibrosis and improved diastolic dysfunction. A large randomised control trial (n=9297) found that those with T2D treated with an angiotensin-converting enzyme inhibitor had a 23% reduced risk of developing congestive HF over 5 years of follow-up. This perceived benefit in T2D may be due to amelioration of diastolic dysfunction via optimisation of haemodynamic responses and improved myocardial compliance.

**Myocardial hypertrophy**

In T2D, concentric remodelling is the most common pattern by which myocardial hypertrophy occurs. Concentric remodelling is associated with diastolic dysfunction and is commonly seen in
**Table 1.** A summary of clinical studies evaluating the predictive values of serum biomarkers for CVD in T2D.

| Author           | Biomarker | Sample details                | Main findings                                                                 |
|------------------|-----------|-------------------------------|-------------------------------------------------------------------------------|
| Soinio et al.57  | CRP       | \(N = 1059\) All T2D (mean age 57 years; 55% male) | ↑ CRP associated with ↑ CHD mortality [RR 1.72 (1.23–2.41), \(p < 0.002\)]   |
| Bruno et al.58   |           | \(N = 2381\) All T2D (mean age 68 years; 50% males) | ↑ CRP (>4.4 mg/dl) associated with ↑ 5-year CV mortality [RR 1.76 (1.09–2.82), \(p < 0.015\)] |
| Herder et al.59  | IL-6      | \(N = 1072\) All T2D (median age 65 years; 54% males) | ↑ IL-6 (>7.44 pg/ml) associated with ↑ risk for CV events \(^a\) [HR 1.90 (1.07–3.40), \(p = 0.009\); follow-up of 5 years] |
| Ofstad et al.60  |           | \(N = 135\) All T2D (mean age 59 years; 65% males) | ↑ IL-6 (>0.6 pg/ml) associated with ↑ risk of MACE \(^b\) [HR 15.8 (2.2–115.8), \(p = 0.007\); mean follow-up of 8.6 years] |
| Kilhovd et al.61 | AGE       | \(N = 87\) 61% T2D (mean age 59 years; 60% males) | ↑ AGE in T2D versus controls (7.4 versus 4.2 U/ml, \(p < 0.0001\))  
↑ AGE in those with T2D and CHD versus those without CHD (8.1 versus 7.1 U/ml, \(p = 0.03\)] |
| Kiuchi et al.62  |           | \(N = 83\) 51% T2D (mean age 64 years; 76% males) | ↑ AGE in those with T2D and obstructive CAD versus those without CAD (5.5 versus 2.8 mU/ml)  
↑ AGE concentrations in those with more severe arteriosclerosis (7.2 versus 3.4 mU/ml) |
| Tuttle et al.63  | TNF-\(\alpha\) | \(N = 63\) 51% T2D (mean age 60 years; all females) | No significant difference in TNF-\(\alpha\) concentrations between those with T2D and CVD |
| Dinh et al.64    |           | \(N = 41\) 67% T2D (mean age 65 years; 70.7% males) | ↑ TNF-\(\alpha\) levels in those with LV diastolic dysfunction \(\text{E/e}'\) ratio > 15) versus those without (7.2 versus 3.1 pg/ml, \(p < 0.001\)) |
| Hotta et al.65   | Adiponectin | \(N = 265\) 69% T2D and prior MI (mean age 60 years; 69% males) | ↓ Adiponectin levels in T2D versus controls [5.7 versus 7.9 \(\mu\)g/ml, \(p < 0.001\), in men]  
↓ Adiponectin levels in those with T2D and CAD versus those with T2D without CAD [4.0 versus 6.6 \(\mu\)g/ml] |
| Mehta et al.66   |           | \(N = 906\) 21% T2D (mean age 55 years; 54% males) | ↓ Adiponectin levels associated with coronary artery calcification in women [OR 0.32 (0.13–0.81)], but not men |

AGE, advanced glycation end products; CV, cardiovascular; CHD, coronary heart disease; CAD, coronary artery disease; CRP, C-reactive protein; IL-6, interleukin-6; MACE, major adverse cardiovascular events; MI, myocardial infarction; T2D, type 2 diabetes; TNF-\(\alpha\), tumour necrosis factor-alpha. 
\(^a\)CV event: non-fatal myocardial infarction, stroke and cardiovascular deaths. 
\(^b\)MACE: myocardial infarction, stroke, hospitalisation for angina and death.

