Chapter

Mechanisms of Diabetes Mellitus-Induced Sudden Cardiac Death

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Abstract

More than 450 million people worldwide have diabetes mellitus (DM), a metabolic disorder characterized by an increase in blood glucose level (hyperglycemia) that arises from insufficient insulin secretion or resistance to insulin's action. More than 70% of individuals with chronic DM will develop cardiovascular diseases (CVDs) including atherosclerosis and coronary artery diseases (CADs), hypertension, cardiac arrhythmias, cardiomyopathy (heart failure), stroke, and chronic kidney disease. A significant number of these individuals will also succumb to sudden cardiac death (SCD). SCD usually occurs in early morning from abnormal heart rhythms or arrhythmias and ventricular fibrillation. When the pumping action of the heart becomes erratic, a reduction in oxygenated blood to the brain leads to unconsciousness and brain damage. SCD is independent of age and sex and positively correlates with impairment in cardiac metabolism, muscle damage, fibrosis, apoptosis, hypertrophy, ischemia, and deranged cation signaling. This review centers on mechanisms by which intracellular cations (Na^+, K^+, and Ca^{2+}) handling, inflammation, and oxidative and carbonyl stresses due to diabetes-induced hyperglycemia can lead to the deterioration of excitation/contraction coupling (ECC), impaired contractility, arrhythmias, and SCD in DM patients. It also discusses the beneficial effects of exercise training to attenuate the risk of SCD.

Keywords: arrhythmias, cardiomyopathy, diabetes, exercise, heart, hyperglycemia, patients, sudden cardiac death

1. Introduction

Sudden cardiac death (SCD) remains a major global public health problem, especially in developed countries such as the United States of America (USA), United Kingdom (UK), Germany and other countries. Moreover, SCD is also the most common cause of death worldwide, accounting for >50% of all cardiovascular disease (CVD)-related deaths. SCD is characterized by unexpected loss of the

pumping action of the heart due to a disturbance in its electrical system that results in irregular and dangerously fast beating of the heart [1]. The ventricles may flutter or quiver (ventricular fibrillation), disrupting the pumping action of the myocardium, thereby stopping blood flow to the body. The blood flow to the brain is a matter of grave concern for the patients since reduced oxygenated blood supply to the brain can lead to unconsciousness and permanent damage to the brain. As such, death can follow unless the patient receives emergency treatment [2, 3]. Therefore, time is extremely critical when someone or a clinician is helping an unconscious person whose heart is not pumping (no pulse). SCD represents a major challenge for the clinician especially in individuals without a previous history of cardiac diseases. Early prediction of individuals at risk of SCD can be life-saving. Currently, most individuals experiencing SCD may not be identified as being a high risk and as such, the patients do not have ready access to a defibrillator. As a result, there must be community-based public access to defibrillation programmes in order to save the lives of the potential victims. SCD seems to occur most frequently in adults in their mid-30s to mid-40s and during working age, affecting both men and women. With SCD, some patients experience tachycardia, dizziness and fainting while in some cases there are no prior symptoms [4, 5].

2. Risk factors

The two major risk factors are previous myocardial infarction and coronary artery disease (CAD). However, there are other risk factors which include age, gender (predominant in males), ethnicity, reduced ejection fraction, a previous sudden cardiac arrest, familial predisposition to SCD, bradycardia, ventricular fibrillation, heart defects at birth, coronary artery abnormalities due to atherosclerosis, dilated cardiomyopathy, hypertrophic cardiomyopathy, significant changes in blood levels of potassium and magnesium, obesity, diabetes, recreational drug abuse and taking drugs that are "pro-arrhythmic" which may increase the risk for life-threatening arrhythmias [4].

3. Management of SCD

In order to prevent SCD, it is imperative to impose an aggressive management of cardiovascular risk factors at all levels including schools, universities, clinics, workplace and others. These include performing moderate exercise regularly, educating patients about the dangers of CVDs, promoting a healthy diet, restricting stress, reducing consumption of sugar, saturated fat and salt and stop smoking to promote a heart healthy behavior to all, particularly in young children and adolescents.

Finally, a preclinical prediction of patients at risk of SCD and early detection of the disease is crucial for early intervention and definitely these will reduce the incidence of SCD dramatically [4, 5]. Screening of family members who are susceptible to arrhythmias and SCD can help with early diagnosis and also and managing the arrhythmias [6].

4. Epidemiology of diabetes-induced sudden cardiac death

SCD is responsible for more than 100,000 deaths annually in the UK and 400,000 in the USA, far more than cancer and other individual non-communicable disease. It is estimated that 27,000 patients in the UK and 80,000 patients in the USA die annually from diabetes-induced SCD. Globally, SCD is responsible for half

of all deaths due to heart disease [7]. Most cases of SCD are related to undetected cardiovascular diseases. SCD are directly linked to DM and CVDs are responsible for over 80% of the mortality in the diabetic population [8]. Epidemiological data show that macro-vascular complications including coronary artery disease (CAD), peripheral vascular disease (PVD) and SCD are 2–4 times more common among diabetic patients when compared with nondiabetic people [9]. According to the Framingham study, the frequency of CAD is twice more common in diabetic patients of both sexes than nondiabetic individuals [10]. This review will now focus on the mechanisms of diabetes-induced SCD, but first it is of paramount importance to understand the structure and function of the heart.

