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Minireview

Molecular and metabolic mechanisms of cardiac dysfunction in diabetes

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ABSTRACT

Diabetes mellitus type 2 (T2DM) is a widespread chronic medical condition with prevalence bordering on the verge of an epidemic. It is of great concern that cardiovascular disease is more common in patients with diabetes than the non-diabetic population. While hypertensive and ischemic heart disease is more common in diabetic patients, there is another type of heart disease in diabetes that is not associated with hypertension or coronary artery disease. This muscle functional disorder is termed "diabetic cardiomyopathy". Diastolic dysfunction characterized by impaired diastolic relaxation time and reduced contractility precedes systolic dysfunction and is the main pathogenic hallmark of this condition. Even though the pathogenesis of "diabetic cardiomyopathy" is still controversial, impaired cardiac insulin sensitivity and metabolic overload are emerging as major molecular and metabolic mechanisms for cardiac dysfunction. Systemic insulin resistance, hyperinsulinemia, dysregulation of adipokine secretion, increases in circulating levels of inflammatory mediators, aberrant activation of renin angiotensin aldosterone system (RAAS), and increased oxidative stress contribute dysregulated insulin and metabolic signaling in the heart and development of diastolic dysfunction. In addition, maladaptive calcium homeostasis and endothelial cell dysregulation endoplasmic reticular stress play a potential role in cardiomyocyte fibrosis/diastolic dysfunction. In this review, we will focus on emerging molecular and metabolic pathways underlying cardiac dysfunction in diabetes. Elucidation of these mechanisms should provide a better understanding of the various cardiac abnormalities associated with diastolic dysfunction and its progression to systolic dysfunction and heart failure.

Contents

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Introduction

Diabetes is a major chronic disease affecting more than 25 million Americans, or greater than 8% of the current US population (Cowie et al., 2010). Diabetes is one of the leading causes of morbidity and mortality in afflicted individuals. In this regard, chronic diabetes can result in progressive deterioration of cardiac function, a condition termed diabetic cardiomyopathy, which develops independently of other risk factors including coronary heart disease. Diabetic cardiomyopathy is characterized in the early stages by diastolic dysfunction and ventricular hypertrophy and in later stages by systolic dysfunction that progresses to decompensated heart failure. A growing body of clinical and experimental data suggest that cardiac insulin resistance and metabolic inflexibility largely contribute to the development of metabolic cardiomyopathy; however, these intracardiac abnormalities are also adversely affected by systemic neurohumoral and cytokine imbalances that contribute to structural and functional abnormalities of the myocardium (Allcock and Sowers, 2010; Cowie et al., 2010; Selvin et al., 2010; Tanti and Jager, 2009). Since, cardiovascular disease accounts for the highest mortality rate in the country (Gregg et al., 2007), it is obvious that early prevention and progression of cardiac function would greatly reduce the prevalence of the dual epidemics of diabetes and heart disease.

Diabetes and cardiac dysfunction

Impact of diabetes and cardiovascular disease

Diabetes is a major chronic disease affecting more than 25 million Americans, or greater than 8% of the current US population (Cowie et al., 2010). Diabetes increases the risk of developing heart disease by several-fold; with greater than half of all diabetic patients going on to develop coronary heart disease and/or hypertension (Allcock and Sowers, 2010; Selvin et al., 2010). However, early heart disease associated with diabetes may only involve abnormalities in muscle function; an abnormality termed "diabetic cardiomyopathy". Since cardiovascular disease accounts for the highest mortality rate in the country (Gregg et al., 2007), it is obvious that prevention of the development and progression of cardiac dysfunction in diabetes would greatly reduce the prevalence of the dual epidemics of diabetes and heart disease.

Metabolic alterations in diabetes contributing to cardiovascular dysfunction

The epidemic of T2DM is driven by a constellation of metabolic abnormalities termed the cardiorenal metabolic syndrome (CRS), which are exemplified by: (a) an obesity or metabolic phenotype resulting from sedentary life style and overnutrition; (b) hyperglycemia as a result of reduced insulin sensitivity; (c) increased vascular tone contributing to pre-hypertension; (d) increased pro-inflammatory and cytokine signaling contributing to dyslipidemia; and (e) kidney dysfunction characterized by microalbuminuria and reduced glomerular filtration (Sowers et al., 2011). More than one quarter of the entire US population is thought to be suffering from the CRS. Various studies have shown that interventional reduction or prevention of metabolic abnormalities, which constitute the CRS, may reduce the incidence of concurrent diabetes, cardiovascular and chronic kidney disease, as well as prevent the recurrence of cardiovascular disease in diabetic patients (Cook et al., 2007; Knowler et al., 2009; Pulakat et al., 2011a).

