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# Inflammation and Diabetic Cardiomyopathy

*Manal M.A. Smail, Chris F. Howarth, Jaipaul Singh  
and Abba Mohamed Ismail*

## Abstract

Diabetes mellitus (DM) is a metabolic syndrome that manifests a low grade of systemic inflammation that contributes to the development of cardiovascular diseases (CVDs). DM is a predominant risk factor for CVDs inducing structural changes in the heart, infiltration of fibrosis, apoptosis, and cardiac remodeling, all leading to myocardial infarction (MI), heart failure (HF), and sudden cardiac death. Furthermore, more than 80% of diabetic patients usually die from heart diseases or diabetic cardiomyopathy (DCM). Currently, HF is one of the main causes of mortality in the world despite advances in drug treatments. According to literature, a strong association exists between chronic inflammation and the development of DCM. In order to have a better appreciation of the effect of diabetes and inflammation on the cardiovascular system (CVS), it is of paramount importance to have a better understanding of diabetes, the physiology of the CVS, and the pathophysiology of DM. Thus, the present review highlights the role of chronic inflammation in the complex interplay between the development of DM and DCM. Our understanding of the process is critical in the discovery of new targeted therapies for DCM and other forms of HF.

**Keywords:** heart, cardiomyopathy, hyperglycaemia, hypertension, inflammation

## 1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death in the world [1, 2]. By the year 2020, it is estimated that nearly 40% of all deaths worldwide will be due to CVDs, more than twice the percentage of deaths from cancer [3]. In line with the 2017 Update: A Report From the American Heart Association, CVDs account for one out of every three deaths or approximately 800,000 deaths in the United States, and coronary heart disease (CHD) accounts for most deaths due to CVDs, followed by stroke (1 of 20 deaths in the United States) and heart failure (HF) [4]. CVDs are considered multifactorial conditions which affect the essential components of the circulatory system of the human body including the heart, blood vessels and blood [5]. CVDs can either be congenital or acquired throughout people's lifespan [6]. The rising incidence of such cardiovascular risk factors as unhealthy life styles (especially eating and physical inactivity), obesity, diabetes and hypertension can underlie an increase in CVDs especially coronary artery disease (CAD). The burden of chronic diseases, including CVDs, obesity, diabetes and cancers, is rapidly increasing worldwide. These non-communicable

diseases have become a major health concern and burden to mankind, not just in developed countries but also in developing countries [7]. Chronic inflammation and oxidative stress are associated with the development of various CVDs including hypertension, arrhythmias, CAD and HF. Globally, CVDs remain a leading cause of death despite the development of new drugs and novel treatments [2]. Recent data showed that the prevalence of macro-vascular complications including coronary artery disease (CAD), peripheral artery disease (PAD) and stroke is two to four times more common in people with diabetes than healthy subjects [8]. According to the Framingham Study, the frequency of CAD is twice as common in diabetic patients of both sexes [1]. Existing data highlight the complex nature of the cardiovascular system, and different signalling pathways may play various roles depending on the stages of the pathology. In order to have a better appreciation of the effect of CVDs on the increased morbidity and mortality rate, it is helpful to have a brief understanding of the physiology and pathophysiology of the cardiovascular system.

