Life Sciences 92 (2013) 601–608

Contents lists available at SciVerse ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

Molecular and metabolic mechanisms of cardiac dysfunction in diabetes

Chirag H. Mandavia [a,c], Annayya R. Aroor [a,c], Vincent G. DeMarco [a,b,c], James R. Sowers [a,b,c,d,*]

[a] University of Missouri School of Medicine, Department of Internal Medicine, Columbia, MO, USA
[b] University of Missouri School of Medicine, Department of Medical Pharmacology and Physiology, Columbia, MO, USA
[c] University of Missouri School of Medicine, Diabetes and Cardiovascular Center, Columbia, MO, USA
[d] University of Missouri School of Medicine, Harry S. Truman Veterans Affair Medical Center, Columbia, MO, USA

ARTICLE INFO

Article history:
Received 4 May 2012
Accepted 22 October 2012

Keywords:
Diabetes
RAAS
Cardiac dysfunction
Cardiorenal metabolic syndrome
Diabetic cardiomyopathy
Insulin resistance

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

Introduction . . . 602
Diabetes and cardiac dysfunction . . . 602
Impact of diabetes and cardiovascular disease . . . 602
Metabolic alterations in diabetes contributing to cardiovascular dysfunction . . . 602
Development and progression of cardiac dysfunction as a result of diabetes . . . 602
Dysregulated cardiac metabolic signaling . . . 602
Inflammation in diabetes contributing to dyslipidemia and cardiac insulin resistance . . . 602
Hyperinsulinemia, systemic and cardiac insulin resistance contributing to cardiac lipotoxicity and reduced cardiac insufficiency . . . 603
Over-activation of the renin–angiotensin II–aldosterone (RAAS) axis . . . 604
Exacerbation of initial oxidative stress from diabetes-induced cardiac metabolic alterations and mitochondrial dysfunction: cause–effect relationship . . . 605
Dysfunction of sarcoplasmic reticulum along with mitochondrial dysfunction contributing to impaired calcium homeostasis . . . 605
Structural and functional changes in the heart as a result of diabetes . . . 605
Diagnostic modalities for evaluating the presence of cardiac dysfunction in diabetes . . . 606
Conclusion . . . 606
Conflict of interest statement . . . 607
Acknowledgments . . . 607
References . . . 607

* Corresponding author at: Diabetes and Cardiovascular Center, University of Missouri, One Hospital Drive, Columbia, MO 65212, USA. Tel.: +1 573 882 2273; fax: +1 573 884 5530.
E-mail address: sowersj@health.missouri.edu (J.R. Sowers).

0024-3205/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.lfs.2012.10.028

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).