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Role of inflammation in diabetic cardiomyopathy

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***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.[1] T2D is characterised by reduced insulin secretion and insulin resistance.[2] Inflammation has emerged as a key component in the pathophysiology of T2D, with damage to the pancreatic islets resulting from pro-inflammatory processes.[2] 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).[3] 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.[4] 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.*[5] who demonstrated evidence of cardiomegaly and congestive cardiac failure on post-mortem of four diabetic individuals with coexistent

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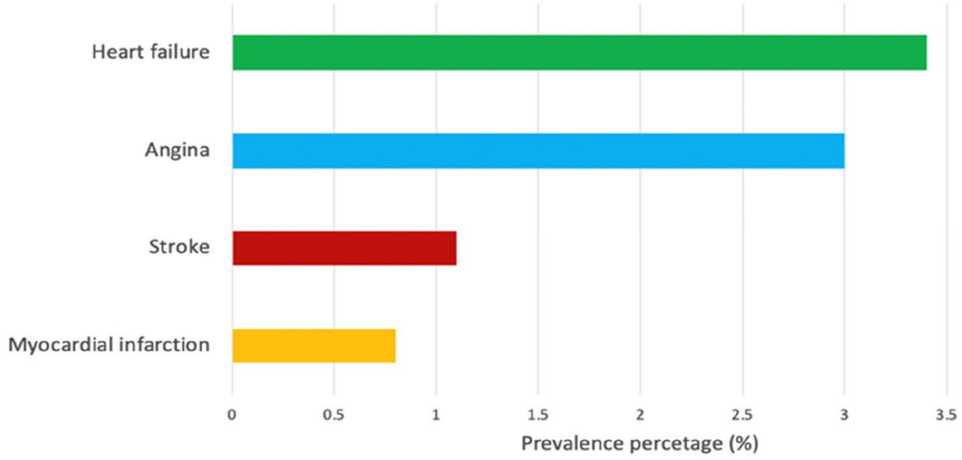

Figure 1. Prevalence of cardiovascular complications in type 2 diabetes collected from the National Diabetes Audit 2018–2019, United Kingdom.

diabetic nephropathy. 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.[6] Clinical classification stages for DC have been proposed by Maisch *et al.*,[7] with semblance to other widely used clinical staging systems, most notably the American College of Cardiology (ACC) classification of HF.[8] 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%.[9] 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.[10,11] Cytokines and chemokines released *via* this mechanism cause reactive oxygen species (ROS) stress to the myocardium, with remodelling, fibrosis and eventual myocardial diastolic dysfunction.[4]