## **2. Cardiovascular system physiology and pathophysiology**

The cardiovascular system (CVS) is composed of the blood, heart and blood vessels. The heart is a relentless muscular organ, which never stops pumping blood during life. It beats approximately 100,000 times per day, and each beat requires a vast amount of energy. The weight of the human heart is around 250–300 g for adult and a size similar to a closed fist. The heart rests on the diaphragm, near the midline of the thoracic cavity, and is surrounded by a fibrous sac called the pericardium [9]. The heart is divided into left and right sides by a septal wall. Each side of the heart is made up of two chambers, the atria and ventricles which are separated by atrioventricular valves [9]. The left side of the heart delivers oxygen-rich blood to the body passing through the aortic valve to the aorta (systemic circulation), while the right side pumps blood to the lungs passing through the pulmonary valve and the pulmonary artery for oxygen replenishment in the lungs (pulmonary circulation). The four valves of the heart ensure unidirectional flow of blood through the heart. The valves are opened and closed due to pressure differences between the heart chambers. The right atrium receives deoxygenated blood from the body through the superior and inferior vena cavae, while the left atrium receives oxygenated blood from the lungs through pulmonary veins. Coronary arteries supply the myocardium with oxygen-rich blood (the left anterior descending coronary artery, the left circumflex artery and the right coronary artery). The apex of the heart is the pointed end, and the area opposite the apex is called the base of the heart [10]. HF develops when the volume of blood pumped from the heart is inadequate to meet the metabolic demands or needs of the body [11]. The traditional hemodynamic hypothesis is that diseases, which normally increase the hemodynamic burden of the heart, ultimately lead to HF by inducing defects in the contractility of cardiac myocytes. The hypothesis of depressed cardiac myocyte contractility in HF is in support of several other related studies [12, 13], but not all [14]. Previous investigations suggested that cardiac myocytes in the failing human heart undergo many alterations which result in a significant loss of contractile function. These alterations involved a reduction in  $\alpha$ -myosin heavy chain gene expression along with a rise in  $\beta$ -myosin heavy chain gene expression, significant loss of myofilaments in myocytes and changes in cytoskeletal proteins [15].

There is general agreement about the contractile properties of the myocardium, which can be similar in both normal and in failing heart muscle under basal conditions. However, the rate-related contractile reserve is absent or significantly reduced in failing human myocardium [16]. Many studies reported that during the

end-stage of HF, basal contractility is well preserved, but the ability to increase contractility with heart rate or sympathetic stimulation is severely depressed [17]. Thus, the fundamental changes in muscle performance and regulation can be explained by the poor pumping function, reduced exercise capacity and tachycardia intolerance of the human failing heart [14]. HF can no longer be considered a simple contractile disorder or a disease of the heart alone [18]. Clinical manifestations are, in fact, the result of changes to the cellular, sub-cellular and molecular components of the heart and to mediators that drive homeostatic control mechanisms. Cardiac remodelling (CR) is now generally accepted as a determinant of the clinical course of HF. CR is defined as genome expression, resulting in molecular, cellular and interstitial changes, and manifested clinically as changes in size, shape and function of the heart. CR is determined by the general process of adaptation, which allows for both the myocyte and the collagen network to adapt to new working conditions [19].

### **3. Inflammation**

Inflammation is one of the body's defence mechanisms, and there are commonly two types of inflammation, namely, acute and chronic inflammation. Acute inflammation starts rapidly and becomes more severe in a short time, and the symptoms may last for a few days. On the other hand, chronic inflammation which is a long-term inflammation in nature can last for prolonged periods of several months to years. Generally, the extent and effects of chronic inflammation vary with the cause of the injury and the ability of the body to repair and overcome the damage [4]. This review now describes the relevant data about inflammation induced by several risk factors leading to the onset of CVDs. Basically, an inflammatory response aims to reduce the agent that causes tissue injury and to induce appropriate wound healing and to restore tissue homeostasis [20]. A cascade of inflammatory pathways and mechanistic effects are supposedly well-orchestrated by the immune system in order to eradicate the causative agent. Several immune cells can change their number, morphology and nature depending on the stage and type of inflammation [20], provided that the immune response succeeds in repairing the initial tissue injury. However, in cases where the inflammation fails to resolve, the tissue injury, due to the persistence of the triggering agent(s) or due to unsuccessful repair of the initial tissue injury or dysfunction, a sustained underlying inflammatory process can develop, leading to further tissue dysfunction and detrimental consequences [21]. Several traditional and emerging risk factors are thought to influence the cardiovascular system especially inflammation-related chronic diseases, by their interrelation with underlying molecular and cellular manifestations. In turn, these can result in chronic inflammatory responses leading to the loss of tissue properties and subsequently dysfunction [22]. Apart from dyslipidaemia, other well-established risk factors are involved in the process including hypertension, diabetes and obesity. Inflammation that causes endothelial dysfunction seems to be the key causative underlying mechanistic player, at the molecular and cellular levels, for the onset and development of subsequent inflammation-related chronic disorders such as atherosclerosis and subsequent CVDs and renal disorders [23, 24]. Hypertension, diabetes and obesity have harmful effects of oxidised low-density lipoprotein cholesterol, initiating a chronic inflammatory reaction, the result of which is a vulnerable plaque, prone to rupture and thrombosis. Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events [3]. Inflammation is widely considered to be an important contributing factor in atherogenesis and the risk