5. Anatomy and physiology of the heart

The mammalian heart is a four-chambered muscular organ, which is located in the anterior mediastinum, posterior to the sternum and encapsulated by the pericardium. The pumping action of the heart is central to the functioning of the circulatory system. The CVS composed of the blood, the heart and blood vessels [11]. The heart is a strong muscular organ, which continues to pump blood to different parts of the body throughout our lives. It beats continuously using up a vast amount of energy daily [12]. The structure of the heart is depicted in **Figure 1** and it is composed mainly of three layers of muscles, namely the epicardium or the external layer, the middle layer or myocardium and the inner most layer or endocardium. Damage to these muscles and other conduction tissues in the heart due to diabetes and other diseases is responsible for SCD.

The larger and strong muscular tissue of the myocardium is responsible for ventricular contraction, and it is also divided into left and right sides by a septal wall. Each side of the heart is made up of two chambers consisting of the upper atria and the lower ventricles [12]. The left side of the heart pumps oxygen-rich blood to the different parts of the body via the aortic valve to the aorta (systemic circulation), while the right side delivers blood to lungs via the pulmonary valve and the pulmonary artery for oxygen replenishment in the lungs (pulmonary circulation). The heart has four valves which allow for unidirectional flow of blood thereby

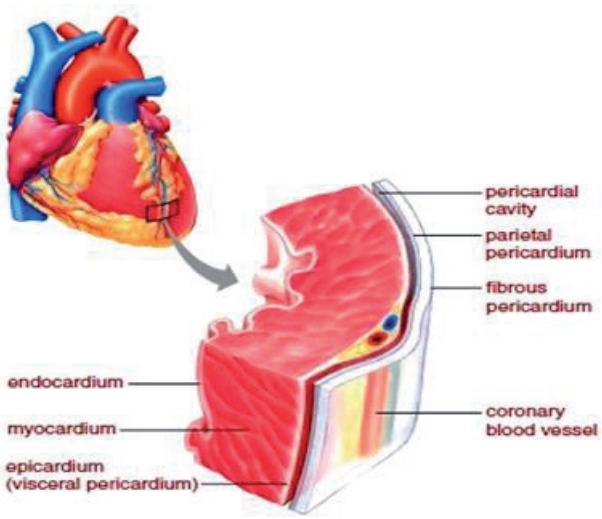

Figure 1.
The mammalian heart. Components are described in the text (image courtesy www.beyondbiology.org).

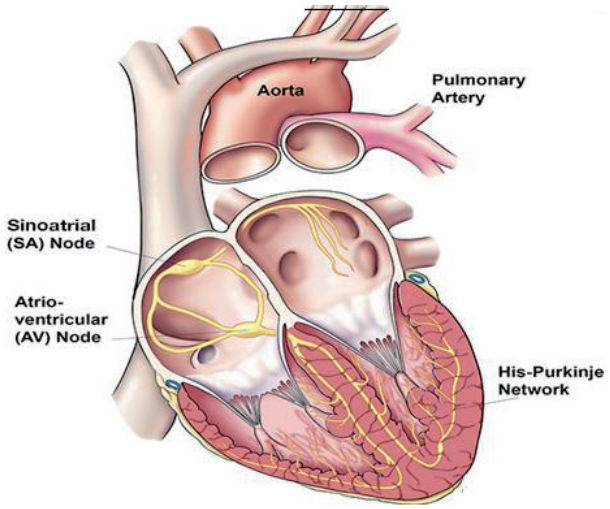

Figure 2.
Diagram showing the electrical system of the mammalian heart with the conducting tissues including the SA node, AV node and Purkinje fiber network. SCD is usually caused by abnormal heart rhythms called arrhythmias and the most common life-threatening arrhythmia is ventricular fibrillation, which is an erratic, disorganized firing of impulses from the ventricles (see lower chambers with Purkinje network of fibers). When this occurs, the heart is unable to pump blood, and death will occur within minutes, if left untreated (image courtesy www.beyondbiology.org).

preventing backflow. In turn, the right atrium receives retuning deoxygenated blood from the body through the superior and inferior vena cavae, while the left atrium receives oxygenated blood from the lungs through pulmonary vein. The heart itself needs a good supply of blood via the coronary arteries. These include the left anterior descending coronary artery, the left circumflex artery and the right coronary artery supplying the myocardium with oxygen-rich blood. The apex of the heart is the pointed end and the other end is called the base of the heart [13].

The orderly events that take place during the cardiac cycle are controlled by the electrical conduction system of the heart (**Figure 2**). An impulse is initiated at the sinoatrial node (SA-node) and then passes on to the atrioventricular node (AV-node) via conducting fibers via the atria. From the AV node, the impulse is conducted throughout the ventricles via the Purkinje fibers resulting in depolarization of the heart. Damage to the conducting tissues can result in sudden arrhythmias and possible SCD. Blood is pumped by the right ventricle into the pulmonary circulation at a lower pressure than blood pumped by the left ventricle into the systemic circulation. It follows that the haemodynamic stresses in the right and left side of the heart are very different. Even within the ventricles, the electro-mechanical properties of ventricular cardiac myocytes vary trans-murally [14].

6. SCD due to diabetes-induced autonomic system neuropathy and brady-arrhythmias

The heart is innervated by the nerves of the autonomic nervous system (ANS) [15]. The ANS consists of sympathetic and parasympathetic nerves which innervate the heart. The parasympathetic or vagus nerve originates from the inhibitory center in medulla of the brainstem. The vagal nerve innervates mainly the atria (sinoatrial node) and the atrio-ventricular node (see **Figure 2**). Upon stimulation, it releases the neurotransmitter, acetylcholine (ACh). The main function of ACh is to activate cholinergic muscarinic receptors in the heart muscles leading to reductions in

conduction of impulse (negative dromotropic effect), rate (negative chronotropic effect), contraction (negative inotropic effect) and metabolism of the myocardium. On the other hand, the sympathetic nerve originates from the thoracic region of the spinal cord and it innervates the whole heart. It releases the neurotransmitter noradrenaline (norepinephrine) (NA) which activates beta-1–adrenergic receptors in the heart leading to increases in conduction of impulse (positive dromotropic effect), rate (positive chronotropic effect), contraction (positive inotropic effect) and enhanced metabolism of the myocardium. The two nerves of the ANS work in tandem to maintain the neural homeostasis of the heart [16].

