

Non ischemic heart failure in diabetes mellitus: still incompletely understood

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Abstract

Independently of conventional factors for coronary artery disease, the risk of death from heart disease is several-fold greater in diabetic patients than in those without diabetes. Although the term “diabetic cardiomyopathy” probably describes a heterogeneous disease for which a clear definition is still lacking, we propose that heart failure in diabetes can be traced to alterations in whole-body energy homeostasis* and myocardial metabolism. Here we review some of the mechanisms that have been proposed to cause the disease.

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Introduction

The increased incidence of vascular disease in patients with diabetes only partially explains the greater incidence of heart failure that they exhibit. Depending on age, the prevalence of heart failure in diabetic individuals is as high as 12–22%, whereas it is only 1–4% in the general population [1]. We present the concept that non ischemic heart failure in diabetes is the result of synergy among several pathophysiological mechanisms (*Figure 1*). These derangements contribute to progressive myocyte dysfunction, cell loss, fibrosis, and hypertrophy, with the clinical consequence of diastolic – and often also systolic – dysfunction. Although different investigators have given different definitions to the term “diabetic cardiomyopathy”, its origin can be traced to a dysregulation of both whole-body energy homeostasis and myocardial metabolism (*Table 1*) [2–7].

In diabetes the heart is exposed to an increased supply of fatty acids and of glucose. The increase in substrate supply is accompanied by systemic and myocardial insulin resistance. This extreme metabolic environment influences energy substrate metabolism and directly affects myocyte survival, together with cardiac structure and contractility. Other postulated causes for non ischemic heart failure in diabetes, not developed in this review, include microangiopathy related to endothelial dysfunction and the development of autonomic neuropathy.

Changes in myocardial metabolism

We have termed the mammalian heart a “metabolic omnivore”, because it uses fatty acids, glucose, lactate, and several other substrates for the production of ATP [8]. Although the heart preferentially oxidizes

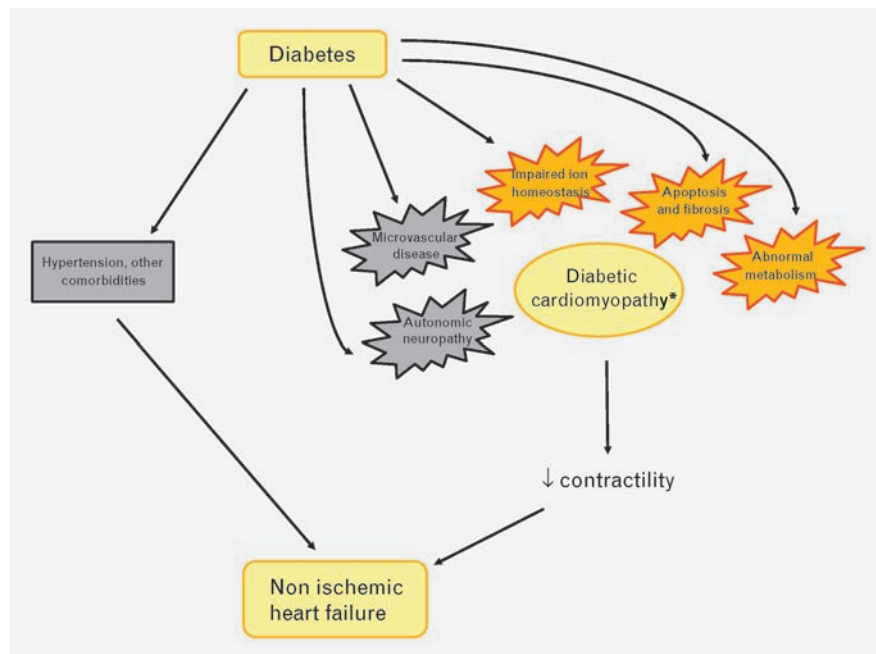


Figure 1. General scheme of proposed mechanisms for the pathogenesis of non ischemic heart failure in diabetes mellitus. Only the mechanisms in orange star-bursts are detailed in the text.

fatty acids, it readily oxidizes more efficient fuels in response to stress or injury [9]. The metabolic “flexibility” of the heart is impaired in diabetes mellitus. Increased reliance of the heart on fatty acid oxidation is induced by the enhanced availability and uptake of free fatty acids and the simultaneous inhibition of glucose oxidation, glycolysis, and glucose uptake, a phenomenon explained by the glucose–fatty acid cycle [10]. Cardiac efficiency* is decreased, because complete oxidation of fatty acids yields less ATP per molecule of oxygen consumed than does oxidation of

glucose, and because fatty acids promote mitochondrial uncoupling [11]. Changes in mitochondrial dynamics and function and their relation to contractile dysfunction in diabetes are therefore of particular interest and the subject of extensive investigation. High rates of uptake of long-chain fatty acid by mitochondria enhance the production of reducing equivalents in the mitochondrial electron transport chain, and cause an overproduction of reactive oxygen species [5,12]. In addition, mitochondrial dysfunction in diabetes is characterized by reduced

Table 1. Metabolic concepts concerning the pathophysiology of diabetic cardiomyopathy.

