Review Article

Diabetic Cardiomyopathy

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ABSTRACT

Individuals with diabetes are at a significantly greater risk of developing cardioymyopathy and heart failure despite adjusting for concomitant risks such as coronary artery disease or hypertension. This has led to the increased recognition of a distinct disease process termed as ''diabetic cardiomyopathy.'' In this article, we perform an extensive review of the pathogenesis and treatment of this disease. From a clinical perspective, physicians should be aware of this entity, and early screening should be considered because physical evidence of early diabetic cardiomyopathy could be difficult to detect. Early detection of the disease should prompt intensification of glycemic control, concomitant risk factors, use of pharmacologic agents such as β-blockers and renin-angiotensin-aldosterone system antagosists. From a research perspective, more studies on myocardial tissue from diabetic patients are needed. Clinical trials to evaluate the development of diabetic cardiomyopathy and fibrosis in early stages of the disease, as well as clinical trials of pharmacologic intervention in patients specifically with diabetic cardiomyopathy, need to be conducted. (*J Cardiac Fail 2010;16:971−979*)

Key Words: Cardiomyopathy, DM, congestive heart failure, diabetes, heart failure, diabetes and cardiomyopathy, systolic dysfunction.

The epidemic of obesity and sedentary lifestyle is projected to result in over 300 million people with diabetes mellitus by 2025.[1] Individuals with diabetes are at a significantly greater risk of developing both micro- and macrovascular disease, and have a cardiac mortality equivalent to that in nondiabetic patients with confirmed heart disease.[2] Diabetics remain at increased risk for heart failure after adjusting for concomitant risks such as coronary artery disease (CAD) or hypertension. This was originally described in 1972 by Rubler et al,[3] who reported data from 4 diabetic patients with heart failure without evidence of hypertension, CAD, or valvular or congenital heart disease. This has led to the increased recognition of a distinct disease process termed ''diabetic cardiomyopathy.''

Diabetes accounted for a significant percentage of patients with a diagnosis of heart failure in numerous epidemiologic studies.[4] The Framingham study,[5] United Kingdom Prospective Diabetic Study,[6] Cardiovascular Health Study,[7] and Euro Heart Failure Survey[8] all suggested that the presence of diabetes may independently increase the risk of developing heart failure. Several clinical studies[9−12] have suggested that there is a consistent association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, both independent of hypertension. Such associations have provided a credible existence of diabetic cardiomyopathy as a unique clinical entity. In the following review we attempt to provide a comprehensive insight into this clinical condition and discuss the possible underlying mechanisms and treatment options.

Definition

Diabetic cardiomyopathy is defined as ventricular dysfunction occurring independently of a recognized cause such as CAD or hypertension. Although diabetics are at increased risk of structural heart disease due to vascular complications, the concept of diabetic cardiomyopathy suggests

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a direct cellular insult to the myocardium. Therefore patients with hypertension and CAD may well have myocardial changes related to these disease processes, but a specific cardiomyopathy may also affect the myocardium secondary to diabetes causing a synergistic adverse effect, as seen with a combination of diabetes and hypertension.

Cardiac Changes

Accumulating data from experimental, pathologic, epidemiologic, and clinical studies have shown that diabetes results in structural and functional cardiac changes.

Structural Changes

In a report from the Strong Heart Study,[10] diabetic patients compared with individuals without diabetes had higher left ventricle (LV) mass, wall thickness, and arterial stiffness and reduced systolic function. These abnormalities were independent of body mass index and blood pressure. Data from the Framingham Heart Study[5] indicated that LV mass and wall thickness were most prominent among female patients with diabetes, and these factors were proportional to the degree of glucose intolerance and obesity. Concentric remodeling, or increased regional wall thickness without left ventricular hypertrophy is also a feature of diabetes,[11] although in isolation it may not affect systolic or diastolic function.[13] Diabetes-associated concentric hypertrophy (defined by LV mass and wall thickness) has been linked to diastolic dysfunction, and eccentric hypertrophy has been linked to systolic dysfunction.[13]