of athero-thrombotic complications. Baseline measurements of some inflammatory markers are well-known to be predictive risk factors for future CVD events in prospective epidemiological studies. Inflammatory markers dominant in the literature are acute phase response (APR)-associated, and they include fibrinogen and C-reactive protein (CRP) [25].

The presence of subclinical inflammation is accompanied by an elevated concentration of high-sensitivity CRP and increased concentrations of other inflammatory markers. Epidemiological studies suggest strong association between high-sensitivity CRP concentrations and CVD risks [37].

#### **4. Risk factors for cardiovascular diseases**

There are a number causal risk factors which are associated with CVDs and it is of paramount importance to understand and recognise these risk factors in order to predict and more so, to prevent CVDs. Risk factors may be causal or just a marker of risk(s) in nature and they are often called “innocent bystanders” [26]. The WHO has identified high blood pressure, tobacco use, physical inactivity, unhealthy diet, overweight, obesity, diabetes, high blood glucose and high cholesterol, as the main causal factors of the global burden of CVDs [27]. This review will now focus on how hypertension and diabetes mellitus can lead to heart failure (HF) and diabetes-induced cardiomyopathy (DCM).

#### **5. Hypertension and ischaemic heart disease**

Hypertension is a well-recognised risk factor for CVDs [28]. In fact, 14 weeks of hypertension can increase left ventricular weight by 30% and wall thickness by 42%, while the number of myocytes and total length of capillaries remain constant. Hypertrophy of myocytes is associated with reduced mitochondria to myofibril ratio [29]. Thus, physiological and pathological cardiac hypertrophies are caused by different stimuli and functionally distinguishable. A pathological stimulus causing pressure overload like hypertension produces an increase in systolic wall stress which results in concentric hypertrophy (a heart with a very thick wall but with relatively small cavities) [30]. In the pathological hypertrophied heart, the function may decompensate, resulting in left ventricle dilation and HF. However, in physiological hypertrophy, the function does not decompensate [30]. Accordingly, regular exercise training (ET) can induce beneficial effects in the myocardium. Cardiac action potential duration (CAPD) of the hypertrophied heart is prolonged compared to control [31]. According to literature, mortality rates from coronary artery and cerebrovascular diseases can increase progressively as blood pressure increases [21]. CAD is caused by the accumulation of lipid and inflammatory cells in the arterial walls to form atherosclerotic plaques. Unstable coronary plaques are prone to erosion or rupture, obstructing coronary blood flow and causing an acute myocardial infarction (MI). It is now known that various CVDs can alter the ultrastructure of the heart. Myocardial ischaemia develops when the coronary blood supply to the myocardium is reduced either in terms of absolute flow rate (low-flow or no flow) or relative to increased tissue demand. The main feature of ischaemia is that oxygen supply to the mitochondria is insufficient to support oxidative phosphorylation [32]. After the onset of ischaemia, ultrastructural changes in the myocardium occur rapidly. These changes can be considered as reversible alterations if reperfusion of the tissue can be effected quickly. However, when ischaemia lasts for more than 20–30 min without collateral flow, the result is a transition from