Our group has also shown that those with T2D and HFrEF have a higher LV mass/volume and this independently correlated with HF prognosis. The Strong Heart Study \((n = 1299, 100\% \text{T2D})\) identified those with T2D and LVH tended to have raised inflammatory markers, such as...
fibrinogen (402 versus 381 mg/dl, \( p < 0.001 \)), compared to those without LVH. Clinical studies have demonstrated increased NF-κB activation in myocardial tissue of HF patients compared to controls, who showed little to no activation of this pathway. In addition, among HF patients, infarcted regions of the myocardium demonstrated a greater activation of NF-κB.

Insulin resistance in T2D leads to reduced myocardial glucose availability. The subsequent switch to FFA utilisation renders the myocardium metabolically inefficient. Over time, the excess FFA supply overwhelms oxidative metabolic pathways, resulting in a shift to non-oxidative metabolism. Consequential products of this alternative metabolic pathway include ceramide and diacylglycerol, both of which induce cardiac toxicity and LVH. In addition, non-oxidative metabolism also increases myocardial triglyceride content thus resulting in myocardial steatosis. Furthermore, myocardial steatosis has been shown to be independently associated with LVH. In animal HF models, increased intramyocardial lipid deposition was associated with upregulated levels of TNF-α. The subsequent lipid deposition was correlated with a negative inotropic response. This suggests that myocardial steatosis, intracardiac lipotoxicity and impaired contractility are influenced by TNF-α concentration. In addition, TNF-α administration in rats promoted LV remodelling and early changes in LV function can be reversed with a TNF-α antagonist.

**Myocardial fibrosis**

Myocardial fibrosis (Figure 2) is characterised by the deposition of collagen, primarily type I and III, due to cardiac fibroblast activation and proliferation. Myocardial fibrosis results in stiffness which subsequently leads to diastolic dysfunction, displaying reduced early diastolic filling and an elevated LV end-diastolic pressure to maintain adequate cardiac output. While cardiac fibrosis occurs with the normal ageing process of the heart, the rate of fibrosis seems to be accelerated in T2D, mediated by hyperglycaemia and accumulation of AGE. Binding of AGE to its respective receptor (RAGE) triggers the production of pro-inflammatory cytokines through intracellular NF-κB activation, which results in ROS stress and cardiomyocyte apoptosis, both of which contribute to fibrosis. In addition, one study found that RAGE silencing ameliorated diastolic dysfunction and impaired contractility in diabetic mice.

In IL-6 infused rats, concentric LVH, fibrosis and diastolic dysfunction were observed. Contrarily, IL-6 knockout yielded lower rates of myocardial fibrosis in diabetic mice through overexpression of microRNA-29 and downregulation of tumour growth factor (TGF) B1. Another study involving diabetic rats demonstrated increased intracellular angiotensin 2 levels within cardiac myocytes and this positively correlated with cardiomyocyte apoptosis and fibrosis secondary to chronic hyperglycaemia. In another animal study, TNF-α inhibitor administration resulted in decreased expression of leukocyte adhesion molecules, reduced intracardiac collagen content and yielded a twofold decrease in intracardiac TNF-α levels. Thus, inhibition of TNF-α is a potential treatment for targeting inflammation and fibrosis in DC.

**Impaired myocardial energetics**

The myocardium relies on both glucose metabolism and FFAs for energy production in the healthy heart. In T2D, alterations in substrate utilisation occur with a switch to almost exclusive FFA metabolism. This causes the activation of peroxisome proliferator-activated receptor alpha, which in turn reduces glucose oxidation and increases FFA uptake into cardiac mitochondria. Chronic myocardial inflammation has been implicated in the development of myocardial glucose abnormalities. Mice infused with IL-6 demonstrated a 50% reduction in myocardial glucose uptake due to disruption of insulin signalling pathways and promotion of insulin resistance via suppression of adenosine monophosphate-activated protein kinase and insulin receptor substrate-1 (IRS-1), key signalling proteins within the heart. In contrast, IL-6 deficiency resulted in a reversal of IRS-1 suppression, thus improving myocardial glucose metabolism. In addition, inhibition of TNF-α resulted in improved PCr/ATP ratios, an indicator of high-energy phosphate availability, further suggesting that TNF-α impairs myocardial energetics and is a potential therapeutic target.