Functional Changes

LV diastolic dysfunction in diabetics has been initially disclosed by cardiac catheterization. Regan et al[14] demonstrated in normotensive diabetic patients without CAD and without clinical evidence of heart failure increased LV end-diastolic pressure and a decreased LV end-diastolic volume with a normal ejection fraction (EF). The noninvasive assessment of diastolic dysfunction mainly relies on the Doppler studies of transmitral inflow, flow velocities, flow patterns, isovolumic relaxation time, and deceleration time. LV ejection time is often reduced, and the length of preejection period and the ratio of the preejection period to LV ejection time are often increased. Diastolic abnormalities have been suggested as an earliest functional effect of diabetic cardiomyopathy. In 20 type I and 20 type II diabetic patients, systolic function parameters were normal, but diastolic function was clearly impaired in diabetic patients without overt cardiovascular disease as compared to 12 healthy controls.[15] In another study of normotensive asymptomatic Type 2 diabetic patients with good glycemic control, 47% were found to have diastolic dysfunction.[16] Other studies using more sensitive methods have reported that as many as 75% of diabetic patients demonstrate abnormalities of diastolic dysfunction.[17]

Although a number of studies have confirmed the association of LV systolic dysfunction with diabetes, this finding has not been uniformly reported.[18] Noninvasive evaluation of cardiac performance in diabetic patients without overt failure has demonstrated a prolonged preejection performance and a shortened ejection period, both of which correlate with reduced resting LV ejection fraction (LVEF) and diminished systolic function.[19] Diabetics also have a lower LVEF in response to exercise, suggesting a reduction in cardiac reserve.[20] Early LV systolic dysfunction with normal LVEF has been described. More sensitive techniques for systolic assessment, such as strain, strain rate, and myocardial tissue Doppler velocity, may detect preclinical systolic abnormalities in diabetic patients. Using these sensitive methods, several studies have demonstrated subtle abnormalities in systolic function in patients with diastolic dysfuction.[21–23] This has led to the question of whether diastolic dysfunction exists in isolation at all,[24] whereas others have questioned the relevance of these subtle systolic abormalities in the presence of diastolic dysfunction.[25]

Right ventricular (RV) function has been practically neglected in most of the studies. A few studies have shown that diabetes impairs both RV diastolic function[26] as well as RV systolic function.[27]

Pathologic Changes

Common findings in biopsies of the diabetic heart are interstitial fibrosis, myocyte hypertrophy, and increase in contractile protein glycosylation.[28–30] They contribute to reduced diastolic compliance and ventricular hypertrophy in diabetic patients. Van Heerebek et al[31] reported that in diabetics, deposition of advanced glycation end-products (AGEs) and deposition of collagen are important determinants of the increased LV stiffness in patients having heart failure with reduced EF, whereas high cardiomyocyte resting tension is the main determinant of increased LV stiffness in those who have heart failure with normal EF.

Pathogenesis of Diabetic Cardiomyopathy

The pathogenesis of diabetic cardiomyopathy is multifactorial. Hyperglycemia, hyperlipidemia, and hyperinsulinemia induce alterations in downstream transcription factors that result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function, and myocardial compliance. These processes are not mutually exclusive and likely synergistically to develop diabetic cardiomyopathy (Table 1; Fig. 1).

Hyperglycemia

Hyperglycemia may mediate its damaging effects through a series of secondary transducers, especially reactive oxygen species (ROS) and AGEs.

ROS encompass a range of highly reactive oxygen base molecules, which consist of both free radicals (superoxide) and chemicals capable of generating free radicals (hydrogen

Table 1. Summary of Different Mechanisms Thought to Be Responsible for Diabetic Cardiomyopathy

Cause	Mechanism
Hyperglycemia	Excess AGE and ROS formation with deactivation of NO, myocardial collagen deposition, and fibrosis.
Fatty acids	Impaired glycolysis, pyruvate oxidation, lactate uptake results in apoptosis, and perturbation of myocardial bioenergetics and contraction-relaxation coupling.
PKC	Activation of DAG/PKC signal transduction pathway leads to reduction in tissue blood flow, increased vascular permeability, alterations in neovascularization, and enhanced extracellular matrix deposition.
RAAS	Cardiomyocyte hypertrophy and apoptosis.
Aldosterone-induced fibrosis	Myofibroblast growth with interstitial and focal perivascular accumulation of collagen.
HIF-1/VEGF	HIF-1 activation via hypoxia/free radicals induces angiopoietin, PGF, PDGFβ, and VEGF but, in diabetes, VEGF and its receptors are decreased significantly, leading to impaired angiogenesis.
Endothelial dysfunction	Impaired endothelial NO production and increased vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules, and platelet and vascular growth factors enhance vasomotor tone and vascular permeability and limit growth and remodeling.
Arterial stiffness	Increased central aortic pressure and left ventricular afterload and lowered central diastolic and coronary perfusion pressures, leading to subendocardial ischemia and interstitial fibrosis.
Autonomic neuropathy	Decreased sympathetic/parasympathetic myocardial innervation with impaired coronary resistance vessel vasodilator response and impaired ventricular diastolic filling.