Figure 3 illustrates the relationship between diabetes-induced cardiac autonomic system neuropathy and brady-arrhythmias in SCD. In diabetes-induced cardiac autonomic neuropathy, the sympathetic nerve to the heart is damaged and its activity is reduced leading to slowing of the heart or brady-arrhythmias, heart rhythm disturbances and even SCD. Moreover, diabetes can also downregulate the beta-adrenergic receptor in the myocardium which in turn synergizes the brady-arrhythmias leading to cessation of the heart or SCD. There is new evidence that diabetes-induced cardiomyopathy is common and there is an increased risk of arrhythmias as a result of dysfunction of the cardiac conduction system (CCS) [17, 18]. This is due mainly to hyperglycemia-induced fibrosis which results in

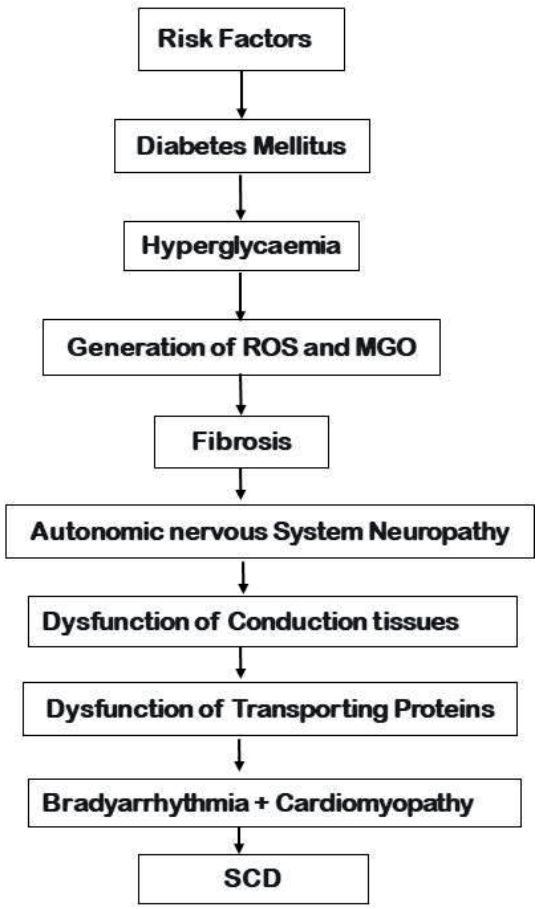

Figure 3.
Flow diagram showing the cellular and molecular events in the myocardium due to diabetes-induced hyperglycemia culminating in Brady-arrhythmias and subsequently SCD. ROS = reactive oxygen species; MGO = methylglyoxal, a reactive carbonyl species.

dysfunction of the CCS in the diabetic heart (see **Figure 2**). Moreover, it was demonstrated by Zhang et al. [18] that diabetes-induced fibrosis of the heart was associated with the reduction of potassium channel (HCN4), $Ca_v1.3$, $Ca_v3.1$ (calcium channel), NCX1, (sodium-calcium exchanger) and connexin (Cx45) protein expression in the sinoatrial node of the heart which in turn resulted in brady-arrhythmia and possibly SCD [18]. Moreover, reduced ryanodine (RyR2) and sodium-calcium exchanger (NCX1) protein expression in the atrio-ventricular junction of the heart (AVJ) is believed to contribute in part to the prolongation of the PR interval. Similarly, reduced protein expressions of RyR2, NCX1, Cx40, Cx43, and Cx45 in the Purkinje fibers (PFs) are responsible for the prolongation of QRS complex. The downregulation of neuro-filament M sub-unit (NF-M) and β_1-adrenergic receptor could also be linked to the reduced autonomic nervous control of the heart [17, 18]. All these cellular and molecular processes subsequently result in cardiac arrhythmias, QT interval prolongation and SCD of diabetic patients [19].

7. Cardiac muscle

In order to appreciate how diabetes-induced hyperglycemia is inducing fibrosis and cardiomyopathy, it is paramount importance to understand first, the structure of the cardiac cell or cardiomyocyte. Cardiac muscle, at the microscopic level, can be described as a composite tissue. It is made of various cell types, mainly myocytes and fibroblasts which are supported by extracellular matrix (ECM), all of which are permeated by fluids [15]. The myocardial ECM is made of macro-molecules which are produced by local fibroblasts. They consist of a fibrillar collagen network, a basement membrane and proteoglycans [20]. The function of the fibrillar collagen network is to strengthen the matrix, thereby giving strong structural support of the adjoining cardiomyocytes and the means by which they shorten to exert their contractile effect efficiently during ventricular pump action and thus, contributes to myocardial diastolic stiffness [21]. The heart is composed of different types of collagens including fibrillar collagen type I with the tensile strength of steel and fibrillary collagen type III which is the most abundant phenotypes [21]. Secondly, the basement membrane which surrounds the myocyte is attached to the sarcolemma and to the fibrillar collagen network. The myocyte adherence to basement membrane is a major determinant in maintaining cell shape and positional integrity within the ventricular wall [22]. Thirdly, the proteoglycans are composed of a protein core to which polysaccharide chains called glycosaminoglycans are covalently bound. These negatively charged molecules possess significant osmotic activity helping to trap and to store growth factors within ECM. Proteoglycan molecules in the connective tissue form a highly hydrated, gel-like "ground substance" in which the fibrous proteins are embedded. [22, 23]. The function of the polysaccharide gel is to prevent any compressive forces on the matrix thereby allowing the rapid diffusion of nutrients, metabolites and hormones between the blood and the cardiac tissue cell [23].