Development and progression of cardiac dysfunction as a result of diabetes

Very recently, alterations in several molecular signaling pathways have been implicated in the development of cardiac dysfunction in diabetes (Aroor et al., 2012a; Zhang and Chen, 2012). Of these, impaired insulin metabolic signaling as a result of hyperinsulinemia, hyperglycemia and insulin resistance, all contributing to increased oxidative stress, may form the basis for the initial metabolic imbalance in "diabetic cardiomyopathy" (Aksakal et al., 2011; Hayden and Sowers, 2007; Matough et al., 2012; Watanabe et al., 2010). Subsequent changes in micro-circulation in coronary and renal blood vessels as a result of impaired vascular permeability and nitric oxide (NO) dysregulation causing vasoconstriction and over-activation of the RAAS contribute further to the metabolic abnormalities (Abu-Saleh et al., 2012; Hayashi et al., 2010). In addition, the increased circulating free fatty acids (FA) and dysregulated lipid signaling results in the accumulation of FAs and lipotoxicity to the heart (Maisch et al., 2011; Mandavia et al., 2012). Diastolic dysfunction characterized by prolonged diastolic relaxation time and increased left ventricular (LV) stiffness arises as a consequence of these metabolic disturbances, and precedes the development of systolic dysfunction and heart failure (Mandavia et al., 2012; Zhang and Chen, 2012). The diastolic dysfunction characterizing early "diabetic cardiomyopathy" may lead to subsequent progressive fibrosis, impaired calcium handling in the heart leading to contractile dysfunction, cardiac autonomic neuropathy and increased mitochondrial and endoplasmic reticulum stress contributing further to the reduced cardiac energetics (Aroor et al., 2012a; Mandavia et al., 2012; Zhang and Chen, 2012).

Dysregulated cardiac metabolic signaling

Inflammation in diabetes contributing to dyslipidemia and cardiac insulin resistance

Diabetes is now known to be associated with chronic low-grade inflammation, as a result of increased secretion and activation of pro-inflammatory adipokines and cytokines from inflamed adipose and other peripheral tissues (Calle and Fernandez, 2012; Miranville et al., 2012). These pro-inflammatory molecules can exacerbate systemic insulin resistance and contribute to cardiac insulin resistance mediated by insulin receptor substrate protein 1 (IRS-1) serine (Ser) phosphorylation (Miranville et al., 2012) (Fig. 1). IRS-1 is a critical docking molecule in the cardiac insulin signaling pathway, with its pleckstrin-homology (PH) domain facilitating binding to the upstream phosphorylated insulin receptor, while its SH2 domain allows docking of the p85 subunit of PI3-kinase (PI3K), the downstream component of the insulin pathway (Pulakat et al., 2012). Phosphorylation of protein kinase B (Akt) via several intermediate steps by PI3K ultimately leads to translocation of glucose transporter 4 (GLUT4) to the cardiomyocyte cell surface and facilitates glucose uptake (Iliadis et al., 2011; Pulakat et al., 2012). Indeed, activation of the nutrient-sensitive and stress-mediated mammalian target of rapamycin complex I (mTORC1)/S6 kinase 1 (S6K1) pathway as a result of the chronic insulin resistance and inflammation-induced oxidative stress seen in diabetes is one of the major causes of cardiac insulin resistance in diabetes (Pulakat et al., 2011b, 2012). The Ser kinase S6K1 is one of the major regulatory molecules of IRS-1 protein expression via its ability to Ser-phosphorylate multiple sites on IRS-1. In addition to S6K1, other mitogen-activated protein (MAP) kinases such as extracellular signal regulated kinase (ERK) can also Ser-phosphorylate IRS-1 in the cytosol thereby targeting it to the proteasomal complex (Aroor et al., 2012a; Iliadis et al., 2011; Pulakat et al., 2011a, 2011b; Zhang et al., 2008). IRS-1 can also be degraded by other pro-inflammatory cytokines. Tumor necrosis factor-alpha (TNF-α) has been shown to cause cardiac insulin resistance through activation of NF-κB as well as the redox-sensitive Ser C-Jun N-terminal kinase (JNK), both of which can cause Ser phosphorylation of IRS-1, targeting it for ubiquitin-proteasomal degradation (Hitomi et al., 2011; Tanti and Jager, 2009; Yang et al., 2009). Interleukin-6 (IL-6) mediates both reduced insulin receptor signaling and increased lipogenesis via signal transducer and activator of transcription (STAT)3-mediated induction of suppressor of cytokine signaling 3 (SOCS3) in adipocytes (Serrano-Marco et al., 2011).