AGE, advanced glycation end-product; HIF, hypoxia-inducible factor; NO, nitric oxide; PGF, platelet growth factor; PDGF, platelet-derived growth factor; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxgen species; VEGF, vascular endothelial growth factor.

peroxide). Oxidative stress exists when the production of ROS outweighs their degradation by antioxidant defenses, and the resultant elevation of ROS has numerous deleterious effects on the cardiovascular system via cellular damage by oxidation, disruption of vascular hemostasis through interference with nitric oxide (NO), and by modulation of detrimental intracellular signaling pathways: the so-called redox signaling. Although under physiologic states most of the ROS generated within cells arises from mitochondria, in diseased conditions they are produced by a range of other sources. The group of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes have been recognized as a source of ROS. These enzymes act as catalysts for electron transfer from NADPH to molecular oxygen, resulting in generation of free radicals. Through interaction with a variety of transcription factors, redox signaling influences the

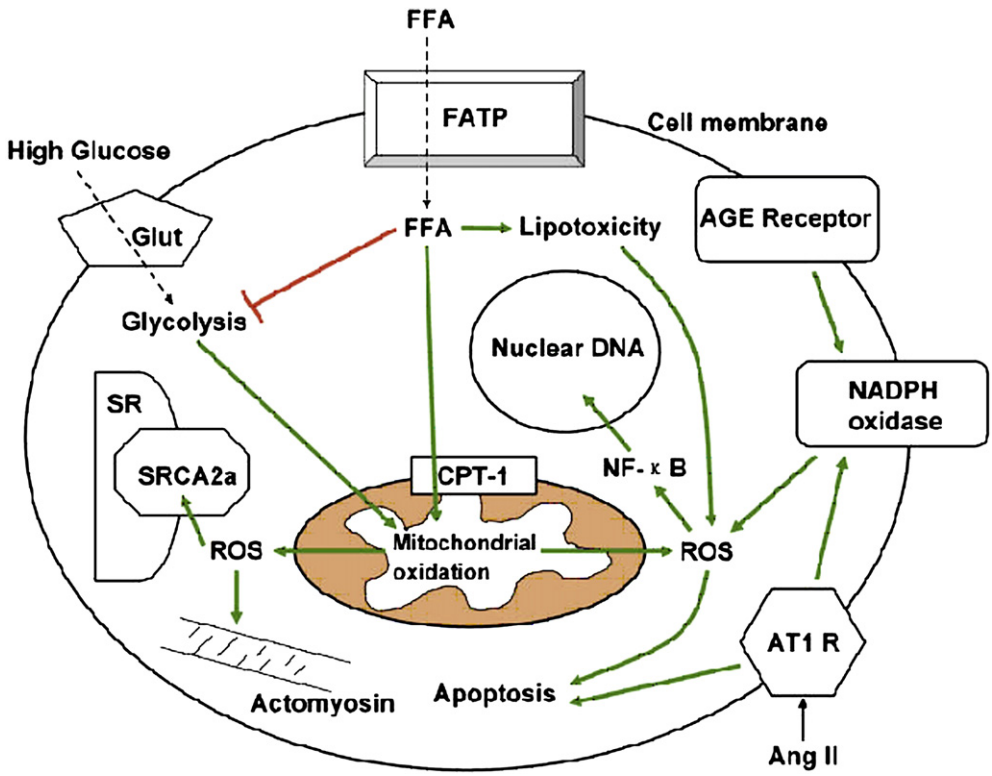

Fig. 1. Potential mechanisms for diabetic cardiomyopathy. ACC, acetyl coenzyme A carboxylase; ACoA, acetyl-coenzyme A; AGE, glycation end-products; CE, cardiac efficiency; CPT1, carnitine palmitoyl transferase 1; TG, triglycerides; GLUT, glucose transporters; MCD, malonyl-coenzyme A decarboxylase; MCoA, malonyl-coenzyme A; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; PKC, protein kinase C.

expression of growth-related genes and in turn affects contractile function.[32] An increase in ROS leads to DNA damage and activation of poly(ADP ribose) polymerase (PARP) as a reparative enzyme.[33] However PARP also mediates the ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GADPH), diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are considered to be the mediators of hyperglycemia-mediated cellular injury. These include increases in AGEs, increased hexosamine and polyol flux, and activation of classic forms of protein kinase C (PKC). PARP also promotes cardiac damage by activating nuclear factor (NF) κβ and inducing overexpression of vasoconstrictor endothelin 1 and its receptors.[34] PKC phosphorylates a number of proteins directly involved in the cardiac excitation-contraction coupling and therefore disturbs calcium handling in myocytes.