8. Sudden cardiac death due to diabetes-induced cardiomyopathy

Figure 4 illustrates the various pathways and events leading to diabetes-induced cardiomyopathy, arrhythmias and SCD due to the diabetes-induced hyperglycemia. These pathways include structural changes to cardiac muscles as well as apoptosis, altered calcium handling, insulin resistance in the heart, increased lipid uptake into the heart, glucotoxicity, metabolic disturbances, fibrosis, hypertrophy and the renin-angiotensin-aldosterone system (RAAS). DM can also affect cardiac structure

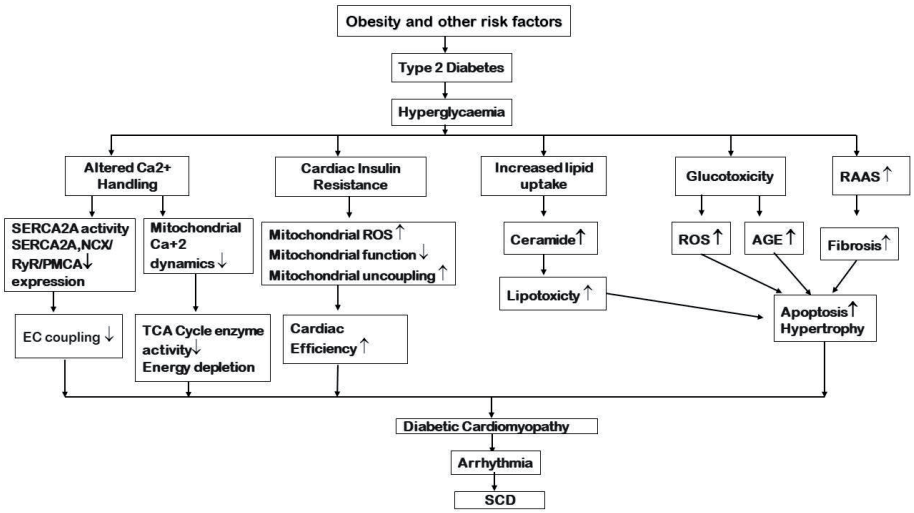

Figure 4.
Flow diagram showing the relationship between obesity and other risk factors-induced diabetes and sudden cardiac death (SCD) in the myocardium. Diabetes-induced hyperglycemia elicits structural, functional, and biochemical changes via different cellular pathways in the heart leading to diabetic cardiomyopathy, arrhythmias, and sudden cardiac death (SCD).

and function without causing changes in either high blood pressure (HBP) or CAD resulting in a debilitating condition called diabetic cardiomyopathy (DC) [24]. This term was first described by cardiac clinicians in 1972 after the examination of patients with DM and HF but without the appearance of HBP or CAD [25]. It is now well established that DC is responsible for mortality and morbidity among diabetics [26]. DC generally refers to the dysfunction of the left ventricle due to an enlarged weak heart in diabetic patients independent of CAD or HBP. The onset of DC is triggered by the diabetes–induced hyperglycemia leading to the production of a number of insults in the myocardium including TGF-beta 1, reactive oxygen species and reactive carbonyl species which in turn induce cellular structural damage to the heart. As a consequence, the initial effect is diastolic dysfunction in which the heart is unable to relax properly due to a derangement in cellular calcium homeostasis or elevated diastolic calcium due to impairment in cellular calcium regulatory transporting proteins in the myocardium. Following this, systolic dysfunction develops in which the heart is unable to pump blood efficiently to meet the demand of the body or heart failure. The final effect over time is arrhythmias and subsequently SCD. The most common contributors to DC onset and progression are left ventricular hypertrophy, metabolic abnormalities, extracellular matrix changes, small vessel disease, cardiac autonomic neuropathy, insulin resistance, oxidative stress and apoptosis, all leading to cardiac remodeling [27].

As DC was first reported in 1972, considerable data on its pathogenesis and clinical feature have been collected. DC affects the heart by enhancing fatty acid metabolism, suppresses glucose oxidation and modifies intracellular signaling, all of which lead to alteration in multiple steps of excitation-contraction coupling process, inefficient energy production, increased susceptibility to ischemia and contractile dysfunction [28, 29].

DM leads to structural and functional changes in the heart. The structural changes are manifested by left ventricular muscle disarray and hypertrophy, interstitial fibrosis, increased cell death (apoptosis) and oxidative stress, all of which result in diastolic and systolic dysfunctions as well as impaired contractile reserve [30]. In DM, the mass of the left ventricle is an independent marker for

SDC, and it often occurs independent of blood pressure in the atria. As such, DM is an independent risk factor which is responsible for enlargement of the left ventricle and generally stiffness of the heart [31].

It is particularly noteworthy that at cellular electrical level in the diabetic heart, the cardiac action potential duration (CAP) is consistently prolonged due to elevated intracellular calcium which is essential for the myocardium contraction [32]. It is now evident that DC-induced abnormalities during cardiac muscle contractility correlate closely with alterations in intracellular free Ca^{2+}concentration $[Ca^{2+}]_i$. It was previously reported that diabetic cardiac dysfunction arises as a result of changes in the expression and/or activity of transporting proteins that regulate Ca^{2+} during the cardiac cycle [33]. Thus, DC results in changes in biomechanical, contractile, and hypertrophic properties of the cardiac myocytes leading subsequently to arrhythmias and SCD.