a state of reversible ultrastructural alterations to a state of irreversible tissue injury [33]. An early consequence of myocardial ischaemia is depression of myocardial contractility. Also during ischaemia, arrhythmias may occur, ranging in severity from isolated ventricular premature beats, through runs of ventricular tachycardia, to ventricular fibrillation [34]. During ischaemia, there is a reduced availability of oxygen and the metabolic substrates, leading to a deficit of high-energy phosphates. In addition, the  $\text{Ca}^{2+}$  uptake mechanisms in the sarcoplasmic reticulum (SR) of cardiac myocytes are impaired, leading to intracellular free  $\text{Ca}^{2+}$  accumulation or elevated diastolic  $[\text{Ca}^{2+}]_i$  [35].

## **6. Diabetes induced cardiomyopathy (DCM)**

CVDs are closely associated with diabetes-induced hyperglycaemia, resulting in the death in 80% of people with diabetes [1]. Diabetic cardiomyopathy (DCM) is defined as a disorder of the heart muscle caused by diabetes. It results in pathological cardiac remodelling without previous incidence of CAD, hypertension and valvular disease. The exact cellular, subcellular and molecular mechanisms of DCM are complex and remain unclear [2]. Thus, further studies are essential for better understanding of the mechanism(s) of DCM and also in reversing the pathological cardiac remodelling induced by diabetes [3]. The increased frequency of HF in diabetic patients can persist despite correction for age, obesity, hypercholesterolemia and CAD. DCM is characterized by diastolic dysfunction, which can lead to the development of systolic dysfunction [36]. Echocardiography for patients with type 1 diabetes mellitus (T1DM) without known CAD shows diastolic dysfunction with a reduction in early diastolic filling, increase in atrial filling, an extension of iso-volumetric relation and increased numbers of supra-ventricular premature beats. The most common abnormality observed in asymptomatic diabetics is left ventricular (LV) diastolic dysfunction, likely resulting from greater LV myocardial and vascular stiffness [37]. A deep understanding of its development is necessary for the early diagnosis and subsequent treatment of diabetes-related cardiovascular diseases.

There is a rapidly growing literature on DCM investigating the structural, functional and metabolic changes that occur in the diabetic myocardium and how these changes contribute to the development of DCM in humans [38, 39]. The structural changes include left ventricular hypertrophy, interstitial fibrosis, increased cell death and oxidative stress and myocardial lipotoxicity [40, 41]. The functional changes include diastolic dysfunction, systolic dysfunction and impaired contractile reserve. Metabolic changes include altered substrate utilisation and mitochondrial dysfunction [42]. In type 2 diabetes mellitus (T2DM), left ventricular mass is an independent marker of cardiovascular risks that often occur independently of atrial blood pressure. Hence, diabetes is an independent risk factor leading to left ventricular hypertrophy, myocardial stiffness and inflammation [43]. DCM is also characterized by interstitial fibrosis, mostly composed of collagen and perivascular fibrosis [44]. In biopsies from diabetic heart patients, the deposition of collagen around the vessel and between myofibres is significantly raised. Furthermore, lipofuscin (which is a brown pigment composed of lipid-containing residues), cholesterol and myocardial triglyceride is also significantly increased in cardiac tissue biopsies from the left ventricle [45].

