Increased Risk of Myocardial Disease by Diabetes-Induced Molecular Disturbances

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Abstract

The incidence and prevalence of Type-2 diabetes mellitus (T2DM) is increasing worldwide. Cardiovascular disease (CVD) is the major cause of morbidity and mortality among subjects with T2DM. The relationship linking diabetes and CVD is complex and multifactorial, and a thorough understanding of the pathophysiological mechanisms underlying diabetes-induced cardiac damage is crucial to the development and improvement of treatment strategies for patients with T2DM at high risk of major adverse cardiovascular events (MACE). Heart failure is more frequent and has an especially adverse outcome in subjects with diabetes. Heart muscle disease not explained by either coronary heart disease or hypertension (diabetic cardiomyopathy), is an important contributing factor to the development of heart failure. This review summarizes the molecular mechanisms of certain key contributors to the progression of diabetic cardiomyopathy including insulin resistance, metabolic disturbances, oxidative stress, altered Ca^{2+} handling, and neurohormonal activation.

Introduction

Due to its increased incidence over the past three decades and current status as one of the most prevalent chronic diseases worldwide, T2DM has been firmly established as a major threat to human health.[1] In addition, a close link exists between T2DM and a variety of CVD, namely the enhanced development of atherosclerosis and coronary heart disease, hypertension, and renal disease. These are known to be the leading causes of morbidity and mortality among patients with T2DM.[2-5] Clinical and experimental studies suggest that patients with T2DM are also at increased risk of a particular form of cardiomyopathy known as diabetic cardiomyopathy.[6-11] The following abnormalities are observed in diabetic cardiomyopathy: left ventricular (LV) diastolic and systolic dysfunction, cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, and microvascular abnormalities.[12-16] While it is not well understood to what extent the presumably 'direct' cardiotoxic effect of T2DM has on heart failure, there is a strong epidemiological relationship between T2DM and heart failure (HF).[7,17,18] This review summarizes our current knowledge of the mechanisms and potential therapeutic targets of diabetes-induced impairments in myocardial structure and function, including the contributions of insulin resistance, metabolic disturbances, oxidative stress, altered Ca^{2+} handling, and neurohormonal activation. We also compared the benefits of novel therapeutic agents targeting the condition of heart failure in diabetic patients at high risk of MACE.

Insulin Resistance

Cellular insulin signaling is known to occur through two key pathways. These include insulin receptor substrate-1 (IRS-1)-mediated stimulation of the phosphatidylinositol 3-kinase (PI3K)-AKT signaling, resulting mainly in metabolic responses and the mitogen-activated protein kinase (MAPK) signal transduction pathway involved in the processes of growth and remodeling.[19] As such, insulin-resistant states result in metabolic imbalances and altered growth. A major underlying imbalance in insulin signal transduction is the increased serine phosphorylation of IRS-1 leading to attenuated engagement of PI3K and subsequent AKT stimulation.[20-23] The responsible serine kinases may be activated by altered oxidation-reduction states or nutrition-related factors.[24-27] More specifically, over-nutrition as well as excess activation of the renin-angiotensin-aldosterone system (RAAS) are known to stimulate the mechanistic target of rapamycin (mTOR)-S6 kinase 1 (S6K1) signaling, subsequently attenuating IRS-1, IRS-2, and PI3K-AKT signaling in cardiovascular tissues.[19,28] A recent study has indicated that angiontensin (Ang)-II may activate S6K1 leading to reduced insulin metabolic signaling,

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impaired nitric oxide (NO)-mediated vascular relaxation, altered myocardial glucose utilization, and compromised diastolic relaxation.[29-31] These findings are supported by existing evidence indicating a causal relationship between hyperinsulinemia, hypertension, and coronary artery disease.[32-34] Forkhead box-containing protein, O subfamily (FOXO) activation has also been shown to lead to altered insulin signaling through downregulation of IRS-1 activity.[35,36] A recent study by Qi *et al.* demonstrated that FOXO-mediated impaired cardiac insulin signaling results in stimulation of the β-myosin heavy chain expression, which leads to cardiac dysfunction.[37] Moreover, defective insulin signaling has often been characterized by reduced GLUT4 translocation to the plasma membrane, resulting in metabolic consequences and contributing to diabetic cardiomyopathy (described in more detail below).[38] Thus, both FOXO1 and mTOR signaling may have essential roles in insulin signaling and subsequent substrate metabolism, potentially providing novel therapeutic and/or preventive targets for diabetic cardiomyopathy. Further metabolic imbalances, which may lead to insulin resistance and are known to precede the development of cardiac dysfunction, include mitochondrial dysfunction, inflammation, cytokine upregulation, endoplasmic reticulum stress, and stress kinase signaling.[39]

