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Diabetic cardiomyopathy: Mechanisms and new treatment strategies targeting antioxidant signaling pathways

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ABSTRACT

Cardiovascular disease is the primary cause of morbidity and mortality among the diabetic population. Both experimental and clinical evidence suggest that diabetic subjects are predisposed to a distinct cardiomyopathy, independent of concomitant macro- and microvascular disorders. 'Diabetic cardiomyopathy' is characterized by early impairments in diastolic function, accompanied by the development of cardiomyocyte hypertrophy, myocardial fibrosis and cardiomyocyte apoptosis. The pathophysiology underlying diabetes-induced cardiac damage is complex and multifactorial, with elevated oxidative stress as a key contributor. We now review the current evidence of molecular disturbances present in the diabetic heart, and their role in the development of diabetes-induced impairments in myocardial function and structure. Our focus incorporates both the contribution of increased reactive oxygen species production and reduced antioxidant defenses to diabetic cardiomyopathy, together with modulation of protein signaling pathways and the emerging role of protein O-GlcNAcylation and miRNA dysregulation in the progression of diabetic heart disease. Lastly, we discuss both conventional and novel therapeutic approaches for the treatment of left ventricular dysfunction in diabetic patients, from inhibition of the renin–angiotensin–aldosterone-system, through recent evidence favoring supplementation of endogenous antioxidants for the treatment of diabetic cardiomyopathy. Novel therapeutic strategies, such as gene

Abbreviations: AAV, adeno-associated virus; ACE, angiotensin converting-enzyme; ACE-I, angiotensin converting-enzyme inhibitor; ACCORD, Action to Control Cardiovascular Risk in Diabetes; AdV, adenovirus; AGE, advanced glycation end product; AMPK, adenosine monophosphate-activated protein kinase; ANBP-2, 2nd Australian National Blood Pressure study; Ang I, angiotensin I; Ang II, angiotensin II; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; AT_1, angiotensin II receptor type 1; BH_4, tetrahydrobiopterin; BNP, B-type natriuretic peptide; BW, body weight; caPI3K, constitutively active phosphoinositide 3-kinase; CAPPP, Captopril Prevention Project; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; CTGF, connective tissue growth factor; CuZnSOD, copper/zinc superoxide dismutase; DAG, diacylglycerol; dnPI3K, dominant negative phosphoinositide 3-kinase; DPP4, dipeptidyl peptidase-4; E/A, ratio of peak early to late (atrial) transmitral blood flow velocities; ECM, extracellular matrix; ecSOD, extracellular superoxide dismutase; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; FAD, flavin mononucleotide; $FADH_2$, flavin adenine dinucleotide; FAO, fatty acid oxidation; FFA, free fatty acid; FMN, flavin mononucleotide; FPG, fasting plasma glucose; GFAT, glutamine:fructose-6-phosphate amidotransferase; GLP-1, glucagon-like peptide-1; GLUT-4, glucose transporter-4; GPCR, G protein coupled receptor; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HbA_{1c}, glycated hemoglobin; HBP, hexosamine biosynthesis pathway; HCV, hepatitis C virus; HDL, high density lipoprotein; HF, heart failure; HIF, hypoxia-inducible factor; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HOPE, Heart Outcomes Prevention Evaluation; HW, heart weight; HW:BW, heart weight: body weight ratio; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IL-1β, interleukin-1β; IL-6, interleukin-6; I-R, ischemia–reperfusion; IRS1, insulin receptor substrate 1; IVRT, isovolumic relaxation time; JNK, c-Jun N-terminal kinases; LC3, light chain 3; LDL, low density lipoprotein; LV, left ventricular; LVDP, left ventricular developed pressure; LVEDP, left ventricular end diastolic pressure; LV±dP/dt, peak rate of rise and fall of left ventricular pressure; LVH, left ventricular hypertrophy; LVSP, left ventricular systolic pressure; MAPK, mitogen-activated protein kinase; MEF2C, myocyte enhancer factor-2C; MI, myocardial infarction; MICRO, Microalbuminuria, Cardiovascular and Renal Outcomes; MMP, matrix metalloproteinase; MnSOD, manganese superoxide dismutase; miRNAs, microRNAs; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NCX, sodium–calcium exchanger; NEFA, non-esterified fatty acid; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NO•, nitric oxide; NOS, nitric oxide synthase; $•O_2^-$, superoxide; OGA, β-N-acetylglucosaminidase or "O-GlcNAcase"; O-GlcNAc, O-linked beta-N-acetylglucosamine; OGT, O-GlcNAc transferase; •OH, hydroxyl radical; $ONOO^-$, peroxynitrite; PDTC, pyrrolidine dithiocarbamate; PI3K, phosphoinositide 3-kinase; Pim-1, pro-viral integration site for Moloney murine leukemia virus-1; PKC, protein kinase C; PLB, phospholamban; PPAR-α, peroxisome proliferator-activated receptor alpha; PPAR-γ, peroxisome proliferator-activated receptor gamma; RAAS, renin–angiotensin–aldosterone system; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; RyR, ryanodine receptor; SAVE, Survival and Ventricular Enlargement; SECURE, Study to Evaluate Carotid Ultrasound changes in patients treated with vitamin E; SERCA2a, sarcoplasmic reticulum Ca^{2+} ATPase; SGK1, serum and glucocorticoid-regulated kinase 1; siRNA, small interfering RNA; SOD, superoxide dismutase; SOLVD, Studies of Left Ventricular Dysfunction; SR, sarcoplasmic reticulum; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumor necrosis factor-alpha; TRACE, Trandolapril Cardiac Evaluation; Trx, thioredoxin; TxNIP, thioredoxin-interacting protein; TZD, thiazolidinediones; UDP-GlcNAc, UDP-N-acetylglucosamine; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

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therapy targeting the phosphoinositide 3-kinase PI3K(p110α) signaling pathway, and miRNA dysregulation, are also reviewed. Targeting redox stress and protective protein signaling pathways may represent a future strategy for combating the ever-increasing incidence of heart failure in the diabetic population.