9. Metabolic disturbances and sudden cardiac death

Metabolic disturbances such as altered lipid handling and substrate utilization, decreased mechanical efficiency, mitochondrial dysfunction, disturbances in non oxidative glucose pathways and increased oxidative stress are all hallmarks of DM [34]. Chronic hyperglycemia leads to non-enzymatic glycation of vascular and membrane proteins, producing advanced glycation end products (AGEs) and reactive oxygen species (ROS) and reactive carbonyl species (RCS) [35]. One major RCS is methylglyoxal (MGO) which is generated during glycolysis and the breakdown of lipids and glucose. In a previous study, it was reported that diabetes was associated with a large amount of collagen deposition around blood vessel and between the myofibers of heart biopsies taken from patients. Moreover, lipofuscins which are brown pigment granules that composed of lipid-containing residues were found to be deposited in left ventricular transmural biopsies. Similarly, myocardial triglyceride and cholesterol were also reported in these biopsies in large amount [36].

Insulin has a vital role to play in the regulation of cardiac metabolism and function [37]. Alterations of myocardial substrate and energy metabolism are considered as significant factors for the development of DC [38]. DM is characterized by reduced glucose and lactate metabolism and increased fatty acid (FA) metabolism [39]. In 1988, the glucose transporter GLUT family was discovered [40] and later, it was reported that glucose transport in the myocardium was impaired during diabetes because of decreased expression of GLUT1 and GLUT4 proteins and mRNA levels [41]. Likewise, glucose oxidation is reduced via the inhibitory effect of FA oxidation on pyruvate dehydrogenase complex due to high circulating FFA [42]. Insulin exerts its effect on glucose uptake in heart muscles by binding to insulin tyrosine kinase receptor (ITKR) via auto-transphosphorylation. In turn, this process initiates a signaling cascade mechanism which is accompanied by phosphorylation of phosphatidyl-inositol-3 kinase (PI3K), phosphoinositide-dependent kinase 1 (PDK1), Akt and protein kinase C (PKC). All these events allow for the translocation of GLUT1 and GLUT4 to the membrane facilitating glucose uptake into cardiac muscle cell. Contraction-evoked GLUT4 translocation represents the major mechanism that regulates glucose uptake by the myocardium heart, with only a small role by GLUT1 [43].

Both insulin resistance (IR) and hyperinsulinemia are risk factors for DC [44]. They seem to disturb insulin-induced glucose metabolism thereby significantly worsen the metabolic efficiency in cardiac and skeletal muscles. Insulin exerts its insulting effect in the diabetic heart via two processes involving the abnormalities of systemic metabolism and insulin signaling pathways, both of which are intrinsic to the cardiac tissue [45]. In the evolution of IR, the initial change that develops in

the hearts of animal models is the impairment in the ability of insulin to increase glucose transport [46]. IR is also associated with cardiac contractile dysfunction and SCD [47]. Moreover, IR is associated with metabolic alteration and the development of DC [45]. Circulating FAs and triglyceride (TG) are increased by enhanced lipolysis in adipose tissue and lipoprotein synthesis in liver as a result of hyperglycemia and IR. It is now known that the FAs are converted to a lipid- like TG or ceramide when the FAs exceed the oxidative capacity of the heart leading to lipotoxicity and cell apoptosis [48]. As a result, DM subsequently leads to an increase in the rate of FA oxidation which is accompanied by a concurrent decrease in the rate of glucose oxidation.

10. Relationship between fibrosis and sudden cardiac death

Diabetes is well known to induce severe structural changes in the heart including replacement of apoptotic myocytes with fibrotic tissue and myocyte enlargement and disarray. These changes can affect electrical and mechanical activities of the heart [47]. Fibrosis can result in stiffness of the heart, remodeling, conduction abnormalities, arrhythmias and even SCD [12, 13, 17, 18]. Moreover, increased interstitial deposits of collagen filaments leading to fibrosis can act as insulating barriers, promoting not only impulse conduction slowing, but also conduction block [17, 18]. Recent experimental findings in isolated whole-heart studies indicate that fibrosis may also modulate the formation and propagation of cardiac-after potentials which can trigger electrical activity of the heart resulting in ventricular tachycardia and ventricular fibrillation (VT/VF). Since the infiltration of the myocardium with fibrosis can induce cardiovascular events as well as impairing cardiac diastolic and systolic function, it is now possible to assess the extent of myocardial fibrosis using cardiac magnetic resonance (CMR). CMR is of paramount importance as a prognostic tool in determining the different types of cardiomyopathies, especially when it is combined with myocardial T_1 mapping [49].

In addition, the replacement of myocytes with fibrotic tissue can reduce the number of force generating sarcomeres leading to a reduction in contractile function and subsequently arrhythmias and SCD [50]. Interstitial and perivascular fibrosis is a histological symptom of DC [25] and the extent of fibrosis correlates closely with the weight of the myocardium. The pathogenesis of fibrosis in the diabetic heart is proposed to be due to diabetic micro-angiopathy. When the diabetic heart is affected by either hypertension or CAD, there may be additive micro-angiopathy and large vessel-induced ischemia, all leading to diffuse myocardial scarring. Generalized fibrosis can result in increased wall stiffness and diastolic dysfunction [18, 51]. It is now well recognized that activation of the renin-angiotensin system (RAS) has an important biochemical role to play in the development of DC [42]. In diabetic heart, Angiotensin II (AngII) receptor density and mRNA expression are elevated [52]. It has been reported that DM can enhance the activation of RAS resulting in an increase in oxidative damage, fibrosis and cell apoptosis [53].