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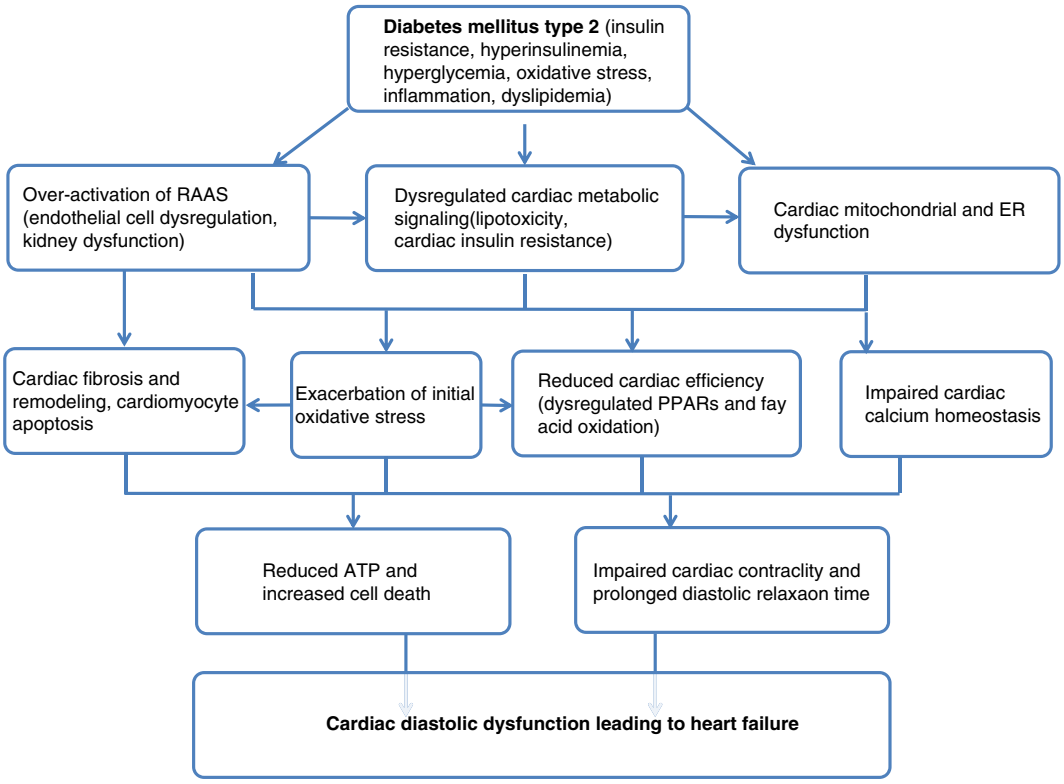

Fig. 1. Proposed scheme of development and progression of cardiac diastolic dysfunction as a result of the metabolic abnormalities seen in diabetes. (RAAS = renin–angiotensin II–aldosterone system, PPARs = peroxisome proliferator activator receptors, ER = endoplasmic reticulum, ATP = adenosine triphosphate).

Macrophage infiltration into peripheral tissue in diabetes serves to further increase the secretion of pro-inflammatory cytokines and chemokines. Monocyte chemo-attractant protein (MCP1) contributes to dyslipidemia by increasing the accumulation of triglycerides directly (Kim et al., 2011). Conversely, the expression of the anti-lipogenic adipokine adiponectin, which stimulates 5-AMP-activated protein kinase (AMPK) to reduce lipogenesis, is decreased (Calle and Fernandez, 2012). Adiponectin is an anti-inflammatory anti-lipogenic complement factor secreted mostly by subcutaneous adipose tissue. It mediates its effects through two receptors AdipoR1 and AdipoR2 on the cardiomyocyte cell surface. Adiponectin has important implications in diabetes, as it is involved in multiple aspects of cardiac metabolic signaling (Yi et al., 2011). It normally serves to reduce the expression of pro-inflammatory factors such as IL-6 and also affords anti-lipogenic protection to the cardiomyocyte mediated by AMPK (Yi et al., 2011). In addition, adiponectin may also be involved in aldosterone signaling in conditions of insulin resistance and diabetic heart disease (Flynn and Bakris, 2011).

Hyperinsulinemia, systemic and cardiac insulin resistance contributing to cardiac lipotoxicity and reduced cardiac insufficiency

Excess insulin promotes increased uptake of free FAs in the heart due to up-regulation of the cluster differentiation protein 36 (CD36), which is a potent FA transporter (Schwenk et al., 2010; Tepavcevic et al., 2011). In fact, ablation of CD36 has been shown to prevent the induction of metabolic stress associated with high-fat diet, even in the presence of an ischemic component such as artificially induced cardiac overload (Steinbusch et al., 2011). Conversely, during metabolic stress, increased expression of CD36 and its chronic displacement to the sarcolemma and over-activation leads to increased FA uptake and subsequent accumulation in the cardiomyocytes, eventually contributing to lipotoxicity (Kennedy et al., 2011; Tepavcevic et al., 2011). Even though about 20% of FA uptake occurs spontaneously across the cell membrane and some of it is mediated by other transporters like plasma membrane FA binding protein (pmFABP) or FA translocase (FAT), fatty-acid uptake is mostly dependent on and directly correlates with the amount of CD36 in the sarcolemmal membrane of the cardiomyocyte (Su and Abumrad, 2009). Insulin is also a potent anti-lipolytic agent, and thus facilitates FA accumulation by preventing breakdown of triglycerides and also reduces the delivery of free FAs to the cell. Thus, insulin resistance in diabetes increases circulating free FAs by accelerating breakdown of esterified long-chain FAs (LCFA). The expression of FA synthase (FAS), which is a rate-limiting enzyme in fatty-acid synthesis, is also decreased in the diabetes-induced insulin-resistant state. Indeed, FAS was found to be reduced in several animal models of diabetes and insulin resistance (Wu et al., 2011). Insulin is known to up-regulate the expression of FAS in adipogenic tissues, and reduction of FAS seen in diabetes exacerbates the amount of circulating plasma free FAs, thereby causing intracellular free FA accumulation in the cardiomyocyte (Wu et al., 2011). Interestingly, the expression of FAS was increased in hearts of patients with end-stage cardiomyopathy and heart failure patients (Razani et al., 2011). All of these molecular mechanisms lead to eventual accumulation of toxic metabolites of glycolysis termed advanced glycation end products (AGE) and toxic intermediates of lipid metabolism such as ceramide and diacylglycerol; causing cardiac lipotoxicity which is a component of "diabetic cardiomyopathy".