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

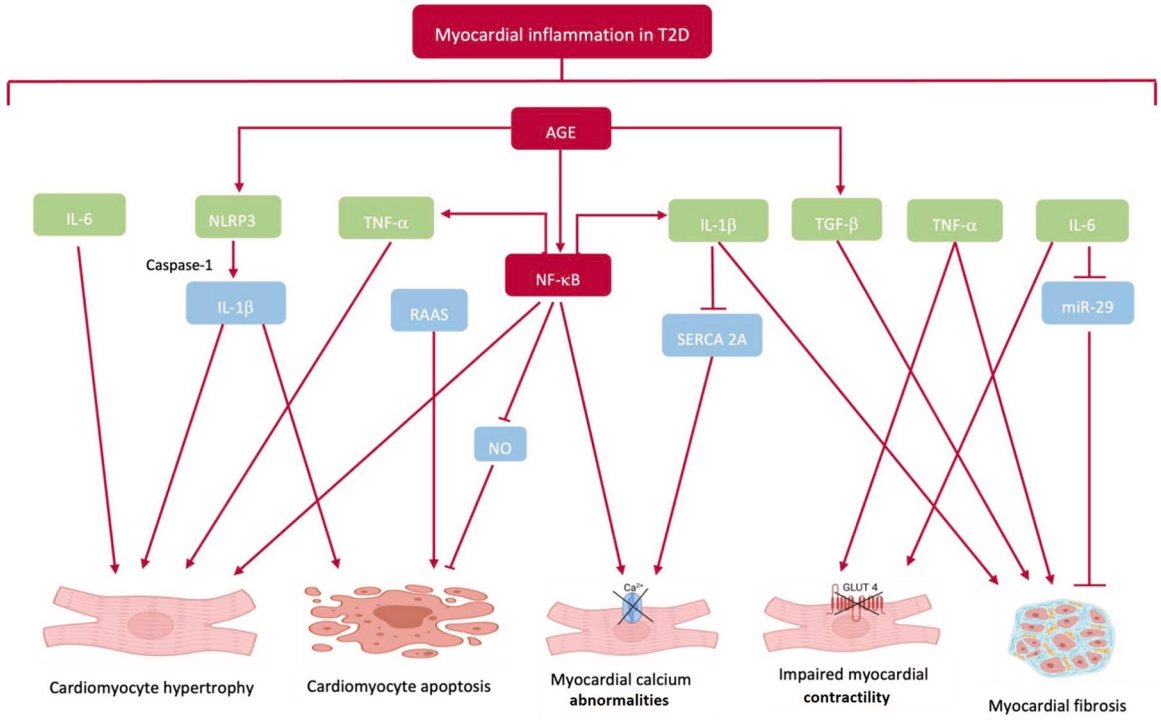

Figure 2. A summary of the inflammatory pathways leading to pathological cardiac remodelling and dysfunction in diabetic cardiomyopathy. Diabetes-associated cytokine release is primarily released *via* two mechanisms: NF-κB activation and AGE accumulation. The resulting mediators directly stimulate fibroblasts resulting in fibrosis, inhibit calcium movement causing impaired contractility and directly stimulate cardiomyocyte apoptosis and hypertrophy.
AGE, advanced glycation end products; IL, interleukin; miR, micro-ribonucleic acid; NF-κB, nuclear factor-enhanced light chain activator of B cells; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; T2D, type 2 Diabetes; TGF-β, tumour growth factor-beta; TNF-α, tumour necrosis factor-alpha.

cytoskeletal protein, all of which contribute to impaired relaxation of the diabetic heart.[12] Indeed, multiple observational studies have concluded that the rates of diastolic dysfunction were up to five times higher in people with T2D.[13,14] Furthermore, diastolic dysfunction persisted in those with adequate control of metabolic risk factors.[14]

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.[15] 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).[11] 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.[16] 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.[17] 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.[18] This perceived benefit in T2D may be due to amelioration of diastolic dysfunction *via* optimisation of haemodynamic responses and improved myocardial compliance.[19]

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-α	*N* = 63 51% T2D (mean age 60 years; all females)	No significant difference in TNF-α concentrations between those with T2D and CVD
Dinh *et al.*[64]		*N* = 41 67% T2D (mean age 65 years; 70.7% males)	↑ TNF-α levels in those with LV diastolic dysfunction (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 μg/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 μg/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-α, 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.

patients with HF with preserved ejection fraction (HFpEF).[20] De Jong *et al.*[21] ($n = 353$, 49% female) found that among normotensive obese individuals, those with T2D had six times greater prevalence of concentric hypertrophy compared to those without T2D (37% *versus* 6%, $p < 0.001$). Our group has also shown that those with T2D and HFpEF have a higher LV mass/volume and this independently correlated with HF prognosis.[22] The Strong Heart Study ($n = 1299$, 100% 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.[23] 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.[24,25] In addition, among HF patients, infarcted regions of the myocardium demonstrated a greater activation of NF-κB.[24]

Insulin resistance in T2D leads to reduced myocardial glucose availability. The subsequent switch to FFA utilisation renders the myocardium metabolically inefficient.[26] 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.[27] 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.[28] In animal HF models, increased intramyocardial lipid deposition was associated with upregulated levels of TNF-α.[29] 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.[30]

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.[4] 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.[31] Binding of AGE to its respective receptor (RAGE) triggers the production of pro-inflammatory cytokines through intracellular NF-κB activation,[32] 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.[33]

In IL-6 infused rats, concentric LVH, fibrosis and diastolic dysfunction were observed.[34] Contrastingly, 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.[35] 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.[36] 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.[37] 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.[7,38] This causes the activation of peroxisome proliferator-activated receptor alpha, which in turn reduces glucose oxidation and increases FFA uptake into cardiac mitochondria.[39] 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.[40] In contrast, IL-6 deficiency resulted in a reversal of IRS-1 suppression, thus improving myocardial glucose metabolism.[40] 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.[41]

Coronary microvascular dysfunction

T2D is associated with numerous vascular abnormalities affecting both the macro- and microvascular circulations. Coronary microvascular

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.[42] Those with diabetes have a lower MPR which was associated with lower peak oxygen consumption on cardiopulmonary exercise testing.[43] 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.[44] 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.[45] Insulin resistance seems to be present in individuals with higher visceral fat but is absent in overweight individuals with normal visceral fat levels.[46]