**Coronary microvascular dysfunction**

T2D is associated with numerous vascular abnormalities affecting both the macro- and microvascular circulations.
dysfunction has been demonstrated through cardiac imaging studies assessing myocardial perfusion reserve (MPR). Determinants of MPR include endothelial dysfunction, reduced capillary density, oxidative stress and myocardial fibrosis. Those with diabetes have a lower MPR which was associated with lower peak oxygen consumption on cardiopulmonary exercise testing. This suggests that coronary microvascular dysfunction, in T2D, may result in myocardial deoxygenation which in turn impairs energetics, in an already metabolically inefficient heart. Inflammatory-mediated vasomotor spasm induces coronary microvascular dysfunction that is exasperated by IL-6 and TNF-α-dependent endothelial dysfunction. Consequently, interstitial fibrosis and myocardial stiffening develop, which contributes to the diastolic HF seen in DC.

Adiposity and inflammation
Adipose tissue is a dynamic endocrine organ secreting a vast array of molecules, called adipokines, which have both immune-modulatory and metabolic effects. Adipokines are associated with insulin resistance, T2D and other metabolic disorders, ultimately leading to CVD. Visceral adiposity is linked with raised levels of CRP, white blood cells and IL-6. Insulin resistance seems to be present in individuals with higher visceral fat but is absent in overweight individuals with normal visceral fat levels.

The adipokine adiponectin has anti-atherogenic and anti-inflammatory properties and is dysregulated in obese individuals. The protective property of adiponectin is thought to be modulated by endothelial adhesion molecules, such as vascular cell adhesion protein-1 (VCAM-1), ICAM-1 and E-selectin, and through inhibition of TNF-α and NF-κB. Furthermore, TNF-α, IL-1β and IL-6 have been shown to have lower levels of adiponectin. Adiponectin also promotes glucose uptake into skeletal muscle and inhibits hepatic gluconeogenesis. Individuals with diabetes and HF have been shown to have lower levels of adiponectin (11.0 versus 15.3 ng/ml, p = 0.034) when compared to those in a similar stage of HF in the absence of diabetes.

Leptin, an adipokine which regulates appetite, is considered pro-inflammatory through activating monocytes, which in turn supports the release of IL-1β and TNF-α. Elevated leptin levels have been shown to correlate with impaired glucose tolerance, body mass index and fasting insulin levels. However, there is conflicting evidence of leptin’s effects on the myocardium, suggesting that leptin has mixed cardioprotective and detrimental roles. Barouch et al. noted that leptin deficiency in mice contributed to LVH which was then reversed with the administration of leptin. Similarly, a study involving the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (n = 1970) found that higher leptin levels were associated with lower rates of LVH and a smaller LV mass. This may be due to leptin’s role in reducing ectopic triglyceride deposition, suggesting that higher leptin levels may reduce myocardial steatosis. However, in vivo studies have demonstrated that raised leptin levels positively correlate with interventricular septum thickness. The mixed contradictory evidence suggests that larger intervention-based studies are needed to investigate the putative role of leptin cardiovascular remodelling in T2D (Table 1).

CMR parametric mapping to detect myocardial inflammation
CMR offers a comprehensive assessment of myocardial structure, function, coronary perfusion, energetics and scarring/fibrosis. The utility of CMR for cardiovascular risk stratification in T2D has been extensively discussed in a previous article. In the current review, we focus on the unique ability of CMR parametric mapping technique to detect myocardial oedema and diffuse fibrosis, a key feature and sequelae of inflammation, and its potential application in T2D (Figure 3).

T1 mapping and myocardial extracellular volume calculation
Myocardial T1 time is elevated by increased myocardial free water content, thus allowing the detection of oedema. Using an inversion recovery sequence, a T1 map can be generated across the myocardium. T1 mapping combined with gadolinium contrast is another relatively newer application of CMR to quantify the myocardial extracellular space. Myocardial extracellular volume (ECV) has a normal value of approximately 25% and is elevated in conditions where there is interstitial expansion, including diffuse fibrosis. This feature provides an advantage over late gadolinium enhancement, which although is excellent in delineating focal scarring, it is not sensitive to
detect diffuse fibrosis. ECV is validated with good correlation to histological collagen volume fraction.\(^7^0\) Importantly, increased myocardial ECV has been shown to be an independent predictor of mortality in people with T2D.\(^7^1\) A summary of studies comparing ECV in people with and without T2D is shown in Table 2. Figure 4 illustrates the examples of T1 mapping and ECV in a myriad of inflammatory cardiac conditions.

**Figure 3.** Type 2 diabetes and associated subclinical inflammation causes oedema, myocardial fibrosis and macrophage infiltration which are detectable using CMR parametric mapping. A raised ECV is associated with increased adverse cardiac events.