Metabolic Disturbances

Disturbances in myocardial substrate and energy metabolism have emerged as important contributors to the development of diabetic cardiomyopathy and heart failure.[40,41] Under normal physiological conditions, the heart utilizes both free fatty acids (FFA) and glucose, allowing for metabolic flexibility.[42,43] Additionally, the heart has a limited capacity to store surplus lipids, as fatty acid uptake and oxidation are tightly controlled to ensure sufficient, but not excessive supply, of fatty acids for the heart's energetic requirements.[44] However in T2DM, myocardial fatty acid uptake is increased, leading to increased fatty acid oxidation and lipid accumulation.[44] In insulin-resistant settings, cluster of differentiation 36 (CD36), which normally mediates the uptake of FFA, is localized to the sarcolemma.[45,46] Moreover GLUT4, which is usually translocated to the sarcolemma due to increased plasma levels of insulin, is internalized to its intracellular location.[45,46] This maladaptive positioning of CD36 and GLUT4 results in cardiac metabolic inflexibility and related abnormalities.[46]

Under normal physiological conditions, insulin inhibits lipolysis and accelerates triglyceride (TG) synthesis in adipose tissue.[47] However in settings of insulin resistance, lipolysis and hydrolysis of TGs is increased, elevating circulating levels of FFAs.[47] Enhanced fatty acid oxidation rates lead to an inhibition of glucose oxidation rates, through negative regulation between fatty acid and glucose oxidation (known as the Randle Cycle).[48] In this manner, insulin-resistance leads to reduced glucose uptake and oxidation rates, increased FFA supply and cellular uptake, and an overall substrate shift toward FFA oxidation as the dominating energy source in metabolism.[49,50] This results in increased myocardial oxygen consumption per ATP produced, reduced cardiac efficiency, and excess lipid deposition in the diabetic heart.[47,51,52] Furthermore, the accumulation of FFA in cardiac tissue further impairs insulin signaling, stimulates apoptosis, and reduces cardiac autophagy. This results in the build-up of toxic intermediates leading to lipotoxicity and ultimately to adverse structural remodeling of the myocardium, as well as, impaired cardiac performance.[50,53-56] In later stages of diabetic cardiomyopathy, expression of transcription factors involved in the regulation of glucose oxidation and β-oxidation, such as peroxisome proliferator activator receptor-α (PPAR α) and peroxisome proliferator-activated receptor gamma co-activator 1α (PGC-1 α), are decreased which further reduces myocardial metabolic efficiency.[57,58] Thus, the metabolic switch from glucose metabolism to β-oxidation and the decreased functional efficiency of the myocardium ultimately imposes increased metabolic stress on the failing heart.[57] It is evident that at the cellular level, mitochondrial dysfunction also contributes significantly to the development and progression of diabetic cardiomyopathy.[41] In addition to altered substrate utilization, changes in mitochondrial morphology, uncoupling, fission-fusion dynamics, Ca^{2+} loading, and ATP generation have all been implicated in exerting detrimental effects on the diabetic myocardium.[41,59,60]

Oxidative Stress

In conditions of excess carbohydrate and fat intake along with insulin resistance, an overflow of nutrients into the cell leads to electron transfer to oxygen in the absence of ATP production, favouring a state of increased reactive oxygen species (ROS) production.[61] Additionally, glucose autoxidation, the accumulation of advanced glycation end products (AGEs), angiotensin-II receptor type-1 (AT1R) signaling, and elevated levels of FFA and leptin have been associated with increases in ROS production in diabetic vessels and myocardium.[62-64] Therefore it should come as no surprise that increased ROS formation is also implicated in the pathophysiology of diabetic cardiomyopathy, playing an integral role in LV dysfunction.[65] Indeed, the oxidation of proteins involved in contractility, excitation-contraction coupling, protein folding, antioxidant defence, substrate metabolism, and Ca^{2+} handling play a key role in the development of diabetic myocardial dysfunction.[66-71] Even short (20 minute) exposures of cardiomyocytes to H_2O_2, one of the least damaging reactive species, has been shown to impair cell shortening and can arrest the cell during diastole.[72] Moreover, deleterious effects of ROS on cardiac function have been reproduced in the intact heart *in vivo*, as demonstrated by the beneficial effects of pharmacological agents and transgenic antioxidant expression in pre-clinical models of HF.[73-76] Indeed, there is an imbalance between the production of ROS and antioxidant scavenging of ROS in the diabetic heart compared to other organs, rendering the heart particularly susceptible to oxidative damage.[77,78] Moreover, diabetic settings have been shown to upregulate major sources of high glucose-induced ROS production, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondrial ROS. This results in damaged proteins, DNA, and lipid membrane components leading to ROS-mediated fibrosis and diastolic dysfunction, contributing to the progression of HF.[64,79,80] How-