In contrast, the inhibition of the RAS can lead to a reduction in reactive oxygen species (ROS) level, similar to the effect observed with antioxidant treatment in streptozotocin-induced diabetic rat model [54]. One example of an ROS generating endogenous molecule is the RCS, methylglyoxal (MGO). Its accumulation to toxic levels during diabetes is due to a decrease in the activity of the enzyme (glyoxylase-1), the primary enzyme responsible for degrading MGO [55]. AngII, given exogenously to rodents, has been shown to cause cellular changes within the myocardium leading to hypertrophy and fibrosis and even SCD [56].

Mitochondria are the powerhouse of cells, and they play a major role in energy production. They are also involved with a number of cellular processes including homeostasis, free radical production and cell death [57]. Mitochondria exert marked biochemical effect on FA and glucose metabolism. However, diabetes can induce mitochondrial dysfunction leading to impaired cellular metabolism. A previous study reported ultrastructural and functional changes, as well as protein composition, in cardiac muscle mitochondria following diabetes [58]. In streptozotocin-induced type 1 diabetic mice, impaired function and ultrastructure abnormalities of cardiac muscles were associated with damage to the mitochondria. The impairment of the mitochondria was accompanied by increases in 11 specific mitochondrial proteins. These include an elevation of mRNA for the mitochondrial regulatory protein and increased total mitochondrial DNA area as well as number. These findings clearly indicate that the mitochondria are the major targets of diabetes-induced damage to the heart [59]. Moreover, a recent study has shown a reduction of ATP production by the mitochondria following diabetes. Another study [60] examined the relationship between impaired insulin signaling and altered mitochondrial energetics in a mouse model of type 1 diabetes with a cardiac-specific deletion of the insulin receptor. The results reveal impaired insulin signaling in the heart and this in turn promotes oxidative stress and mitochondrial uncoupling. These processes were associated with reduced fatty acid oxidative capacity and impaired mitochondrial energetics [61]. It is now well established that mitochondria from the diabetic heart can produce more reactive oxygen species (ROS) and reactive carbonyl species (RCS) than normal mitochondria [62]. According to the molecular theory of DC, hyperglycemia (HG) is the main pathogenic factor or insult resulting in arrhythmias and SCD [60].

11. Obesity and sudden cardiac death

DC is also accompanied by other comorbidities such as obesity and hypertension and these two complications often precede the development of fibrosis, apoptosis, hypertrophy, remodeling of the myocardium, diastolic and systolic dysfunctions, CAD, arrhythmias and SCD [63]. SCD in the young obese population normally happens in individuals without a known cardiac history [64]. More recently, chronic obese patients have been reported to be more susceptible to increased risk of SCD. As such, this is becoming a major concern and challenge for clinicians and health services globally, especially since the prevalence of obesity has been increasing steadily in both developed and developing countries around the world. Both obesity and DM share the main risk factors including inactivity, smoking and diets rich in sugar and fats. Most obese patients are hypertensive, pre-diabetic, as well as having fully blown diabetes, experiencing obstructive sleep apnea due to their excessive weight and metabolic syndrome. All of these pathological parameters are well-known risk factors for CVDs, including SCD. It is now evident that structural, functional and metabolic factors modulate and influence the risk of SCD in the obese population [65]. Obesity exerts numerous haemodynamic changes on the CVS such as increased cardiac output and diastolic filling pressures, both of which result in LV hypertrophy and dilatation. In addition, obesity can induce adverse electrical changes in the myocardium including prolongation of the QRS and increase in QT intervals on the ECG, as well as an increase in QT dispersion. Moreover, the late potentials on signal averaged ECG are also more common in obese compared with lean individuals. These obese-induced adverse structural and electrical insults on the heart seem to create a substrate that is susceptible to SCD [66].

Obesity-induced pathogenesis of the myocardium is associated with the production of lipids, oxidized LDL particles and free FAs which activate the inflammatory process in the body and thus, trigger the development of cardiac dysfunction. Inflammation is responsible for the steps toward the development of atherosclerosis, from early endothelial cell dysfunction to the late atherosclerotic plaque formation causing complications. All these pathological processes are related to obesity, IR and diabetes. During diseased processes in the heart, fatty tissue releases adipocytokines which in turn induce IR, endothelial cell dysfunction, hypercoagulability and systemic inflammation, thereby facilitating the atherosclerotic process. Likewise, the inflammatory adipocytokine such as TNF-α also rises to higher levels in visceral obesity. As a result, the heart releases an increased level of C-reactive protein (CRP) which is associated with an enhanced risk of ischaemia, myocardial infarction and peripheral vascular disease, all of which can facilitate arrhythmias and SCD [67].