The reduced glucose uptake as a result of systemic and cardiac insulin resistance facilitates a substrate shift towards increased FA oxidation in diabetes, resulting in reduced cardiac efficiency (Dirkx et al., 2011; Jellis et al., 2011). The normal heart derives most of its energy from FA metabolism, with only about 30% of its energy coming from glucose oxidation. Even though in ischemic conditions, there is a shift in substrate utilization from free FAs to glucose in an effort to improve cardiac energetics; during insulin resistance and diabetes, the rate of glucose uptake is reduced while that of circulating free

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FAs is increased, leading the heart to utilize even more FAs for its energy needs (Aroor et al., 2012a; Falcão-Pires and Leite-Moreira, 2011; Maisch et al., 2011; Mandavia et al., 2012; van de Weijer et al., 2011). This occurs through the following mechanisms: the increased FAs within the heart act as ligands and stimulate the peroxisome proliferator activator receptor (PPAR) isoforms, the expression of which has been found to be increased in diabetes (Nicholls and Uno, 2012; van de Weijer et al., 2011). The PPARs are involved in multiple aspects of cardiac lipid metabolism. The expression of FA oxidation genes, which represent an endogenous substrate for the activity of the PPAR isoforms PPAR-γ and PPAR-α, is also increased (Nicholls and Uno, 2012). Accordingly, the PPAR receptors have been shown to mediate and increase both FA uptake and utilization in the cell by modulating the expression of FA transporter protein (FATP) as well as CD36, and also of enzymes involved in beta-oxidation such as CYP4A and carnitine-palmitoyl-transferase (CPT1) (Mandavia et al., 2012; Song et al., 2010). Even though FA oxidation is increased; it may be impaired due to a defect in adenosine triphosphate (ATP) synthase, resulting in uncoupling of oxidation and ATP generation (Kota et al., 2011).

Enhanced PPAR-α signaling is especially associated with increased FA oxidation in the cardiomyocyte. In mice with PPAR-α overexpression, increased FA oxidation and decreased glucose utilization were found (Duncan et al., 2010). Conversely, in PPAR-α knock-out mice, even though no severe developmental phenotype was observed, upon FA challenge, the mice were unable to process the increased FA, resulting in accumulation and lipotoxicity (Duncan et al., 2010). PPAR-γ co-activator (PGC)-1α, which is a co-activator for both isoforms, has been shown to up-regulate and improve mitochondrial biogenesis, as well as enhance and facilitate binding of the PPAR-retinoid X receptor (RXR) heterodimer to PPAR-response elements (PPRE) on the genes they regulate (Kim et al., 2008; Song et al., 2010). PPAR-α is also thought to reduce glucose utilization as a compensatory mechanism to protect the cell against increased glucose overload by reducing the expression of an enzyme called pyruvate dehydrogenase kinase 4 (PDK4) (van de Weijer et al., 2011). While functional PPREs have been identified in most of the genes that PPAR-α regulates, no PPRE was identified in CD36 which is believed to be indirectly regulated by PPAR-α (Duncan et al., 2010). In addition, PPAR-α is also known to increase expression of the cardiac-abundant mitochondrial uncoupling protein 3 (UCP3) (Duncan et al., 2007). This mechanism is thought to protect against increased oxidative stress by permanently eliminating damaged mitochondria (van de Weijer et al., 2011).

In conditions of reduced cardiac efficiency such as "diabetic cardiomyopathy", an important enzyme AMPK gets stimulated (Lakshmanan et al., 2012). It is important to note that AMPK has no preference for glucose or fatty-acid substrates and stimulates both equally (Hue and Taegtmeyer, 2009). AMPK is activated in response to decreased ATP and serves to increase the trafficking of both CD36 and GLUT4 to the plasma membrane as a compensatory mechanism to increase FA and glucose uptakes respectively (Lakshmanan et al., 2012; Schwenk et al., 2010). AMPK can also be activated by anti-inflammatory adipokines such as leptin and adiponectin (Essick et al., 2011). It acts on FA synthesis by phosphorylation-mediated direct deactivation of the enzyme acetyl-coenzyme A (CoA) carboxylase (ACC) which produces malonyl-CoA that is a substrate for FA synthase in the biosynthetic pathway (Stride et al., 2012). In this way, AMPK induces an anti-lipogenic effect while at the same time promoting oxidation and utilization of FAs through modulation of CPT-1 activity. CPT-1 serves as a rate-limiting enzyme in FA oxidation by catalyzing the transfer of the acyl group from CoA across the outer mitochondrial membrane, and is inhibited by malonyl-CoA (Ussher et al., 2009). Conversely, insulin can inhibit AMPK through Akt-mediated Ser phosphorylation on its residues, thereby indirectly activating ACC and thus causing increased lipogenesis and decreased β-oxidation. In addition, atypical forms of protein kinase C (PKC) such as PKC-ε are thought to mediate AMPK phosphorylation and its effect on GLUT4 translocation (Chen et al., 2002).