Contents

1. Diabetic cardiomyopathy

1.1. Introduction and overview of type 1 and type 2 diabetes

Diabetes mellitus is firmly established as a major threat to human health in the 21st century due to its alarming rise in incidence over the past two decades, which has attracted considerable attention. This rise in incidence is largely attributed to environmental and lifestyle changes, where increased occurrence of obesity is accompanied by an increasing number of people diagnosed with diabetes mellitus (Zimmet et al., 2001). An estimated 285 million adults globally were burdened by this chronic disease in 2010; this number is projected to increase to 439 million by 2030 (Shaw et al., 2010). Diabetes is regarded as the 5th leading cause of death worldwide, following infectious diseases, cardiovascular disease, cancer and trauma (Roglic et al., 2005). The rise in incidence and prevalence of diabetes also imposes a significant economic burden globally, particularly in developed countries, with an estimated 12% of the worldwide health care expenditure spent on the treatment and prevention of diabetes (Farag & Gaballa, 2011).

Diabetes is a chronic, progressive metabolic disorder characterized by insulin deficiency and/or resistance, resulting in elevated plasma glucose levels. There are two predominant types of diabetes; type 1 diabetes mellitus (T1DM), formerly known as insulin-dependent or juvenile diabetes and type 2 diabetes mellitus (T2DM), otherwise known as non-insulin-dependent or adult-onset diabetes. T1DM, which accounts for approximately 5–10% of all cases of diabetes (Raskin & Mohan, 2010), has a steadily increasing incidence worldwide (Karvonen et al., 2000). Auto-immune mechanisms (at least in genetically-predisposed individuals) and/or environmental risk factors are regarded as key triggers of T1DM (Zimmet et al., 2001; Di Lorenzo et al., 2007). T2DM, characterized by insulin resistance, accounts for the remaining ~90% of all cases of diabetes, and occurs predominantly, but not exclusively, in the older population (Zimmet et al., 2001). The global rate of mortality attributable to T2DM has been estimated at 2.9 million, or 5.2% of all deaths (Roglic et al., 2005; Nolan et al., 2011). In contrast to developed countries (where T2DM is most evident in individuals over 60 years of age), people aged 40–60 years old comprise the majority of T2DM cases in developing countries (Shaw et al., 2010), thus likely to impact on productivity in those of working age. The rising incidence of T2DM is strongly associated with environmental factors such as obesity and sedentary lifestyle (Zimmet et al., 2001) that accompany an increasingly 'westernized-diet', higher in fat, sugar and energy density (Astrup et al., 2008). Genetic factors such as family history of diabetes and ethnic background are also important for the development of the disease (Nolan et al., 2011). Insulin resistance is the primary metabolic abnormality among T2DM patients, resulting in both hyperglycemia and hyperinsulinemia. Pancreatic β-islet cell dysfunction is also implicated in the progression of T2DM (Kahn, 2003; Muoio & Newgard, 2008). Glucotoxicity and lipotoxicity may further impair and reduce the rate of insulin secretion from dysfunctional β-islet cells (Nolan et al., 2011).

1.2. Microvascular and macrovascular complications of diabetes mellitus

As has been widely reviewed, both T1DM and T2DM are associated with increased risk of macrovascular and microvascular complications (Williams et al., 2002; Forbes & Cooper, 2013). These vascular injuries often coexist and can result in hypertension, altered vascular permeability and ischemia (Krentz et al., 2007; Calcutt et al., 2009). Common microvasculature defects evident in diabetes include retinopathy, nephropathy and peripheral neuropathy, each of which can impart debilitating consequences. Diabetic retinopathy can lead to blindness (Cheung & Wong, 2008), diabetic nephropathy can result in end-stage renal failure (Calcutt et al., 2009) and diabetic neuropathy can progress to peripheral nerve dysfunction in distal regions such as the hands and feet (Bansal et al., 2006). Diabetic retinopathy also serves as a marker of generalized hyperglycemic damage in the microvasculature (Cheung & Wong, 2008). In addition to these widespread defects in the diabetic systemic microvasculature, macrovascular complications such as coronary heart disease, stroke and peripheral vascular disease are thought to be the primary causes of morbidity and mortality in diabetic patients (Williams et al., 2002; Forbes & Cooper, 2013). Increased plaque formation, atherosclerosis progression and vasodilator/vasoconstrictor dysregulation are evident in larger arteries (Vinik & Flemmer, 2002), as well as impairments at the level of platelet function (hyperaggregability, reduced fibrinolysis, etc.) and alterations in blood flow. The combination of all of these vascular defects contributes to the high incidence of cardiovascular disease, cerebrovascular disease (including stroke) and peripheral arterial disease in diabetes (Cade, 2008).

Independent of the macrovascular complications of the disease, both clinical and experimental studies have highlighted the existence of a specific diabetic cardiomyopathy, in which alterations at the level of the cardiomyocyte are evident (Davidoff et al., 2004). Rubler et al. first described diabetic cardiomyopathy as a distinct entity 40 years ago, in a small cohort of diabetic patients with adverse myocardial structural changes at post-mortem, in the absence of coronary arterial disease, hypertension or valvular complications (Rubler et al., 1972). Considerable attention was dedicated to identifying and characterizing this distinct cardiomyopathy in the following four decades, thus profoundly increasing