12. Impaired calcium and potassium homeostasis and sudden cardiac death

Calcium (Ca^{2+}) is a major trigger, a modulator, a second messenger and a regulator of cardiac contractility [24, 68, 69]. It is well known that most of the Ca^{2+} that activates contraction is released from sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs). RyRs are themselves activated by Ca^{2+} which enters the myocyte via voltage-dependent L- type Ca^{2+} channels and this mechanism is known as Ca^{2+}-induced Ca^{2+} release (CICR) [68]. The cytosolic Ca^{2+} in turn interacts with cardiac contractile proteins. By binding to troponin C, the Ca^{2+} triggers the sliding of thin and thick filaments, which results in cardiac contraction. Ca^{2+} then returns to diastolic levels mainly by the uptake of Ca^{2+} into the SR via the SR Ca^{2+} pump (SERCA2a) and extrusion of Ca^{2+} from the cell via the sarcolemmal Na^{+}-Ca^{2+} exchanger and the sarcolemma Ca^{2+}-ATPase pump [24]. DM leads to mitochondrial dysfunction which contributes to the development of DC by altering ATP generation and Ca^{2+} mobilization [69]. A previous study has shown that diabetes-induced HG plays an integral role in altering the expression and function of RyRs, Na^{+}-Ca^{2+} exchanger and SERCA. Failure of these three major calcium transporting proteins to function efficiently in cardiac muscles is the pivotal factor which is responsible the impairment of myocardial systolic and diastolic functions [30]. In such situations, Ca^{2+} homeostasis is altered during DC thereby affecting the ability of SR to take up Ca^{2+} and the Na^{+}-Ca^{2+} exchanger, and the sarcolemma Ca^{2+} ATPase to move Ca^{2+} out of the cell leading to elevated diastolic $[Ca^{2+}]_{i.}$ Second, in diabetes, channel proteins within RyRs undergo carbonylation leading to asynchronous release of calcium into the cytoplasm from the SR [57]; (see **Figure 4**).

Like cellular calcium, potassium homeostasis is of crucial importance for normal cellular function and it is regulated by ion-exchange pumps, co–transporters and channels. Normal plasma potassium values range between 3.8 to5.1 mmol/l [70]. The deviations to both extremes (hypo- and hyperkalaemia) are associated with increased risk of arrhythmias and SCD especially in diabetes-induced chronic kidney failure. Moreover, diabetic patients are at high risks when the failing kidneys are unable to remove potassium from the plasma and as such it builds up in the body leading to hyperkalaemia. Potassium levels below 3.0 mmol/l cause significant Q-T interval prolongation with subsequent risk of torsade des pointes, ventricular fibrillation and SCD. Potassium levels above 6.0 mmol/l cause peaked T waves, wider QRS komplexes and may result in bradycardia, asystole and SCD [70]. Tight regulation of serum potassium levels is necessary for many physiologic processes, including normal cardiac conduction and function [71].

13. Beneficial effect of daily exercise in sudden cardiac death

The beneficial cardiac protection, following regular exercise training (ET) in diabetic patients, has been reported in both clinical and experimental animal studies. It is now known that acute endurance ET is accompanied with significant increase in maximum oxygen consumption and enhanced cardiac output, stroke volume and systolic blood pressure which are all associated with decreased peripheral vascular resistance. On the other hand, long-term cardiovascular adaptation to dynamic training results in increased maximal oxygen uptake due to increased cardiac output and arteriovenous oxygen difference. In contrast, strength exercise training induces little or no increase in oxygen uptake. Thus, endurance exercise predominantly produces volume load on the left ventricle (LV), and strength exercise causes largely a pressure load [72]. It is now well established that LV physiological hypertrophy due to daily endurance exercise training can result in a proportional increase in myocardial cell length and width without evidence of myocardial hyperplasia in the majority of cases. This beneficial process is mediated via an increase in the expression of cardiac insulin-like growth factor-1 (IGF-1) and a concurrent activation of phophoinositide-3 kinase (PI3K) [73].

Both physiological and pathological cardiac enlargement (hypertrophy) is caused by different stimuli and both are functionally distinguishable. A pathological stimulus is normally caused by a pressure overload due to either aortic stenosis or hypertension producing an increase in systolic wall stress. In turn, this results in a concentric type of hypertrophy. This process occurs when the heart develops a thick wall with relatively small cavities. [74]. ET can also induce an adaptation of the coronary artery circulation which is divided into two main processes. Firstly, angiogenesis is initiated leading to an expansion of the capillary network by the formation of new blood vessels which occur at the level of capillaries and resistance arterioles, but not in large coronary arteries [75]. The cellular and subcellular mechanisms underlying ET-induced angiogenesis are still unknown. A number of studies [76–78] have demonstrated that growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietins (AQP) and their corresponding receptors are involved in the angiogenesis process. Studies have also shown that sprouting angiogenesis is associated with a number of proteases which are relevant for the breakdown of the capillary basement membrane. These functional proteins include matrix metalloproteinases (MMPs), urokinase, tissue plasminogen activator and plasminogen [76–79]. Cardiac muscle function is highly dependent on an adequate coronary blood flow due to high metabolic demand. Thus, coronary artery dysfunction can have a direct impact on myocardial function. It was demonstrated that an eight-week moderate-intensity exercise training regime in individuals with T2DM can significantly enhance endothelial cell function in the brachial coronary artery. This was associated with a significant improved blood flow-mediated dilation [76].

It is now known that repetitive exercise training sessions can stimulate other adaptive changes in the myocardium contributing to both improved insulin sensitivity and metabolic health of the organ. A previous study has revealed that increased oxidative capacity and capillary density were observed in skeletal muscle in response to aerobic exercise [77]. Similarly, insulin sensitivity in adipose tissue is increased within 72-hours after completion of a 6-week exercise intervention [78]. Likewise, calcium homeostasis has a major role in the excitation contracting-coupling process of the heart and ET has been shown to improve significantly cardiac myocytes contractility during diabetes due to an improvement of Ca^{2+} homeostasis. It was reported that ET can also prevent the development of SCD and the dysregulation of SR protein content in an inducible animal model of T2DM [80]. It is now

well established that most athletes have a low resting heart rate (brady-arrhythmias), typical of 40–60 beats per minute due to high vagal tone in the heart.