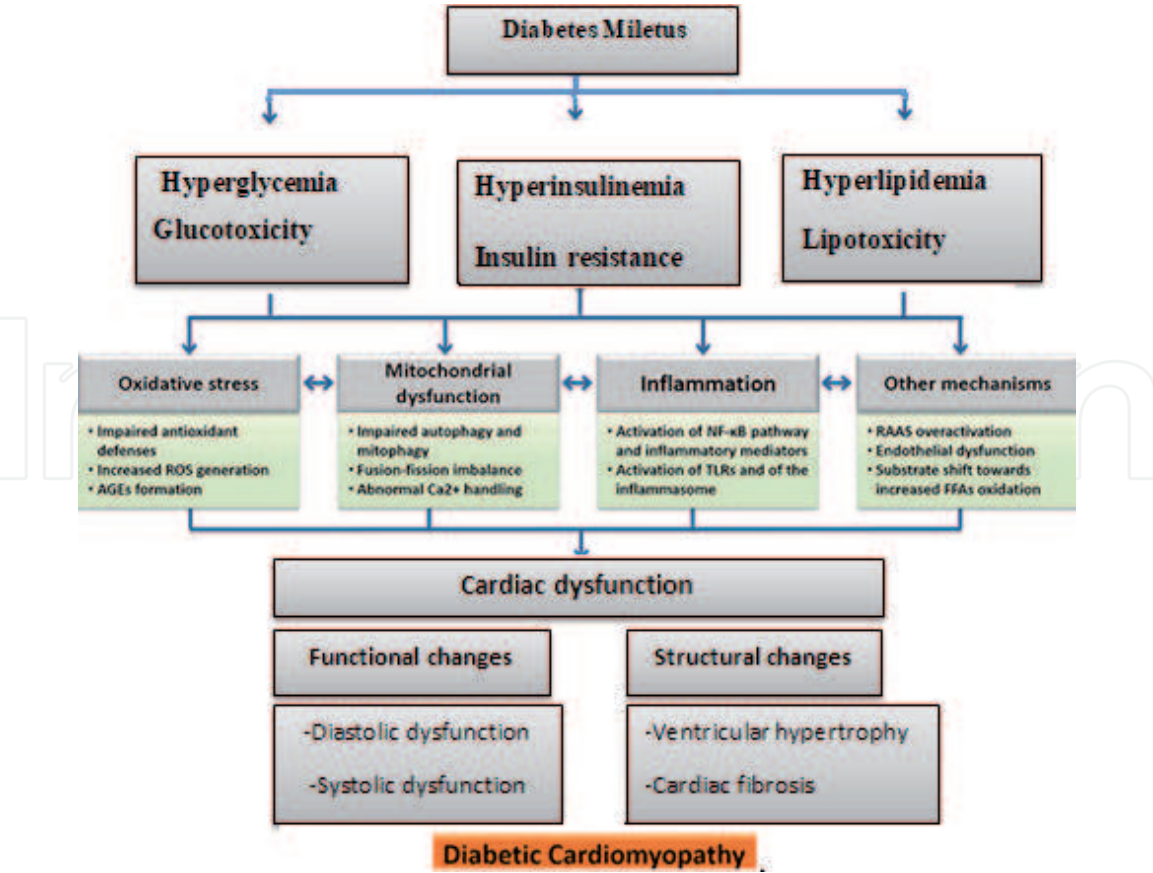
During DCM, hyperglycaemia (HG) can lead to both acute reversible cellular metabolism damage and irreversible changes in endogenous macromolecules in the heart [46]. Elevated blood HG can affect many organs in the body including the kidneys, the eyes, the nerves and the heart resulting in long-term damage and

failure [47, 48]. The first target of HG-induced damage is the microvasculature. As a result, the small blood vessels will initiate a systematic complication [49, 50]. Increased oxidative stress (OS) is a key contributor to HG-induced diabetic damages [51]. Increased OS is a possible biochemical mechanism linking the onset of DM and its complications due to OS [52–54]. Furthermore, hypertrophy and myocardial fibrosis are also associated with endothelial cell dysfunction (ECD), inflammation and abnormal vascular remodelling seen in DCM [45]. The activation of endothelial cells (ECs) from a quiescent phenotype to vasoconstriction, pro-inflammatory and pro-apoptotic state can also result in ECD [55]. The exposure of the blood vessels to high fluctuating levels of elevated blood glucose (HG) is a known factor for ECD [56].