ever, the heightened activity and expression of NADPH oxidase 4 (NOX4) can be targeted by NOX4 inhibitors for the treatment of a number of cardiovascular derangements.[81,82] In addition, treatment of a rodent model of T1DM with the antioxidant steroid hormone, dehydroepiandrosterone, inhibited the increased expression of several markers of myocardial fibrosis including collagen-I, collagen-IV, and transforming growth factor (TGF)-α, a known activator of fibrosis.[83]

Ca^{2+} Handling

Dysregulation of basal levels of Ca^{2+} in cardiomyocytes as well as irregular Ca^{2+} oscillations during the cardiomyocyte contraction-relaxation cycle are mainly due to deviations in Ca^{2+} transport.[65] More specifically, defects in regulators of intracellular Ca^{2+} concentration have been linked to diabetic cardiomyopathy.[84-89] These include the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum (SR) Ca^{2+} release channel, SR Ca^{2+}-ATPase (SERCA2a), the SERCA2a regulator phospholamban, ryanondine receptor 2 (RyR2), and the sarcolemmal Na^{+}/Ca^{2+} exchanger (NCX). Studies of obese diabetic *db/db* mice have reported elevated resting levels of intracellular Ca^{2+}, prolonged intracellular Ca^{2+} decay, slower and smaller Ca^{2+} transients, decreased sensitivity to extracellular Ca^{2+}, reduced SERCA2a activity, impaired Ca^{2+} reuptake, and leakage from the SR.[86,90] Likewise, pre-clinical models of type-1 diabetes have also demonstrated increased basal Ca^{2+} levels, attenuated Ca^{2+} release and reuptake by the SR, delayed recovery Ca^{2+} transients, reduced SERCA2a and NCX expression, as well as aberrant mitochondrial Ca^{2+} handling.[91-96] These impairments said to be a direct result of hyperglycemia, as insulin supplementation can normalize SERCA2a content and activity.[85,94,97] Furthermore, several studies have reported decreased SERCA2a-to-phospholamban ratio, contributing to attenuated cardiac relaxation in diabetic hearts.[98-100] As such, efforts to elevate SERCA2a expression and/or decrease phospholamban expression have been shown to enhance SR function by increasing its capacity to sequester Ca^{2+} during relaxation.[98,101] Transgenic overexpression of SERCA2a in diabetic rodents was able to partially restore diabetes-induced contractile dysfunction by enhancing SR Ca^{2+} uptake.[102] More recent studies have implicated diabetes-induced (glucose-dependent) post translation modifications (PTMs) of Ca^{2+}/calmodulin-dependent protein kinase 2 (CAMK-II), including oxidation and/or O-linked N-acetyl glucosamine addition or removal in the impairment of SERCA2a or ryanodine receptor function in diabetes.[103-105] In addition, SERCA itself is subject to modifications from oxidative stress, ROS and/or AGEs, ultimately leading to the impaired electromechanical coupling and reduced contractility seen in diabetic cardiomyopathy.[72,106,107] The SERCA 674Cys is susceptible to thiol oxidation in the diabetic hyperlipidemic aorta, which has been shown to significantly impair vascular SERCA activity and attenuate SR Ca^{2+} re-uptake.[106] Likewise, exposure to ROS has been shown to reduce cardiomyocyte SR Ca^{2+} content and to inhibit SERCA2a activity resulting in functional defects.[72] Lastly reactive carbonyl species, known to be upregulated in diabetes, induce PTMs to SERCA2a by reacting with its exposed arginine, lysine and histidine residues, impairing its function along with the mechanical function of the entire cardiomyocyte.[71] In addition to therapies designed to increase SR Ca^{2+} uptake, others have aimed to prevent Ca^{2+} leakage. Since unstable or hyperphosphorylated RyR2 channels result in SR calcium leak, one therapeutic strategy is to overexpress its regulatory protein, FKBP12.6.[108,109] Indeed, cardiac-specific overexpression of FKBP12.6 in mice and its adenoviral-mediated delivery in isolated rabbit ventricular cardiomyocytes has resulted in the stabilization of RyR2, greater SR Ca^{2+} content, and improved myocyte shortening.[110,111] Pharmacological intervention inhibiting SR calcium release by altered RyR2 gating or ion translocation has also been investigated. The benzothiazepine, JTV-510 (K201), improved cardiac function by stabilizing the closed state of RyR2, while its derivatives reduced arrhythmic episodes and potentially acting as protective agents against the progression of heart failure. These drugs act as protective agents against heart failure by reducing SR calcium leak through stabilizing the RyR2 to FKBP12.6 interaction.[112-114] An additional therapeutic target for heart failure is S100A1, a calcium-sensing protein that interacts with RyR2 and SERCA2a in the SR.[115] Overexpression of this down-regulated protein in settings of heart failure significantly improved contractile function, calcium handling, and cardiac energetics.[116,117] This may be attributed to its interaction with the F1F0 ATP synthase, thus improving phosphocreatine:ATP and NADH:NAD+ ratios in failing human cardiomyocytes.[118] In summary, some therapeutics such as modulators of SERCA2a expression and activity have shown early signs of success and have progressed to evaluation phases, while others are in relatively earlier stages of development (S100A1). Regulation of SR calcium handling proteins and associated cardiac energetics may represent new treatment options for heart failure.