CMR, cardiac magnetic resonance; CV, cardiovascular; ECV, extracellular volume; USPIO, ultrasmall superparamagnetic iron oxide.

**T2 mapping**

Like T1, T2 time is sensitive to myocardial water content and is useful for detecting oedema.\(^7^4\) T2 mapping is used clinically to identify acute myocardial injury and inflammation, such as myocardial infarction, myocarditis (infective or autoimmune) and transplant rejection. Compared to T1, T2 time is valuable in differentiating acute from chronic/resolving inflammation as demonstrated in a study (\(n=18\)) of patients with myocarditis which showed increased myocardial T2 time in the acute inflammatory phase, but normalised 6 months later, while T1 time remained persistently elevated.\(^7^5\) While there have been multiple studies of T1-based imaging reported in people T2D, similar data on T2-based imaging are scarce.

**Ultrasmall Superparamagnetic Iron Oxide particles for detection of myocardial inflammation**

Ultrasmall superparamagnetic iron oxide (USPIO) is a contrast agent used largely in a research setting, as a method to quantify inflammation *in vivo*. USPIO is phagocytosed and accumulates in macrophages, altering the local magnetic field properties. This is detectable by CMR parametric mapping and thus identifies myocardial areas with active macrophage infiltration. Multiple studies have shown the use of USPIO in the detection of active inflammation in different pathological processes, including acute myocardial infarction, chronic ischaemic cardiomyopathy, non-ischaemic dilated cardiomyopathy and chronic obstructive pulmonary disease.\(^7^6,^7^7\) However, there are no studies reporting the use of USPIO for the detection of inflammation in T2D at the time of writing this review.

**Clinical perspectives**

Current data show that the inflammatory response is detrimental to myocardial function. Amelioration of myocardial dysfunction has already been shown through the inhibition of specific cytokine mediators (e.g. TNF-\(\alpha\) inhibition) in animal models. However, in clinical practice, these
Table 2. CMR studies comparing ECV in those with and without T2D.

| Author          | Sample details                                                                 | Key inclusion criteria                              | Main findings                                                                                     |
|-----------------|--------------------------------------------------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Levelt et al.   | T2D \((n = 46)\), mean age 55 ± 9 years, 50% males, median diabetes duration 7 years, mean HbA1c 7.5 ± 0.2%, mean BMI 29.6 ± 5.7 | Cases – T2D, no known diabetic complications, no history of chest pain or CVD, non-smokers, normotensive and HbA1c < 9% | No significant difference in myocardial ECV between T2D and controls \((29 ± 2\% \text{ versus } 29 ± 3\% \text{ respectively, } p = 0.773)\) |
| Shang et al.    | T2D \((n = 38)\), mean age 55 ± 9 years, 53% males, median diabetic duration 7 years, median HbA1c 7.4%, mean BMI 24.3 ± 2.7 | Controls \((n = 32)\), matched for age 51 ± 14 years and BMI 23.5 ± 3.1, 47% males | Myocardial ECV (%) in T2D versus controls \((30.4 ± 2.9\% \text{ versus } 27.1 ± 2.4\%, \ p < 0.001)\) ECV in patients with a diabetic duration > 10 versus 5–10 versus < 5 years versus controls \((32.2 ± 3.1\% \text{ versus } 30.9 ± 2.1\% \text{ versus } 28.3 ± 2.3\% \text{ versus } 27.1 ± 2.4\%, \ p < 0.0001)\) |
| Cao et al.      | T2D \((n = 50)\), mean age 55 ± 7 years, 56% males, mean diabetic duration 10 years, mean HbA1c 8.9%, mean BMI 24.7 ± 3.7 | Controls \((n = 32)\), matched for age 54 ± 6 years, sex (53% male) and BMI \([23.7 ± 2.3]\) | Myocardial ECV in T2D versus controls \((27.4 ± 2.5\% \text{ versus } 24.6 ± 2.2\%, \ p < 0.001)\) |
| Khan et al.     | T2D \((n = 70)\), median age 61.5 years, 47.1% males, median HbA1c 6.5%, median BMI 29.7 | Prediabetes \((n = 76)\), median age 59 years, 48.7% males, median HbA1c 6.0%, median BMI 27.5 | ECV in T2D and prediabetes versus controls \((30.3 \text{ versus } 29.1\% \text{ versus } 27.9\%, \ p < 0.001)\) T2D and ECV > 30 were independently associated with composite HF events \((HR 2.74, 95\% \text{ CI } 1.49–5.04 \text{ and } HR 3.31, 95\% \text{ CI } 1.93–5.67, \text{ respectively})\) |

CVD, cardiovascular disease; ECV, extracellular volume; HF, heart failure; LV, left ventricular; T2D, type 2 diabetes.