An increase in myocardial stiffness is an early sign in the pathogenesis of DCM. This increase in myocardial tissue stiffness is a result of increased collagen production by fibroblasts along with the fibrotic replacement of apoptotic/necrotic cells [57]. Collagen type I and type III fibres accumulate in the epicardial (EPI) layer of the heart and perivascular domains, whereas type IV is mostly found in the endocardial (ENDO) layer of the myocardium [58]. The increased stiffness in diabetic hearts may be due to an increase in the stiffness of cardiac myocytes within the myocardium. Although the changes in stiffness are not dramatic, they may be enough to cause or to contribute to increased cardiac workload over time, leading to DCM progression [59]. At the molecular level, DCM leads to prolongation and enhanced temporal dispersion of the repolarization phase of cardiac action potential (CAP) in myocytes leading to alterations of the spatial heterogeneity of ion channel expression and AP duration [60]. The major recognised factors of DCM are insulin resistance (IR) and hyperinsulinemia [61]. A disruption of insulin-mediated glucose metabolism occurs during IR and hyperinsulinemia which can significantly alter the efficiency of metabolism in cardiac muscle as well as skeletal muscle. The diabetic heart is affected by insulin in both systematic metabolism abnormalities via direct effects on insulin signalling pathways in the myocardium [62]. The early recognised change in insulin resistance in the heart is the impaired ability of insulin to increase glucose transport [63]. Recently, it was found that IR is linked to cardiac contractile dysfunction. In addition, a previous study, has developed a new IR rat model in which the animals were fed on a high cholesterol fructose (HCF) diet [63]. These results demonstrate that IR is directly linked to biochemical changes in the heart, thereby contributing to the development of DCM. Despite the recent advances in this field, our understanding of the initiation and progress of DCM is still very limited.

## 7. Conclusion

CVDs are considered as the leading cause of deaths globally and they are multifactorial in nature affecting the heart, the blood vessels and the blood. The flow diagram in **Figure 1** reveals the processes and mechanism(s) whereby diabetes-induced elevated hyperglycemia, hyperinsulinemia and hyperlipidemia can lead to oxidative stress, inflammation, mitochondrial dysfunction and other mechanisms, all resulting in cardiac dysfunction, including HF, DCM, arrhythmias and sudden cardiac death. Initially, these dysfunctions are induced at the cellular, sub-cellular and molecular levels in the heart and they include changes in size, shape and function of the myocardium, including cellular calcium homeostasis. If the heart is left untreated, then it can develop, hypertrophy and disarray of the myofilaments and subsequently apoptosis and infiltration of fibrosis leading to remodeling of the myocardium. Moreover, chronic inflammation associated with cardiac dysfunction



**Figure 1.**  
*Changes occurring in the heart during diabetic cardiomyopathy. DCM in turn can lead to structural and functional changes at cellular and subcellular levels in the myocardium.*

can also result in damage and subsequent failure to a number of organs in the body including the heart and kidneys where the dynamics of blood flow is disturbed. In relation to the myocardium, there is an increase in CAPD and subsequently elevated diastolic  $[Ca^{2+}]$ . The end-result is a delay in contraction and blood ejection from the heart. This leads to slower relaxation and filling process in the heart. Over time, the whole process will lead to a weak heart or DCM and subsequently, death of the patient. The cellular and molecular mechanisms associated with chronic inflammation and the cardiovascular system are not fully known and the literature suggests the need for further research into novel inflammatory markers of CVD risk.



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## **Author details**

Manal M.A. Smail<sup>1,2</sup>, Chris F. Howarth<sup>1</sup>, Jaipaul Singh<sup>3\*</sup> and Abla Mohamed Ismail<sup>4</sup>

1 Department of Physiology, College of Medicine and Health Sciences,  
United Arab Emirates University, United Arab Emirates


2 Fatima College for Health Sciences, United Arab Emirates

3 School of Forensic and Applied Sciences, University of Central Lancashire,  
Preston, Lancashire, England, United Kingdom

4 Corniche Hospital, United Arab Emirates

\*Address all correspondence to: jsingh3@uclan.ac.uk

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