Over-activation of the renin–angiotensin II–aldosterone (RAAS) axis

Hyperinsulinemia seen in T2DM, along with resultant endothelial cell fibrosis and kidney dysfunction causes over-activation of RAAS (Lastra et al., 2010; Pulakat et al., 2011b; Wong et al., 2010). This, in turn, leads to cardiac insulin resistance via Ser-phosphorylation-mediated proteasomal degradation of IRS-1 and/or decreased binding and activation of PI3K and downstream Akt (Kim et al., 2012; Pulakat et al., 2012). Indeed, both Ang II and aldosterone induce Ser-phosphorylation of IRS-1 via different pathways in multiple tissues and organ systems (Hitomi et al., 2007; Kim et al., 2012; Luther and Brown, 2011; Olivares-Reyes et al., 2009; Pulakat et al., 2012; Wada et al., 2009; Whaley-Connell et al., 2009). In addition, Ang II and aldosterone can cause activation of mitogen activated protein kinases (MAPKs) such as p38, which promote fibroblast proliferation while inducing cardiomyocyte fibrosis and apoptosis (Palomeque et al., 2009). Both Ang II and aldosterone cause significant cytosolic oxidative stress in the cardiomyocyte via trans-activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and production of reactive oxygen species (ROS) (Habibi et al., 2011; Manrique et al., 2007; Whaley-Connell et al., 2009). As such, activation of the redox-sensitive mTORC1/S6K1 pathway via oxidative stress-mediated pathway by both Ang II and aldosterone has been shown to be a major cause of systemic and cardiac insulin resistance (Pulakat et al., 2012; Whaley-Connell et al., 2009; Zhang et al., 2008). Both Ang II and aldosterone cause oxidative stress-induced calcium overloading in the cardiomyocyte in concert with decreased activity of the sodium–calcium exchanger (Cooper et al., 2007). In addition, the increased oxidative stress causes cardiomyocyte cell damage, resulting in apoptosis, fibrosis, and increased cell death (Cooper et al., 2007; Manrique et al., 2007).

Plasma Ang II and aldosterone levels have also been implicated in the pro-fibrotic effects observed in patients with cardiac dysfunction as a result of diabetes (Maisch et al., 2011; Manrique et al., 2007; Steckelings et al., 2009). Early studies identified Ang II and its signaling effectors as potential culprits for triggering LV hypertrophy (LVH), fibrosis and cardiac remodeling; but many studies are now supporting at least a synergistic role for aldosterone in the pathogenesis of cardiac fibrosis observed as a result of the diabetes-induced metabolic impairment (Dong et al., 2012; Fredersdorf et al., 2009; Kato et al., 2011; Maisch et al., 2011; Pulakat et al., 2011a; Weir et al., 2009; Yoshimura et al., 2008). These observations are also supported by the fact that the serum levels of aldosterone have been found to be increased in the pre-diabetic and diabetic conditions and contribute to the LVH and cardiac fibrosis seen in these conditions (Fredersdorf et al., 2009; Yoshimura et al., 2008). Even though the normal heart does not express aldosterone synthase mRNA, serum aldosterone levels are increased after myocardial infarction (Weir et al., 2009). Although aldosterone can directly cause or aggravate cardiac fibrosis by triggering pro-inflammatory factors leading to activation of matrix metalloproteinases (MMPs), as well as increased collagen and elastin deposition, some of its actions are thought to be mediated by the cardiomyocyte mineralocorticoid receptor (MR) (Catena et al., 2012; Karagueuzian, 2011; Nguyen Dinh Cat and Jaisser, 2012). Aldosterone competes with cortisol for MR binding in the heart, and once bound, induces its internalization where MR exerts its genomic effects by enhancing transcription of pro-inflammatory genes (Sun et al., 2002; Weir et al., 2011).

Aldosterone/MR binding can trigger myofibroblast replacement via ERK1/2 activation that leads to fibroblast proliferation and JNK MAPK signaling pathway activation (Rude et al., 2005; Stockand and Meszaros, 2003). Aldosterone/MR effect on p38 MAPK pathway has been shown to induce connective tissue growth factor (CTGF) (Lee et al., 2004). In addition, aldosterone also increases transforming growth factor (TGF-β), which is a well-known activator of fibrosis and extracellular matrix (ECM) proteins; and plasminogen activator inhibitor 1 (PAI-1), which is an important fibrinolysis factor and is also involved in atherogenesis; causing increased remodeling (Booz

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and Baker, 1995; Rude et al., 2005). Ang II can also stimulate increased cardiac fibroblast proliferation via angiotensin receptor type 1 (AT1R)-ERK1/2 pathway mediated by PKC-δ and intracellular calcium, at the same time causing cardiomyocyte apoptosis through inhibition of the mitogenic pathway (White et al., 2012). In addition, over-nutrition induced hyperglycemia and subsequent oxidative stress trigger activation of NF-κB and other pro-inflammatory pathways, as well as increased deposition of AGEs, which in turn interact with their receptor for AGE (RAGE) to increase CTGF, thereby promoting fibrosis (Lemarié et al., 2009; Zelarayan et al., 2009). This results in arterial wall stiffness contributing further to the already impaired diastolic dysfunction due to deposition of ECM proteins such as fibronectin and collagen.