Medications are often not licenced for use in HF or are they readily available. Thus, the anti-inflammatory properties of the current medications used in T2D and HF must be evaluated.

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial investigated the effects of an IL-1β inhibitor, in those with a history of myocardial infarction and elevated high-sensitivity CRP despite aggressive secondary prevention therapies. The main outcome paper reported that canakinumab led to a lower rate of recurrent major cardiovascular events (non-fatal myocardial infarction, stroke and cardiovascular death) \((HR 0.85, 95\% \text{ CI } 0.74–0.98, \ p = 0.021)\) at a median follow-up of 3.7 years. In a subgroup
analysis of people with T2D, canakinumab led to a significant reduction in CRP and IL-6, although it did not reduce the incidence of T2D and showed that efficacy for lowering cardiovascular events was similar in both people with (HR 0.90, 95% CI 0.77–1.05) and without T2D (HR 0.81, 95% CI 0.56–1.19). A small study (n = 40) found that Colchicine, a drug used in inflammatory arthritis, reduced the levels of CRP, erythrocyte sedimentation rate and white blood cells in those with metabolic syndrome. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are a newer class of medication which improve glycaemic control through increased excretion of glucose in the urine. Recent studies have evaluated the use of dapagliflozin in DC. Arow et al. found that DC-induced mice treated with dapagliflozin exhibited lower rates of myocardial fibrosis and a reduced expression of serum inflammatory markers (TNF-α, TLR4 and IL-1β). This suggests that inflammation and myocardial fibrosis may be limited by SGLT-2i treatment. Human
studies have echoed similar anti-inflammatory findings with SGLT-2i therapy, demonstrating a decrease in leptin, TNF-α, CRP and IL-6 and an increase in adiponectin levels. Future intervention studies may benefit from CMR to evaluate whether a reduction in systematic inflammation results in improved LV function.

Conclusion

Inflammation has been described as a key pathophysiological trigger to the hallmark changes occurring within the diabetic heart. Inflammatory pathways and mediators trigger early changes, such as LV hypertrophy, impaired contractility, fibrosis, cardiomyocyte apoptosis, calcium abnormalities and impaired myocardial energy utilisation. Amelioration of adverse myocardial changes has also been demonstrated through specific inhibition of these pathways and mediators. Cardiac MRI parametric mapping provides a non-invasive method for the detection of oedema and fibrosis. In addition to circulating serum biomarkers, CMR may provide incremental diagnostic benefit in identifying subclinical inflammatory changes in the myocardium, which in turn allows earlier risk factor modification and prevention of HF progression.

Author contributions

Pranav Ramesh: Data curation; Writing – original draft.
Jian L. Yeo: Supervision; Writing – review & editing.
Emer M. Brady: Writing – review & editing.
Gerry P. McCann: Conceptualization; Supervision; Writing – review & editing.

Conflict of interest statement

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References

1. Ginter E and Simko V. Type 2 diabetes mellitus, pandemic in 21st century. *Ado Exp Med Biol* 2012; 771: 42–50.
2. Oh YS, Bae GD, Baek DJ, et al. Fatty acid-induced lipotoxicity in pancreatic beta-cells during development of type 2 diabetes. *Front Endocrinol (Lausanne)* 2018; 9: 384.
3. NHS Digital. National diabetes audit, 2017–18, 2019, https://files.digital.nhs.uk/91/084B1D/National%20Diabetes%20Audit%2C%202017-18%2C%20Report%202a.pdf
4. Jia G, Hill MA and Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res* 2018; 122: 624–638.
5. Rubler S, Dlugash J, Yuceoglu YZ, et al. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972; 30: 595–602.
6. Kannel WB, Hjortland M and Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; 34: 29–34.
7. Maisch B, Alter P and Pankuweit S. Diabetic cardiomyopathy – fact or fiction? *Herz* 2011; 36: 102–115.
8. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 2001; 104: 2996–3007.
9. Tillquist MN and Maddox TM. Update on diabetic cardiomyopathy: inches forward, miles to go. *Curr Diab Rep* 2012; 12: 305–313.
10. Song MJ, Kim KH, Yoon JM, et al. Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. *Biochem Biophys Res Commun* 2006; 346: 739–745.
11. Frati G, Schirone L, Chimenti I, et al. An overview of the inflammatory signalling mechanisms in the myocardium underlying the development of diabetic cardiomyopathy. *Cardiovasc Res* 2017; 113: 378–388.
12. Salvatore T, Pafundi PC, Galiero R, et al. The diabetic cardiomyopathy: the contributing pathophysiological mechanisms. *Front Med (Lausanne)* 2021; 8: 695792.
13. Patil VC, Patil HV, Shah KB, et al. Diastolic dysfunction in asymptomatic type 2 diabetes
mellitus with normal systolic function. J Cardiovasc Dis Res 2011; 2: 213–222.