The increased formation of AGEs secondary to hyperglycemia may alter structural proteins and lead to increased myocardial stiffness. AGEs arise from intracellular autooxidation of glucose to glyoxal, decomposition of the Amadori product, and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal. These reactive dicarbonyls interact with the amino acid residues of the proteins to alter the functional properties of matrix components that mediate sustained cellular changes.[35] The modifications can be a single isolated change on the peptide chain or multiple AGE modifications that can produce crosslinks within or between proteins. Long-lived extracellular proteins, such as collagen and elastin, are particularly vulnerable to accumulation of AGE crosslinks.[36] This can impair the ability of collagen to be degraded, leading to collagen accumulation or fibrosis. Crosslinks in collagen and elastin and the resulting fibrosis also cause increased myocardial stiffness and impaired cardiac relaxation. Aminoguanidine (an inhibitor of AGE formation and protein crosslinking) has been shown to ameliorate changes in LV structure and function.[37] Furthermore, the use of crosslink breakers, such as alagerium chloride and ALT-711, have resulted in reduced LV mass and stiffness in animal models.[38,39]

AGE receptors (RAGEs) are found in cardiomyocytes[40] and are a significant components of cardiac ischemia reperfusion injury in rodent models.[41] Oxidative stress increases expression of AGE and RAGE, leading to activation of NF-κβ which leads to a switch in the gene expression of cardiac myosin heavy chain (MHC) from the α-MHC to the β-MHC isoform, altering myocardial contractility.[42] Dehydroepiandrosterone has been shown to reduce tissue levels of collagen I, collagen IV, and fibronectin in streptozotocin− rats and restore papillary muscle contractility.[43] RAGE provides another target for potential therapeutics for diabetic complications.[44]

The process of advanced glycation has been related to alterations in myocardial calcium handling and therefore contractility.[45] Sarcoplasmic/endoplasmic-reticulum Ca^{2+}−ATPase (SERCA) 2a is responsible for replenishing intracellular calcium stores following release; this results in the termination of contraction, thus playing an integral part in cardiac relaxation. For relaxation to occur, calcium ions must be removed from the cytosol, the majority of which is pumped back into the sarcoplasmic reticulum by SERCA, while the remainder is ejected out of the cell through the sarcolemmal Na^{+}-Ca^{2+} exchange (NCX), plasma-membrane Ca^{2+} ATPase (PMCA), or mitochondrial calcium uniport.[46] In both type 1 and type 2 rodent models of diabetes, there is altered expression, activity, and function of all transporters involved in excitation-contraction coupling (SERCA,[47] NCX, ryanodine receptor, and PMCA) as well as dysfunctional intracellular calcium signaling.[48]

Fatty Acids

A significant metabolic alteration in diabetes is an increase in free fatty acid (FFA) concentrations and an increase in myocardial FFA uptake and oxidation. Experimental models have shown an increase of FFA use and oxidation by the heart, which increases susceptibility to ischemia and can lead to lipid accumulation, energy deprivation, worsening insulin resistance, and ultimately cardiomyopathy.[49] Cardiac myocytes respond to increased FFA by up-regulating the expression of the enzymes necessary for their disposal through mitochondrial B-oxidation. These enzymes are under transcriptional control of the nuclear transcriptional factor peroxisome proliferator−activated receptor (PPAR). High FFA levels activate PPAR, leading to increased FFA use through myocardial fatty acid oxidation and myocardial fatty acid utilization.[50] In addition, FFAs inhibit pyruvate dehydrogenase, which impairs myocardial energy production and leads to accumulation of glycolytic intermediates and intracellular lipids.[51,52] This accumulation can result in an increased nonoxidative production of a family of ceramide molecules, which are toxic lipid products. Ceramides are composed of sphingosin and a fatty acid and are found in high concentrations within the cell membrane of cells, where they make up a component of sphingomyelin, a major constituent of the lipid bilayer. Investigators have reported that increase in the ceramide levels in the cardiac myocyte are associated with increased oxidative stress, apoptosis, and decreased contractile function.[53]