Exacerbation of initial oxidative stress from diabetes-induced cardiac metabolic alterations and mitochondrial dysfunction: cause–effect relationship

The major common feature linking diabetes-induced metabolic dysregulation to the development of subsequent cardiac dysfunction is oxidative stress (Aroor et al., 2012a; Hayden and Sowers, 2007; Mandavia et al., 2012; Selvaraju et al., 2012; Watanabe et al., 2010; Zhang and Chen, 2012; Zhou et al., 2010). An imbalance between nutrient intake and energy needs caused by over-nutrition or lifestyle factors, leading to diabetes, forms the basis for the initial oxidative stress (Aroor et al., 2012b; Mandavia et al., 2012; Newsholme et al., 2012; Whaley-Connell et al., 2011). ROS are a normal by-product of cellular metabolism and mitochondrial oxidative phosphorylation, and are produced and removed by the existing balance between them and the intracellular anti-oxidant machinery during the normal physiological state. Pathology occurs when the formation of ROS exceeds the antioxidant capacity of tissue, or when the antioxidant mechanisms are somehow suppressed and unable to scavenge the toxic radicals, creating an imbalance (Aroor et al., 2012b; Newsholme et al., 2012; Whaley-Connell et al., 2011). Over-nutrition or sedentary lifestyle seen in the majority of patients with diabetes and/or cardiomyopathy can induce excess ROS formation through the chronic increased supply of nutrients to the cell, which in turn leads to increased mitochondrial oxidative function, leading to excess electron generation and ROS (Aroor et al., 2012b; Mandavia et al., 2012; Newsholme et al., 2012; Ren et al., 2010; Thandavarayan et al., 2011). Once oxidative stress develops, it turns into a vicious self-sustaining cycle of generating more free radicals and causing more stress as a result of activation of multiple stress-induced pathways and also due to its ability to cause damaging effects on multiple components within the cell (Aroor et al., 2012b; Hayden and Tyagi, 2003; Mandavia et al., 2012; Newsholme et al., 2012; Santos et al., 2011). In this regard, ectopic lipid deposition in the cardiomyocyte leads to mitochondrial damage and exacerbation of oxidative stress (Aroor et al., 2012b; Mandavia et al., 2012; Newsholme et al., 2012). In addition, free FAs have a direct toxic effect on the mitochondria, leading to increased mitochondrial uncoupling (Boudina et al., 2007; Duncan et al., 2007; Mandavia et al., 2012; Ren et al., 2010). This, along with increased FA oxidation in the mitochondria, leads to the excess generation of free radicals such as superoxide, as a result of increased activity of the electron transfer chain and incomplete transfer of electrons (Aroor et al., 2012b; Newsholme et al., 2012). As mentioned above, excess ROS has the capability to exert direct toxic effects on genes and transcription factors controlling the oxidative phosphorylation (OXPHOS) of mitochondria, thus contributing to mitochondrial dysfunction and leading to generation of even more free radicals (Aroor et al., 2012b; Ren et al., 2010). The majority of mitochondrial OXPHOS genes is encoded by mitochondrial DNA (mtDNA), and thus is increasingly accessible and therefore susceptible to damage by superoxide and other free radicals produced within the mitochondria. In addition, generation of superoxide in the cytosol through the action of over-activated NADPH oxidase contributes further to this cycle (Aroor et al., 2012b; Mandavia et al., 2012). Cytosolic NADPH oxidase activity is increased due to the action of both Ang II and aldosterone as a result of over-activation of the RAAS (Aroor et al., 2012b; Cooper et al., 2007; Habibi et al., 2011; Manrique et al., 2007). Thus, increased mitochondrial turnover and increased FA metabolism seen in the early stages of diabetes, mediated by obesity and insulin resistance, contributes to the development of cardiomyopathy.

Dysfunction of sarcoplasmic reticulum along with mitochondrial dysfunction contributing to impaired calcium homeostasis

Oxidative stress can cause endoplasmic reticulum (ER) stress due to its ability to cause damaging effects on multiple components within the cell (Gray and Kim, 2011; Leem and Koh, 2012). The ER is an important post-translational modification site in eukaryotic cells, and is responsible for proper protein folding of almost a third of proteins synthesized in the cell. The presence of ROS can cause cellular damage through protein oxidation, improper protein folding caused by ER stress, DNA damage, and intrinsic action on mitochondria, cell toxicity and several other mechanisms. ER stress results in an adaptive response, termed the unfolded protein response (UPR), which results in increased proteasomal degradation of improperly folded proteins (Ron and Walter, 2007). This results in increased oxidative stress which exacerbates both mitochondrial and ER dysfunction. ER stress also contributes further to cardiac lipotoxicity by increasing lipogenesis through increased activation of the sterol regulatory element binding protein (SREBP1c) (Basseri and Austin, 2012).