14. Jørgensen PG, Jensen MT, Biering-Sørensen T, et al. Burden of uncontrolled metabolic risk factors and left ventricular structure and function in patients with type 2 diabetes mellitus. J Am Heart Assoc 2018; 7: e008856.

15. Sciarretta S, Paneni F, Palano F, et al. Role of the renin-angiotensin-aldosterone system and inflammatory processes in the development and progression of diastolic dysfunction. Clin Sci (Lond) 2009; 116: 467–477.

16. Van Tassell BW, Seropian IM, Toldo S, et al. Interleukin-1β induces a reversible cardiomyopathy in the mouse. Inflamm Res 2013; 62: 637–640.

17. Mori J, Patel VB, Alrob OA, et al. Angiotensin 1-7 ameliorates diabetic cardiomyopathy and diastolic dysfunction in db/db mice by reducing lipotoxicity and inflammation. Circ Heart Fail 2014; 7: 327–339.

18. Yusuf S, Slevit P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145–153.

19. Satpathy C, Mishra TK, Satpathy R, et al. Diagnosis and management of diastolic dysfunction and heart failure. Am Fam Physician 2006; 73: 841–846.

20. Shah AM. Ventricular remodeling in heart failure with preserved ejection fraction. Curr Heart Fail Rep 2013; 10: 341–349.

21. De Jong KA, Czececor JK, Sithara S, et al. Obesity and type 2 diabetes have additive effects on left ventricular remodelling in normotensive patients – a cross sectional study. Cardiovasc Diabetol 2017; 16: 21.

22. Gulsin GS, Kanagala P, Chan DCS, et al. Differential left ventricular and left atrial remodelling in heart failure with preserved ejection fraction patients with and without diabetes. Ther Adv Endocrinol Metab 2019; 10: 204201819861593.

23. Palmieri V, Tracy RP, Roman MJ, et al. Relation of left ventricular hypertrophy to inflammation and albuminuria in adults with type 2 diabetes. Diabetes Care 2003; 26: 2764–2769.

24. Wong SCY, Fukuchi M, Melnyk P, et al. Induction of cyclooxygenase-2 and activation of nuclear factor-kappaB in myocardium of patients with congestive heart failure. Circulation 1998; 98: 100–103.

25. Saito T and Giaid A. Cyclooxygenase-2 and nuclear factor-kappaB in myocardium of end stage human heart failure. Congest Heart Fail 1999; 5: 222–227.

26. Zhang J, Duncker DJ, Ya X, et al. Effect of left ventricular hypertrophy secondary to chronic pressure overload on transmural myocardial 2-deoxyglucose uptake. A 31P NMR spectroscopic study. Circulation 1995; 92: 1274–1283.

27. Brindley DN, Kok BPC, Kienesberger PC, et al. Shedding light on the enigma of myocardial lipotoxicity: the involvement of known and putative regulators of fatty acid storage and mobilization. Am J Physiol Endocrinol Metab 2010; 298: E897–E908.

28. Nelson MD, Victor RG, Szczepaniak EW, et al. Cardiac steatosis and left ventricular hypertrophy in patients with generalized lipodystrophy as determined by magnetic resonance spectroscopy and imaging. Am J Cardiol 2013; 112: 1019–1024.

29. Sharma S, Adroge JV, Golzman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. FASEB J 2004; 18: 1692–1700.

30. Bozkurt B, Kribbs SB, Clumbo FJ Jr, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation 1998; 97: 1382–1391.

31. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens 2003; 21: 3–12.

32. Lappas M, Permezel M and Rice GE. Advanced glycation endproducts mediate pro-inflammatory actions in human gestational tissues via nuclear factor-κB and extracellular signal-regulated kinase 1/2. J Endocrinol 2007; 193: 269–277.