The adipokine adiponectin has anti-atherogenic and anti-inflammatory properties and is dysregulated in obese individuals.[47] 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.[48] Furthermore, TNF-α, IL-1β and IL-6 have been shown to have lower levels of adiponectin.[49] Adiponectin also promotes glucose uptake into skeletal muscle and inhibits hepatic gluconeogenesis.[50] 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.[51]

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.[52] Elevated leptin levels have been shown to correlate with impaired glucose tolerance, body mass index and fasting insulin levels.[53] However, there is conflicting evidence of leptin's effects on the myocardium, suggesting that leptin has mixed cardioprotective and detrimental roles. Barouch *et al.*[54] 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.[55] 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.[56] 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.[67] 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.[68] 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.[69] This feature provides an advantage over late gadolinium enhancement, which although is excellent in delineating focal scarring, it is not sensitive to

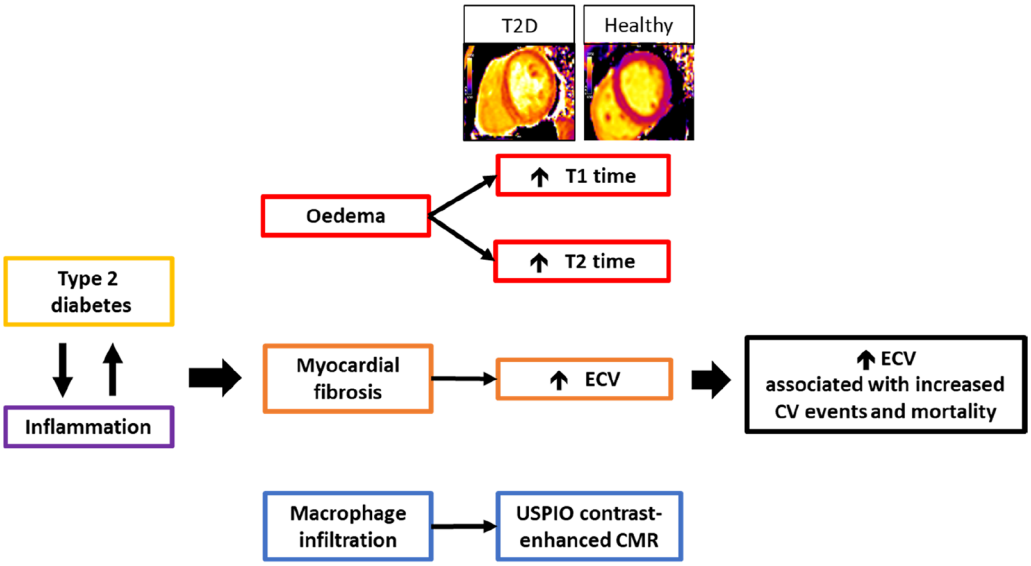

Figure 3. Type 2 diabetes and associated subclinical inflammation causes oedema, myocardial fibrosis and macrophage infiltration which are detectable using CMR parametric mapping. A raised ECV is associated with increased adverse cardiac events.
CMR, cardiac magnetic resonance; CV, cardiovascular; ECV, extracellular volume; USPIO, ultrasmall superparamagnetic iron oxide.

detect diffuse fibrosis. ECV is validated with good correlation to histological collagen volume fraction.[70] Importantly, increased myocardial ECV has been shown to be an independent predictor of mortality in people with T2D.[71] 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.

T2 mapping

Like T1, T2 time is sensitive to myocardial water content and is useful for detecting oedema.[74] 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.[75] 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.[76,77] 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-α 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.*[38]	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 Controls ($n=20$), mean age 54 ± 10 years, 45% males, BMI 28.6 ± 2.8	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% *versus* 29 ± 3% respectively, $p=0.773$)
Shang *et al.*[72]	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	Cases – T2D, LV diastolic dysfunction, asymptomatic with no history of CVD and normotensive	↑ Myocardial ECV (%) in T2D *versus* controls (30.4 ± 2.9% *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% *versus* 30.9 ± 2.1% *versus* 28.3 ± 2.3% *versus* 27.1 ± 2.4%, $p<0.0001$)
Cao *et al.*[73]	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)	Cases – T2D, aged 30–70 years, no previous history of CVD, no symptoms of CVD, normal ECG Controls – aged > 30 years, no history of T2D, hypertension and dyslipidaemia	↑ Myocardial ECV in T2D *versus* controls (27.4 ± 2.5% *versus* 24.6 ± 2.2%, $p<0.001$)
Khan *et al.*[71]	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 Controls ($n=296$), median age 53 years, 48.6% males, median HbA1c 5.3%, median BMI 25.8	T2D – HbA1c > 6.5%, clinical symptoms of T2D, using oral hypoglycaemic medication Prediabetes – HbA1c 5.7–6.4% Controls – did not meet T2D or prediabetes criteria	↑ ECV in T2D and prediabetes *versus* controls (30.3 *versus* 29.1% *versus* 27.9%, $p<0.001$) T2D and ECV > 30% were independently associated with composite HF events (HR 2.74, 95% CI 1.49–5.04 and HR 3.31, 95% CI 1.93–5.67, 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% CI 0.74–0.98, $p=0.021$) at a median follow-up of 3.7 years.[78] In a subgroup