ER stress is characterized by disrupted membrane stability leading to release of calcium from sarcoplasmic reticulum stores into the cytosol and reduced activity of the sarcoplasmic reticulum calcium pump (SERCA) which is responsible for calcium sequestration during cardiomyocyte diastolic relaxation (Borradaile et al., 2006; Lebeche et al., 2008; Minamino et al., 2010). Along with dysregulated mitochondrial calcium uptake due to mitochondrial dysfunction, reduced activity of sodium–calcium exchanger process and the sarcolemmal calcium-ATPase pump and reduced expression of the ryanodine receptor observed in T2DM, this causes a calcium imbalance within the diabetic cardiomyocytes, which is characterized by calcium cytosolic overloading and reduced mitochondrial ATP production (Aroor et al., 2012a; Falcão-Pires and Leite-Moreira, 2011; Gorman et al., 2012; Lebeche et al., 2008; Minamino et al., 2010; Zhang and Chen, 2012). This, in turn, leads to the prolonged diastolic relaxation time seen in initial diastolic dysfunction, and causes cardiomyocyte apoptosis and cell death as a result of the mitochondrial permeability transition pore (MPTP) response in the later stages (Gorman et al., 2012; Zhang and Chen, 2012). In addition, ER stress exacerbates the impaired calcium response further, through contributing to cardiac insulin resistance by activation of redox-sensitive kinases, such as JNK, which is a known negative regulator of insulin metabolic signaling in the heart (Lebeche et al., 2008; Ron and Walter, 2007).

Structural and functional changes in the heart as a result of diabetes

Diabetic cardiomyopathy is characterized by a disproportionate increase in LV mass and myocardial fibrosis. Hyperinsulinemia, insulin resistance, increased non-esterified fatty acids, higher circulating levels of the hormone leptin and activation of RAAS have been linked to the development of LVH. The continuous cycle of increasing ROS formation promotes chronic cardiac remodeling and structural changes in the heart (Abel et al., 2008; Dirkx et al., 2011; D'Souza et al., 2011; Falcão-Pires and Leite-Moreira, 2011; Maisch et al., 2011; Mandavia et al., 2012; Pulakat et al., 2011a; Watanabe et al., 2010). Diastolic dysfunction characterized by increased ventricular wall stiffness and increased diastolic relaxation time is prevalent at early stages of cardiomyopathy (D'Souza et al., 2011; Mandavia et al., 2012). Increased accumulation of triglyceride and impaired calcium reuptake has been shown to contribute to diastolic dysfunction

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(D'Souza et al., 2011; Mandavia et al., 2012; Zhang and Chen, 2012). Insidious progression towards systolic dysfunction (SD) is characterized by eccentric (dilated) cardiac remodeling slowly progressing towards heart failure (Hayden and Tyagi, 2003). Cardiomyocyte death is paralleled by fibroblast replacement, and leads to interstitial fibrosis mediated primarily by TGF-β (Booz and Baker, 1995; Rude et al., 2005; Schreier et al., 2011). Eventually the toxic action of accumulated free FAs on mitochondrial biogenesis leads to mitochondrial apoptosis and reduced ATP yield which cannot match the heart needs; precipitating impaired cardiac contractility and diminished ejection fraction. Impaired endothelial function associated with insulin resistance also contributes to myocardial dysfunction (Aroor et al., 2012a; Boudina et al., 2007; Kota et al., 2011; Mandavia et al., 2012; van de Weijer et al., 2011; Watanabe et al., 2010; Zhang and Chen, 2012). Triggering factors such as ischemia or hypertension caused by severe volume or pressure overload on the heart can precipitate decompensated heart failure due to the inadequate ability of the already compromised heart to respond to the extra insult (Hayden and Tyagi, 2003; Maisch et al., 2011; Melenovsky et al., 2011). When decompensated heart failure ensues, the condition of increased FA oxidation is partially reversed and the heart tries to utilize more glucose towards metabolism as a compensatory mechanism to preserve limited resources. However, insulin resistance under these conditions results in further deterioration of cardiac function. (Aroor et al., 2012a; Hue and Taegtmeyer, 2009; Mandavia et al., 2012; Nagoshi et al., 2011; van de Weijer et al., 2011; Zhang and Chen, 2012).

Diagnostic modalities for evaluating the presence of cardiac dysfunction in diabetes

As previously discussed, cardiac dysfunction as a result of metabolic alterations of insulin resistance and diabetes is manifested initially by diastolic dysfunction characterized by increased ventricular wall fibrosis/stiffness, and prolonged diastolic relaxation time. Various traditional diagnostic methods and their variations are available to assess the subtle hemodynamic perturbations arising due to these mild cardiac structural–functional alterations (Gropler et al., 2010). These include non-invasive techniques such as cinematic magnetic resonance image (cine-MRI), echocardiography, and computed tomography (CT) and positron emission tomography (PET) scans, as well as experimental invasive methods in rodent models such as pressure–volume (PV) loop measurements by means of cardiac catheterization (Demarco et al., 2012; Gropler et al., 2010; Jellis et al., 2011; Maisch et al., 2011; Zhang and Chen, 2012; Zhou et al., 2010). In experimental models, PV loop analysis yields multiple indices of diastolic and systolic functions that are relatively insensitive to preload and afterload conditions, cardiac mass and heart rate, and that reflect real differences in relaxation or contractile properties of the ventricular wall (Demarco et al., 2012). Among non-invasive methods, cine-MRI imaging allows visual characterization of the heart cavity, including size of the chambers, wall thickness, in addition to blood flow monitoring (Demarco et al., 2012; Habibi et al., 2011; O'Donnell et al., 2012; Zhou et al., 2010).