33. Ma H, Li SY, Xu P, et al. Advanced glycation endproduct (AGE) accumulation and AGE receptor (RAGE) up-regulation contribute to the onset of diabetic cardiomyopathy. J Cell Mol Med 2009; 13: 1751–1764.

34. Meléndez GC, McLarty JL, Levick SP, et al. Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension 2010; 56: 225–231.

35. Zhang Y, Wang JH, Zhang YY, et al. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGFβ1 and miR-29 pathways. Sci Rep 2016; 6: 23010.
36. Singh VP, Le B, Khode R, et al. Intracellular angiotensin II production in diabetic rats is correlated with cardiomyocyte apoptosis, oxidative stress, and cardiac fibrosis. Diabetes 2008; 57: 3297–3306.

37. Westermann D, Van Linthout S, Dhayat S, et al. Tumor necrosis factor-alpha antagonism protects from myocardial inflammation and fibrosis in experimental diabetic cardiomyopathy. Basic Res Cardiol 2007; 102: 500–507.

38. Levelt E, Mahmood M, Piechnik SK, et al. Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. Diabetes 2016; 65: 44–52.

39. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest 2002; 109: 121–130.

40. Ko HJ, Zhang Z, Jung DY, et al. Nutrient stress activates inflammation and reduces glucose metabolism by suppressing AMP-activated protein kinase in the heart. Diabetes 2009; 58: 2536–2546.

41. Stamm C, Friehs I, Cowan DB, et al. Inhibition of tumor necrosis factor-alpha improves posts ischemic recovery of hypertrophied hearts. Circulation 2001; 104: 1350–1355.

42. Steadman CD, Jerosch-Herold M, Grundy B, et al. Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis. JACC Cardiovasc Imaging 2012; 5: 182–189.

43. Gulsin GS, Henson J, Brady EM, et al. Cardiovascular determinants of aerobic exercise capacity in adults with type 2 diabetes. Diabetes Care 2020; 43: 2248–2256.

44. Zanatta E, Colombo G, D’Amico G, et al. Inflammation and coronary microvascular dysfunction in autoimmune rheumatic diseases. Int J Mol Sci 2019; 20: 5563.

45. Yu JY, Choi WJ, Lee HS, et al. Relationship between inflammatory markers and visceral obesity in obese and overweight Korean adults: an observational study. Medicine (Baltimore) 2019; 98: e14740.

46. Lebovitz HE and Banerji MA. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care 2005; 28: 2322–2325.

47. Nigro E, Scudiero O, Monaco ML, et al. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int 2014; 2014: 658913.

48. Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 2000; 102: 1296–1301.

49. Simons PJ, van den Pangaart PS, Aerts JM, et al. Pro-inflammatory delipidizing cytokines reduce adiponectin secretion from human adipocytes without affecting adiponectin oligomerization. J Endocrinol 2007; 192: 289–299.

50. Achari AE and Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci 2017; 18: 1321.

51. Baldasseroni S, Antenore A, Di Serio C, et al. Adiponectin, diabetes and ischemic heart failure: a challenging relationship. Cardiovasc Diabetol 2012; 11: 151.

52. Andrade-Oliveira V, Câmara NO and Moraes-Vieira PM. Adipokines as drug targets in diabetes and underlying disturbances. J Diabetes Res 2015; 2015: 681612.

53. Leyva F, Godsland IF, Ghatei M, et al. Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. Arterioscler Thromb Vasc Biol 1998; 18: 928–933.

54. Barouch LA, Berkowitz DE, Harrison RW, et al. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. Circulation 2003; 108: 754–759.

55. Allison MA, Bluemke DA, McClelland R, et al. Relation of leptin to left ventricular hypertrophy (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2013; 112: 726–730.

56. Paolissio G, Tagliamonte MR, Galderisi M, et al. Plasma leptin level is associated with myocardial wall thickness in hypertensive insulin-resistant men. Hypertension 1999; 34: 1047–1052.

57. Soinio M, Marniemi J, Laakso M, et al. Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. Diabetes Care 2011; 34: 1321.

58. Bruno G, Fornengo P, Novelli G, et al. C-reactive protein and 5-year survival in type 2 diabetes. Diabetes 2009; 58: 926–933.

59. Herder C, Schöttker B, Rothenbacher D, et al. Interleukin-6 in the prediction of primary cardiovascular events in diabetes patients: results from the ESTHER study. Atherosclerosis 2011; 216: 244–247.