Neurohormonal Activation

Neurohormonal activation is an important contributing mechanism to the functional and structural abnormalities observed in diabetic cardiomyopathy.[119] Hyperactivation of the RAAS plays a pivotal role in pathological vasoconstriction, and eventual cardiac hypertrophy and fibrosis as a result of increased oxidative stress.[120-122] Indeed, both Ang-II and aldosterone cause oxidative stress-induced calcium overload in cardiomyocytes as well as dampened activity of the sodium-calcium exchanger.[123] Furthermore, this pathway increases myocyte apoptosis and collagen deposition, causing increased cell death, fibrosis, and cardiomyocyte damage.[124,125] Elevated circulating levels of Ang-II and aldosterone have been linked to the pro-fibrotic and hypertrophic outcomes observed in pre-diabetic and diabetic patients with cardiac dysfunction.[126-128] Aldosterone may directly cause or exacerbate cardiac fibrosis by stimulating pro-inflammatory factors leading to the activation of matrix metalloproteinases (MMPs) and increased deposition of collagen and elastin.[125,129] Alternatively, it has been suggested that aldosterone may mediate some of its actions through the cardiomyocyte mineralocorticoid receptor (MR).[130] In the heart, aldosterone is thought to compete with cortisol for MR binding which induces its internalization, where the MR may enhance transcription of pro-inflammatory genes.[131,132] Moreover, aldosterone-MR binding can lead to

activation of ERK1/2 resulting in fibroblast proliferation as well as activation of the JNK MAPK signaling pathway, which has been shown to induce connective tissue growth factor (CTGF), resulting in myofibroblast replacement.[133-135] Aldosterone has also been reported to increase TGF-α and extracellular matrix proteins, as well as the fibrinolysis factor, plasminogen activator inhibitor (PAI-1), which leads to enhanced myocardial remodeling.[133,136] Accordingly, pre-clinical studies report attenuation in increased connective tissue in the hearts of streptozocin (STZ)-induced diabetic mice treated with spironolactone, an aldosterone antagonist.[137-139] On the other hand, Ang-II is reported to further stimulate cardiac fibroblast proliferation through the AT1R-ERK1/2 pathway, while also triggering cardiomyocyte apoptosis by inhibiting the MAPK pathway.[124] Likewise, treatments with angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors have been shown to partially inhibit elevated Ang-II receptor content, superoxide production, and apoptosis in STZ-diabetic hearts.[138,140]