Hyperinsulinemia

Because of the similarities in the extracellular domains between the insulin receptor and the insulin-like growth factor (IGF) 1 receptor, increased levels of insulin can promote cellular hypertrophy by binding to the IGF-1 receptor, although binding would be with much less affinity.[54] IGF-1 stimulates skeletal muscle hypertrophy and a switch to glycloytic metabolism via activation of the calcium calmodulin-dependent phosphatase calcineurin and by inducing nuclear translocation of transcription factor nuclear factor in activated T cells (NFATC) 1.[55] Insulin also stimulates cardiac hypertrophy through the same P13Kα/Akt-1 pathway by which it mediates glucose uptake. Akt-1 phosphorylates and inactivates

glycogen synthases kinase 3β, a well recognized inhibitor of nuclear transcription governing the hypertrophic process via the NFATC-3.[56,57]

Renin-Angiotensin-Aldosterone System (RAAS)

The role of activation of the RAAS in the development of diabetic cardiomyopathy is well recognized. Activation of the RAAS during diabetes mellitus has been shown to be associated with increased oxidative damage and cardiomyocyte and endothelial cell apoptosis and necrosis in diabetic hearts,[58] which contributes to increased interstitial fibrosis. The basis for this dysfunction is not clear; however, direct signaling via the angiotensin-1 receptors result in increased NADPH oxidase activity and elevation of ROS, which cause oxidative damage to cardiomyocytes and endothelial cell apoptosis.[59] It has been suggested that aldosterone and glucose mediate cardiac fibrosis through stimulation of myofibroblast growth in patients with a dysregulated RAAS. Clinical studies have demonstrated a reduction in cardiovascular mortality in patients with heart failure treated with aldosterone antagonists.[60]

Disordered Copper Metabolism

Elevated serum copper levels are found in patients with diabetes, and the highest levels are found in those with microvascular complications and hypertension.[61] Hyperglycemia can damage the copper-binding properties of ceruloplasmin and albumin, resulting in increased copper levels in the extracellular matrix.[62] Also, glycated proteins might have an increased affinity toward copper.[63] Therefore, an abundance of copper in the extracellular matrix is thought to activate the oxidation-reduction system, leading to an enhanced production of free radicals resulting in increased oxidative stress and fibrosis.

Cardiac Autonomic Neuropathy

Diabetic cardiovascular autonomic neuropathy results from changes in sympathetic innervations, disordered adrenergic receptor expression, and altered catecholamine levels in the myocardium that manifest clinically as resting tachycardia, orthostasis, exercise intolerance, and silent myocardial infarction.

Both sympathetic and parasymapathetic dysfunction have been related to cardiac autonomic abnormalities. Higher prevalence of ventricular fibrillation in diabetes patients is suggestive of higher sympathetic tone in this population.[64] On the other hand, diabetic autonomic neuropathy can lead to bradyarrhythmias and conduction abnormalities.[65,66] An abnormal systolic blood pressure response to standing was correlated significantly with a reduced mitral E/A ratio. The mitral E/A ratio has been shown to be significantly reduced in patients with autonomic neuropathy, and a significant correlation was observed between the E/A ratio and autonomic neuropathy.[67] However, the exact role of authonomic neuropathy in the pathogenesis of diabetes cardiomyopathy remains unknown.

Hypoxia-Inducible Factor (HIF) 1 and Vascular Endothelial Growth Factor (VEGF)

During ischemic events, an adequate response to hypoxia is paramount in protecting against myocardial injury. The hypoxic stimulus is mediated chiefly through HIF-1, a transcriptional regulator complex which operates through a specific promoter motif (hypoxia response element) present in many gene promoters, including VEGF.[68] Several observational studies suggest that VEGF may play an important role in the response of cardiac injury. After myocardial infarction, the expression of VEGF mRNA is markedly increased in the cardiac myocytes, arteriolar smooth muscle cells, and infiltrating macrophages.[69] However, the expression of VEGF protein and mRNA, as well as its receptors, are significantly decreased in the myocardium of both diabetic and insulin-resistant nondiabetic rats.[70] This suggests that in diabetic patients, the normal molecular processes that regulate angiogenesis may be impaired. In one animal study, it was noted that VEGF down-regulation preceded the development of diabetic cardiomyopathy, and improvements in both structure and function followed the restoration of VEGF expression by intramyocardial gene transfer of plasmid DNA encoding human VEGF.[71] Reductions in VEGF and impaired angiogenic responses have also been linked with increased levels of endothelin 1 in ventricles from diabetic rodents, and endothelin receptor antagonism was shown to increase VEGF signaling and improve cardiac function.[72]