Conclusion

Diabetes-induced impaired cardiac insulin metabolic signaling is initially characterized by impaired diastolic relaxation, and is termed "diabetic cardiomyopathy". Depending upon other accompanying abnormalities, this condition can rapidly or gradually deteriorate into an advanced pathological state of cardiomyopathy and cardiovascular disease, with resultant cardiac complications (Fig. 2). When an uncompensated systolic dysfunctional state is precipitated and chronic heart failure ensues, the mortality rate is significant. Since

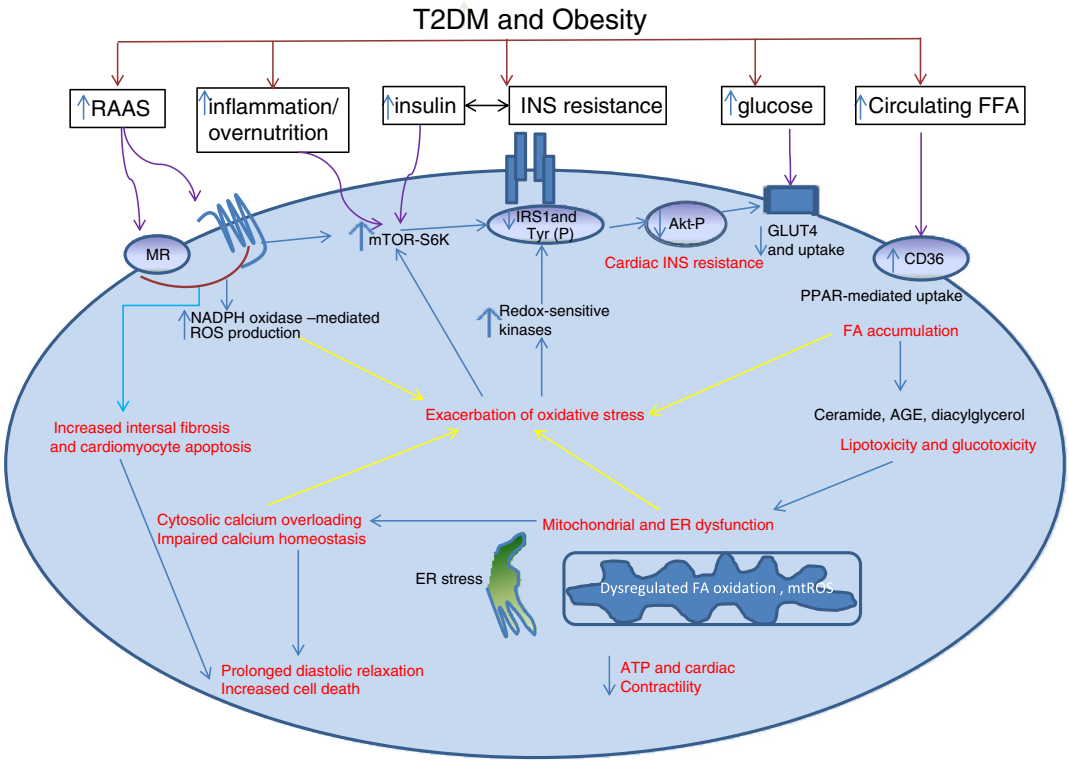

Fig. 2. Development of diastolic dysfunction in the diabetic cardiomyocyte. Diabetes leads to systemic metabolic impairments resulting eventually in the development of diastolic dysfunction in the cardiomyocyte. (T2DM = diabetes mellitus type 2, RAAS = renin–angiotensin II–aldosterone system, INS = insulin, FFA = free FAs, mTOR = mammalian target of rapamycin, S6K = S6 kinase 1 protein, IRS1 = insulin receptor substrate 1 protein, GLUT4 = glucose transporter 4, FA = fatty acids, AGE = advanced glycation end-products, PPAR = peroxisome proliferator activator receptor, CD36 = cluster differentiation protein 36, ER = endoplasmic reticulum, MR = mineralocorticoid receptor, ROS = reactive oxygen species, mtROS = mitochondrial ROS, NADPH oxidase = nicotinamide adenine dinucleotide phosphate-oxidase, ATP = adenosine triphosphate).

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early pre-diabetes and diabetes-related changes can be reversed with proper diet and exercise, the morbidity associated with this condition can perhaps be avoided by proper prophylactic intervention.

Conflict of interest statement

The authors have nothing to disclose.

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