14. Treatment of sudden cardiac death

Therapy of SCD includes non-pharmacological and pharmacological interventions. There are a number of therapeutic options, but the main non-pharmacological therapy is the use of defibrillators [5, 6, 81–83]. However, there must be more community-based public access to defibrillation programs in order to save the lives of those patients who are more impacted. Other factors include screening of family members who are susceptible to arrhythmias and SCD and this in turn will help with early diagnosis and also and managing the arrhythmias. Generally, potential patients have to change their lifestyle habits by reducing their stress level, avoid smoking and drinking alcohol, eat a heart healthy Mediterranean diet and participate in moderate daily exercise. Moreover, potential patients should also education themselves about the signs and symptoms of SCD and how to obtain early treatment. Likewise, public health services globally should introduce health education on SCD to students, workers, patients and others. In terms of pharmacological intervention, SCD patients are treated mainly with beta blockers, ACE inhibitors, anti-arrhythmic drugs and in some cases, amiodarone. These drugs exert their beneficial effects via different cellular and subcellular mechanisms by slowing the rate and force of contraction of the myocardium [81].

It is now the general consensus that the implantable cardioverter-defibrillators (ICD) which was first implanted in patients in the 1980 is the mainstay life-saving and cost-effective clinical device in treating cardiac patients with dangerous abnormal life-threatening arrhythmias and also in the treatment of resuscitated survivors of sudden cardiac arrest substantially and with increased life expectancy compared to pharmacological therapies, including amiodarone [82]. ICD is also employed for primary prevention in high-risk patients, and in biventricular pacing of patients at high risk for arrhythmic events. More recent studies have reported that subcutaneous implantable cardioverter defibrillator (SIDC) is both safe and effective instead of the ICD as an alternative to prevent SCD [83]. The indications and use of the ICDs and SIDCs will continue to grow, resulting in increasing discussions about costs compared to other forms of therapy and the necessity of better selection of ICD/SIDC recipients depending on age, duration of the illness, risks and others [84]. Improvement of results of resuscitation from out-of-hospital cardiac arrest remains an important challenge. Both better methods to recognize asymptomatic patients at risk including genetic screening and development of new technologies to shorten the time interval between cardiac arrest and the resuscitation effort are urgently needed [84]. Further information can be found in the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and prevention of sudden cardiac death [85].

15. Conclusion

Figure 5 summarizes the major events leading to SCD during the development of DM as a result of the various risk factors. It is proposed that during elevated or uncontrolled level of blood glucose (hyperglycemia) due to DM, the body produces a number of endogenous pathological compounds called oxidants, which are classified either as reactive oxygen species (ROS such as $2O^{-}$, H_2O_2, and others) or RCS. One particular RCS is methylglyoxal (MGO), which is elevated to toxic levels.

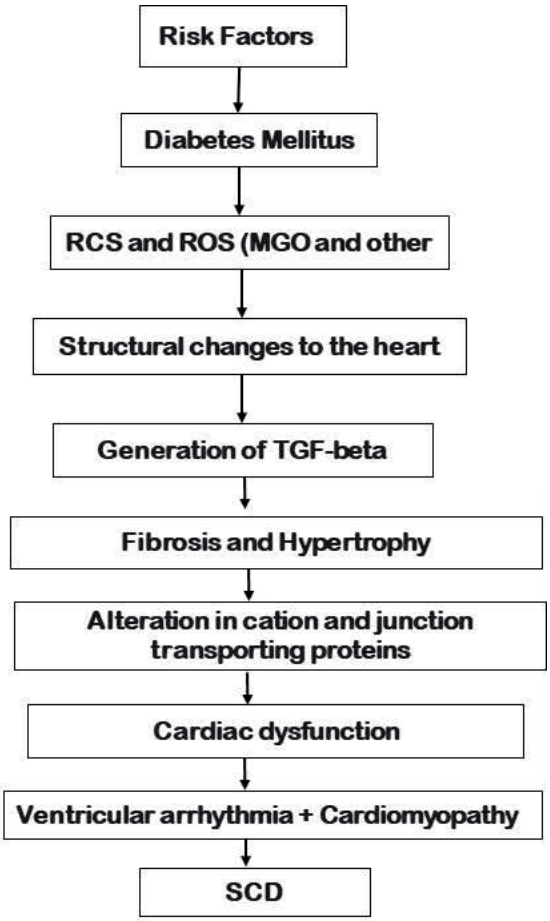

Figure 5.
A flow diagram illustrating the events, starting from the risk factors that lead to sudden cardiac death in diabetes mellitus. ROS, reactive oxygen species; MGO, methylglyoxal; TGF-beta, transforming growth factor-beta; SCD, sudden cardiac death.

This is due to increased synthesis and a decrease in the activity of glyoxylase-1, the enzyme that metabolizes MGO in the different organs of the body [55]. In the heart, MGO exerts a deleterious effect resulting in death of some cells (apoptosis), enlargement and disarray of the structure of cardiac muscles and other tissues which are associated with an elevation of transforming growth factor beta-1 (TGF-beta-1), which in turn elicits hypertrophy of the heart and infiltration of fibrosis [86]. These processes lead to a derangement in cellular calcium homeostasis (elevated diastolic calcium) followed by DC. The resulting effect is remodeling of the heart so that it can maintain its function to pump blood around the body but not at physiological level [87]. Thus, the pathogenesis of diabetic cardiomyopathy in diabetic patients is multifactorial and complex, eventually leading to an energetically compromised heart with reduced working capacity or heart failure, arrhythmias, and SCD. Luckily, patients now have a number of therapies including non-pharmacological and pharmacological interventions to treat SCD.

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