Diabetic Vasculopathy and Microangiopathy

Studies have demonstrated that in patients with diffuse CAD without focal stenosis at coronary angiogram, the diffuse disease process can lead to a significant continuous pressure fall along the epicardial coronary arteries, i.e., the functional equivalent of a stenosis.[73] Coronary blood flow reserve in diabetics is reduced even in the absence of obstructive CAD.[74] Hyperglycemia results in impairment of NO production, increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules, and platelet and vascular growth factors, which cumulatively enhance vasomotor tone and vascular permeability, growth, and remodeling. The microangiopathic changes include basement membrane thickening, arteriolar thickening, capillary microaneurysm, and reduced capillary density, which may be the results of periarterial fibrosis and focal subendothelial proliferation and fibrosis, possibly due to the abnormal permeability of diabetic capillaries. Endothelial dysfunction, altered protein synthesis, and altered expression/production of adhesion glycoproteins on endothelial cells promote attachment of monocytes and leukocytes, as well as their transendothelial migration. This results in myocardial and ventricular hypertrophy,[75,76] impaired formation of collateral circulation, and enhanced distal atherosclerosis which may not be evident in coronary angiogram and may play an important role in the pathogenesis of diabetic cardiomyopathy.[77]

Serum Bioassays

B-Type natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from ventricular myocardium in response to increase in wall stress. In studies in which BNP was examined in relation to echocardiography, it was clear that patients with diabetes often had high BNP levels and LV dysfuction.[78] BNP levels showed a high positive predictive value for the detection of LV dysfunction (96% with BNP levels $>$ 90pg/mL).[79] There is mixed evidence for the use of BNP to detect asymptomatic diastolic dysfuction.[79–82] Further studies with large number of patients are required to determine more precisely the value of BNP as a screening tool for diastolic dysfunction in asymptomatic patients.

There are a range of other emerging experimental biomarkers that may provide good correlation between serum indicators of diabetes status and potential changes in the cardiac structure/function. One such group of candidate assays are those that measure levels of enzymatic beta O-linkages of GlcNAc to proteins.[83]

Treatment of Diabetic Cardiomyopathy

Glycemic Control

Studies have shown that for each 1% elevation in glycosylated hemoglobin, the risk of developing heart failure increases by 8%.[84] Evidence suggests that good glycemic control is beneficial, at least in early stages of myocardial dysfunction.[85] Evidence also suggests that diabetic cardiomyopathy does not develop in patients with tightly controlled type 1 diabetes, supporting an important role for hyperglycemia in the pathogenesis of diabetic cardiomyopathy.[86] Although the UKPDS (United Kingdom Prospective Diabetes Study)[87] provided an epidemiologic link between hyperglycemia and increased cardiovascular risk, until recently there was no direct trial evidence that intensive glucose lowering in type 2 diabetics could reduce this excess cardiovascular risk. The publication of 2 recent randomized intervention trials raised the possibility that lowering blood glucose in type 2 diabetics to near-normal levels may at best have no benefits and at worst increased macrovascular cardiac events,[88,89] although it may significantly reduce the incidence of nephropathy. Because microvascular alterations are thought to contribute significantly to the pathogenesis of diabetic cardiomyopathy, good glycemic control remains instrumental to the overall management of diabetic cardiomyopathy.

Glucagon-like peptide (GLP) 1 is an incretin hormone which stimulates postprandial insulin secretion and improves insulin sensitivity. There are some promising data from a trial of GLP-1 analogues in patients after successful coronary intervention for acute myocardial infarction, in which the treated group demonstrated a greater improvement in LVEF with concomitant improvements in global and regional wall motion.[90] Dipeptidyl peptidase (DPP) 4 inhibitors, or gliptins, are a group of drugs which increase incretin levels by inhibiting the enzyme DPP-4. Long-term data are required for these drugs to determine their safety and efficacy in heart failure. Thiazolidinediones are primarily insulin-sensitizing agents, but in addition to their antihyperglycemic action these drugs also exert beneficial effects on the myocardium, vascular endothelium, myocardium, and lipid profile.[91] However, their use is problematic because of a propensity for fluid overload and is contraindicated in New York Heart Association functional class III or IV heart failure. In general, the choice of antidiabetic agents in diabetic cardiomyopathy should be based on clinical characteristics, risk of hypoglycemia, age, volume status, and concomitant drug therapy.