Conclusion

Although numerous pharmacological agents are available to help patients with T2DM improve glycemic control, until recently very few of these have demonstrated any effect on the incidence of CVD.[141-149] Treatment with newly approved drugs, including certain thiazolidinediones (TZD), incretins (ie. glucagon-like peptide-1 receptor agonists [GLP-1RA] and dipeptidyl peptidase-4 inhibitors [DPP4]), and sodium glucose transporter 2 inhibitors (SGLT2i), all of which have anti-hyperglycemic and varying benefits on cardiovascular disease mechanisms, hold promise for the treatment of both the metabolic and cardiovascular challenges of diabetes.[146,147,149-153] More specifically, animal studies of TZDs have demonstrated protective properties such as improved glucose metabolism (by enhancing insulin sensitivity in fat, muscle, and liver cells), inhibition of systemic inflammation, improved endothelial function and blood pressure, inhibition of cardiac hypertrophy and collagen accumulation, and ameliorated LV diastolic function.[154-156] However, major drawbacks associated with the use of TZDs include weight gain, peripheral edema, and the increased risk of HF (due to renal sodium retention and fluid). This renders TZDs (namely rosiglitazone) unsuitable for the treatment of patients at high risk of MACE.[143,157-159] On the other hand, incretin-based agents exert their actions by potentiating signaling via the incretin receptor.[65] The advantage of incretin-based therapies in the treatment of diabetes is the glucose-dependent mechanism underlying insulin-secretion by GLP-1R activation, thereby reducing the risk of hypoglycemia.[65] In addition to maintaining glycemic control, the LEADER study revealed that treatment with liraglutide, a GLP-1RA, resulted in a 21% reduction in cardiovascular death, without a significant effect on hospitalization for HF *vs.* placebo.[146] In a shorter term post-MI study (POST-CON II), treatment with another GLP-1RA, exenatide, was associated with a 23% decrease in infarct size relative to area at risk (AAR) in patients with ST-segment-elevation MI.[160] Most recently, the SUSTAIN-6 study reported a 26% reduction in non-fatal MI and a 41% reduction in non-fatal stroke, with no difference in cardiovascular deaths in patients treated with semaglutide *vs.* placebo.[147] Indeed, *in vitro* and *in vivo* studies have contributed to our understanding of the cardioprotective mechanisms of GLP-1RA, including attenuated hypertrophy and fibrosis of infarcted hearts, and improved recovery of left diastolic ventricular pressure (LDVP).[161] GLP-1RA treatment have also been shown to significantly induce anti-oxidative defence genes, dose-dependently attenuate senescent-positive cells, attenuate thrombus growth, prevent oxidative stress-induced reductions of cellular respiratory capacities, and increase carbohydrate *vs.* fat oxidation in the myocardium.[161-164] Overall, this class of anti-hyperglycemic agents seems to improve cardiac efficiency and functional recovery, proving to be a favorable candidate therapy in the treatment of diabetic patients at high risk of MACE. In comparison, negative findings have been reported for DPP4 saxagliptin, which tended to increase the risk of HF whereas sitagliptin did not appear to increase the risk of MACE, hospitalization for HF, or other adverse events, overall conferring no cardiobenefit.[151,165] Similar to the GLP-1RA, an exciting newer class of anti-hyperglycemic agents, SGLT2i, has recently shown to confer cardioprotective benefit for diabetic patients at risk of HF.[149] The EMPA-REG OUTCOME study demonstrated a remarkable 38% reduction in cardiovascular death and 35% reduction in hospitalizations for HF in patients with T2DM at high cardiovascular risk treated with empagliflozin *vs.* placebo.[149] However, the mechanisms underlying these benefits are not fully understood. It is also not known which of these two seemingly beneficial approaches (the GLP-1RA or the SGLT2i) is best suited to the clinical condition of HF. Nevertheless, preliminary cardiovascular outcome studies such as DURATION-8 have demonstrated that employing combination therapy with both drug classes holds some promise for the management of hyperglycemia and possibly cardioprotection.[166] Conversely, strategies to reduce the production of ROS, or increase its degradation as with antioxidant supplementation, may also be protective against diabetes-induced cardiac dysfunction and remodeling. Additionally, specific inhibitors or gene-targeted therapies of disturbed protein signaling, Ca^{2+} handling (in addition to Ca^{2+} channel blockers), or neurohormonal activation apart from ACE inhibitors, AT1R blockers, and aldosterone agonists represent future options for the treatment of diabetic cardiomyopathy.[167-174] Advances in the elucidation of mechanisms responsible for the development of functional and structural complications in the diabetic heart will certainly aid in the design of more specific therapeutics.

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Conflicts of Interest

Dr. Husain has received consulting fees from Astra-Zeneca, Boehinger-Ingelheim, Merck, and Novo-Nordisk.

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