60. Ofstad AP, Gullestad L, Orvik E, et al. Interleukin-6 and activin A are independently associated with cardiovascular events and mortality in type 2 diabetes: the prospective Askner study.
and Berum Cardiovascular Diabetes (ABCD) cohort study. *Cardiovasc Diabetol* 2013; 12: 126.

61. Kilhovd BK, Berg TJ, Birkeland KL, *et al.* Serum levels of advanced glycation end products are increased in patients with type 2 diabetes and coronary heart disease. *Diabetes Care* 1999; 22: 1543–1548.

62. Kiiuch K, Nejima J, Takano T, *et al.* Increased serum concentrations of advanced glycation end products: a marker of coronary artery disease activity in type 2 diabetic patients. *Heart* 2001; 85: 87–91.

63. Tuttle HA, Davis-Gorman G, Goldman S, *et al.* Proinflammatory cytokines are increased in type 2 diabetic women with cardiovascular disease. *J Diabetes Complications* 2004; 18: 343–351.

64. Dinh W, Füth R, Nickl W, *et al.* Elevated plasma levels of TNF-alpha and Interleukin-6 in patients with diabetic dysfunction and glucose metabolism disorders. *Cardiovasc Diabetol* 2009; 8: 58.

65. Hotta K, Funahashi T, Arita Y, *et al.* Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20: 1595–1599.

66. Mehta A, Patel J, Al Rifai M, *et al.* Inflammation and coronary artery calcification in South Asians: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. *Atherosclerosis* 2018; 270: 49–56.

67. Shah RV, Abbasi SA and Kwong RY. Role of cardiac MRI in diabetes. *Curr Cardiol Rep* 2014; 16: 449.

68. Moon JC, Messroghli DR, Kellman P, *et al.* Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013; 15: 92.

69. Haaf P, Garg P, Messroghli DR, *et al.* Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson* 2016; 18: 89.

70. Miller CA, Naish JH, Bishop P, *et al.* Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. *Circ Cardiovasc Imaging* 2013; 6: 373–383.

71. Khan MA, Yang EY, Nguyen DT, *et al.* Examining the relationship and prognostic implication of diabetic status and extracellular matrix expansion by cardiac magnetic resonance. *Circ Cardiovasc Imaging* 2020; 13: e011000.

72. Shang Y, Zhang X, Leng W, *et al.* Assessment of diabetic cardiomyopathy by cardiovascular magnetic resonance T1 mapping: correlation with left-ventricular diastolic dysfunction and diabetic duration. *J Diabetes Res* 2017; 2017: 9584278.

73. Cao Y, Zeng W, Cui Y, *et al.* Increased myocardial extracellular volume assessed by cardiovascular magnetic resonance T1 mapping and its determinants in type 2 diabetes mellitus patients with normal myocardial systolic strain. *Cardiovasc Diabetol* 2018; 17: 7.

74. Ferreira VM and Piechnik SK. CMR parametric mapping as a tool for myocardial tissue characterization. *Korean Circ J* 2020; 50: 658–676.

75. von Knobelsdorff-Brenkenhoff F, Schuler J, Doganguzel S, *et al.* Detection and monitoring of acute myocarditis applying quantitative cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2017; 10: e005242.

76. Lagan J, Naish JH, Simpson K, *et al.* Substrate for the myocardial inflammation-heart failure hypothesis identified using novel USPIO methodology. *JACC Cardiovasc Imaging* 2021; 14: 365–376.

77. Lagan J, Schelbert EB, Naish JH, *et al.* Mechanisms underlying the association of chronic obstructive pulmonary disease with heart failure. *JACC Cardiovasc Imaging* 2021; 14: 1963–1973.

78. Ridker PM, Everett BM, Thuren T, *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377: 1119–1131.

79. Everett BM, Donath MY, Pradhan AD, *et al.* Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018; 71: 2392–2401.

80. Demidowich AP, Levine JA, Onyekaba GI, *et al.* Effects of colchicine in adults with metabolic syndrome: a pilot randomized controlled trial. *Diabetes Obes Metab* 2019; 21: 1642–1651.

81. Arow M, Waldman M, Yadin D, *et al.* Sodium–glucose cotransporter 2 inhibitor Dapagliflozin attenuates diabetic cardiomyopathy. *Cardiovasc Diabetol* 2020; 19: 7.

82. Bonnet F and Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diabetes Metab* 2018; 44: 457–464.