RAAS

Angiotensin-converting enzyme (ACE) inhibitors have widespread effect on micro- and macrovascular complications in diabetes and may affect myocardial fibrosis through effects on angiotensin II. Meta-analyses of the major ACE inhibitor trials showed that diabetic patients achieve similar reductions in mortality as nondiabetic patients with LV systolic dysfunction.[92] Evidence also suggests a beneficial effect of aldosterone antagonism in diastolic heart failure by virtue of their beneficial effects on cardiac hypertrophy and fibrosis.[93] These findings underscore the critical importance of inhibiting the RAAS in diabetic patients, especially when diastolic dysfunction is present and the process is potentially reversible.

β-Blockers

β-Blockers are now well defined in the treatment of heart failure. Concerns in diabetic patients regarding blood sugar, insulin resistance, and dyslipidemia meant that diabetic patients with heart failure were less likely to be on β-blockers. However, with the recent advances in the understanding of heart failure and the realization of the importance of the sympathetic nervous system in the release of vasoactive substances, they have become essential in the treatment of heart failure. A meta-analysis of the 6 main heart failure trials—CIBIS-II (Cardiac insufficiency Bisoprolol Study II), BEST (β-Blocker Evaluation of Survival Trial), ANZ (Australia and New Zealand) Carvedilol, Carvedilol US Trials, COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival), MERIT-HF (Metoprolol Controlled Release Randomized Intervention Trial in Heart Failure)—has subgroup data available that has enables analysis of the diabetic cohort.[94] The pooled relative risk of mortality in patients with diabetes mellitus and congestive heart failure on β-blocker treatment compared with placebo was 0.84 (95% CI, 0.73–0.96; $P < .011$). In one study, carvedilol was shown to have has better effects on glycemic control and insulin resistance compared with metoprolol in the presence of RAAS blockade or in the absence of insulin sensitizers.[95,96] In summary, β-blockers should be given to all diabetic patients with any evidence of heart failure, unless specifically contraindicated. The effect may not be as pronounced as in nondiabetics, but it will result in relative risk reduction of mortality.

Statins

A recent meta-analysis of 13 trials demonstrated a 13% reduction in mortality with statin use in individuals with heart failure.[97] This effect was similar when subanalyzed including only patients with heart failure of nonischemic cause. This was in contrast with the largest prospective study of statins in heart failure, CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure),[98] which randomized 5,011 elderly patients with heart failure to rosuvastatin or placebo and reported no benefit from rosuvastatin. This study consisted of a cohort of patients with ischemic cardiomyopathy and cannot be extended to patients with nonischemic cardiomyopathy. The efficacy of statins in diabetic cardiomyopathy therefore remains to be determined.

Conclusion

Diabetic cardiomyopathy has evolved from a nebulous concept to concrete reality over the years. Evolving evidence supports a strong association between diabetes and cardiomyopathy. In one of the largest epidemiologic studies, involving over 800,000 patients, diabetes was found to be independently associated with the occurrence of congestive heart failure after adjusting for LV hypertrophy, hypertension, coronary artery disease, and atrial fibrillation.[99] Furthermore, higher prevalence of biventricular cardiomyopathy in diabetes patients[27] is also suggestive of diabetes as an independent cause of cardiomyopathy. Whether there are other confounding factors that could lead independently to cardiomyopathy in diabetics is unclear. However, it is important to note that actually no specific histologic and/or biochemical markers for so-called ''diabetes cardiomyopathy'' has been found, so other mechanisms of damage can coexist or be responsible of a cardiomyopathy developing in a diabetic patient. Hyperglycemia, insulin resistance, increased fatty acid metabolism, microcirculatory changes, sympathetic dysfunction, and fibrosis are considered to collectively contribute to its pathology. It is hoped that as the mechanisms of this cardiomyopathy in diabetics continue to be elucidated, they will provide the impetus for generating novel therapies tailored to reduce the risk of heart failure in patients with diabetes mellitus.

Disclosures

None.

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