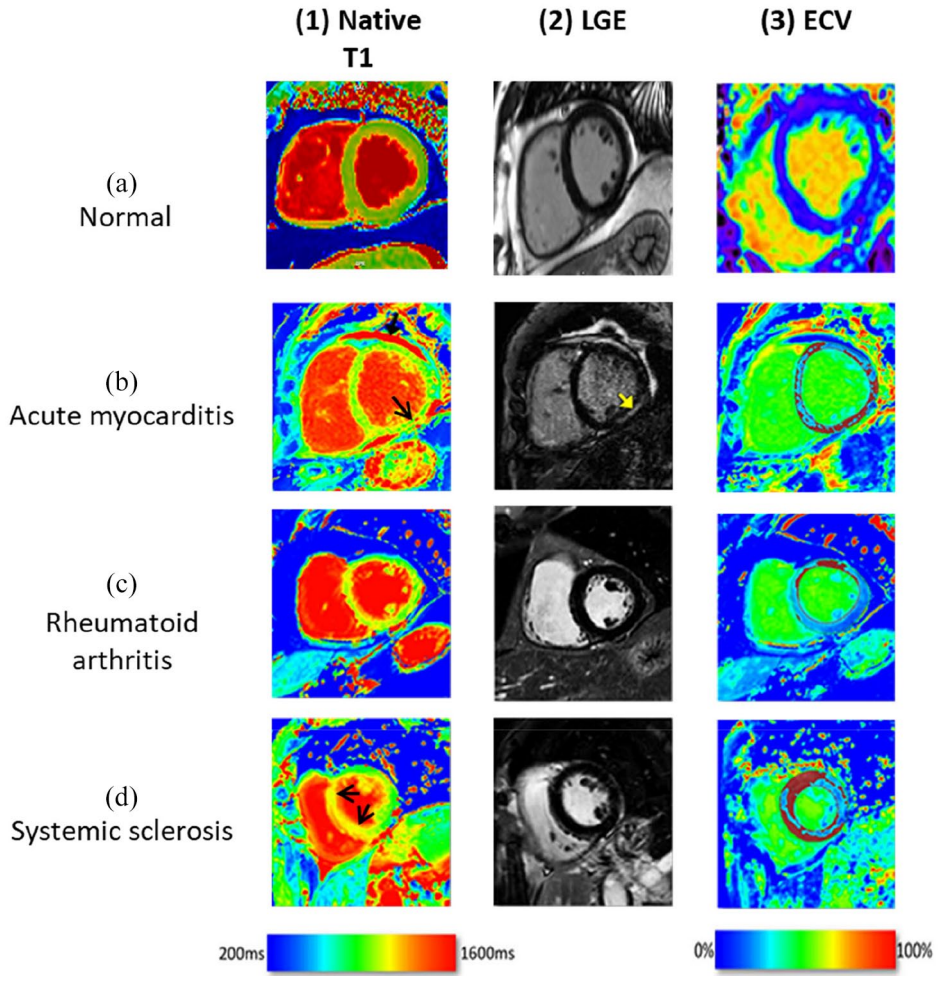

Figure 4. Multi-parametric tissue characterisation at mid-slice in inflammatory diseases involving the myocardium. On ECV maps, red areas represent abnormal ECV (greater than 30%). (a) Images of a healthy volunteer. (b) Acute myocarditis with higher native T1 values in the inferolateral wall of the left ventricle (B1, black arrow) consistent with LGE in the mid inferior-lateral wall (B2, yellow arrow). The ECV map demonstrates diffusely increased extracellular space. (c) Established rheumatoid arthritis with some rise in native T1 (C1) and ECV (C3). (d) Established systemic sclerosis with rise in native T1 predominantly in the septum (D1, black arrows) and widespread increase in ECV (D3). Images adapted from Haaf *et al.*[69]
ECV, extracellular volume; LGE, late gadolinium enhancement.

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).[79] 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.[80]

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.*[81] 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.[82] 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 in 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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