Reference	Authors	Year	Metabolic concepts
[2]	Rubler et al	1972	The myocardial disease might be produced by the metabolic derangements associated with diabetes, ie, limited glucose utilization and increased extraction of fatty acids and ketone bodies
[3]	Kannel et al	1974	The major metabolic disturbances could provide a metabolic basis for eventual myocardial failure: an energy crisis originating from faulty utilization of both fatty acids and glucose
[4]	Taegtmeier et al	2002	Altered metabolism and impaired insulin action in heart and skeletal muscle are both cause and consequence of altered cardiac function
[5]	Boudina and Abel	2007	The potential contributors to the development of diabetic cardiomyopathy include altered substrate metabolism, increased oxidative stress, and mitochondrial dysfunction
[6]	Witteles and Fowler	2008	Insulin resistance probably creates an environment in which the addition of another stressor (eg, pressure/volume overload, drugs/toxins, tachycardia) is poorly tolerated and enough to “tip the balance” in favor of developing a cardiomyopathy
[7]	Harmancey and Taegtmeier	2008	Diabetic cardiomyopathy may originate from the failure of the heart to adapt to chronic changes in systemic metabolism. Insulin resistance may be a short-term protective mechanism that becomes maladaptive in the long term

expression of components of the electron transport chain, and impaired mitochondrial respiration [11]. It has also been shown that, in myocardial insulin resistance, tricarboxylic acid flux is impaired, predisposing the mitochondria to oxidative stress [13]. Lastly, the diabetic heart shows an increased phosphocreatine to ATP ratio, suggesting impaired flux through creatine kinase [14].

In spite of the increased reliance on fat metabolism, the heart in diabetes is characterized by a reduced capacity for fatty acid oxidation [11]. This observation led to the concept of “glucolipototoxicity”, a mechanism by which increased non oxidative metabolism of fatty acids and glucose leads to intramyocardial accumulation of metabolic byproducts that mediate noxious stimuli. Excess ceramide directly inhibits phosphorylation of the insulin signaling mediator, Akt/protein kinase B [15], and diacylglycerol mediates insulin resistance through the activation of protein kinase C [16]. Increased flux of glucose to the polyol and hexosamine biosynthetic pathways exacerbates intracellular oxidative stress and promotes protein O-linked β -N-acetylglucosamine glycosylation (O-GlcNAcylation), respectively. O-GlcNAcylated proteins include key players in the insulin signaling pathway and mitochondrial factors [17,18]. Glucose and lipid byproducts can thus directly contribute to myocardial insulin resistance and mitochondrial dysfunction in diabetes. Nevertheless, there is some controversy over whether glucolipototoxicity contributes to heart failure in diabetic patients. The data collected from rodent genetic models are limited, as metabolic disorders are exaggerated far beyond what is usually observed in humans. For instance, cardiac-restricted overexpression of the “lipostat”, peroxisome proliferator activated receptor alpha (PPAR α)*, mediates lipotoxicity in mice [19], whereas PPAR α is usually downregulated in the heart of diabetic patients with non ischemic heart failure [20].

Activation of apoptosis and myocardial fibrosis

Echocardiographic studies have shown that, in diabetes, the heart hypertrophies and stiffens [21] – phenomena that are caused by the neurohumoral and metabolic changes that accelerate processes naturally occurring with aging. The impairment of cardiac progenitor cell function provides evidence for a causal link between diabetes mellitus, premature myocardial aging, and heart failure [22]. Increased resistance to insulin-like growth factor 1 is likely to diminish the survival of cardiomyocytes [23]. Insulin resistance and hyperglycemia activate the local renin–angiotensin–aldosterone system, which

increases oxidative damage and stimulates hypertrophy and fibrosis in the heart [24]. Hyperglycemia also promotes the formation of reactive intracellular dicarbonyls, which react with amino groups of intracellular and extracellular proteins to form advanced glycation end products (AGEs)*. AGEs increase myocardial chamber stiffness by inducing irreversible crosslinks in long-living matrix structural proteins such as collagen, laminin, and fibronectin [25]. Lastly, excess availability of glucose and fatty acids can induce cell death through oxidative stress generated by mitochondrial hyperpolarization or increased flux of glucose to the pentose phosphate and polyol pathways [12], and by the generation of proapoptotic molecules such as ceramide [26]. All these metabolic signals are likely candidates for driving cardiac remodeling in diabetes.

Impaired calcium homeostasis

Diabetes also causes abnormal intracellular calcium ion cycling, resulting in slowed myocyte contraction and relaxation. Calcium derangements are caused by both transcriptional and post-translational modifications (for review see [27]). Hyperglycemia promotes the phosphorylation of cardiac troponin I through angiotensin II-mediated activation of protein kinase C, resulting in reduced calcium sensitivity and reduced rates of crossbridge cycling of the contractile machinery [27,28]. Ryanodine receptors and sarcoplasmic reticulum calcium ATPase (SERCA2a) are inactivated by AGEs [29,30]. In diabetes and in failing hearts, ryanodine receptors are hyperphosphorylated and become leaky to Ca²⁺ during diastole [31,32]. Excess protein glycosylation reduces SERCA2a expression, possibly through the regulation of the transcription factor, Sp1 [33]. The reduction in SERCA2a function seems also to be the result of increased inhibition of the protein by phospholamban [34]. In this context, it is of interest that diabetic patients with non ischemic heart failure present with lower levels of expression of the transcription factor MEF2C and its target genes, including *SERCA2a* [20]. Depressed β -adrenergic receptor signaling in the heart and autonomic neuropathy further impair excitation–contraction coupling. Lastly, mitochondria constitute a calcium sink, and reduced mitochondrial uptake of Ca²⁺, which is related to an enhanced susceptibility to permeability transition, may contribute to impaired cardiac relaxation [35].

Summary and conclusions

It can be concluded that cardiac metabolism has a key role in diabetes-induced contractile dysfunction. Although diabetic cardiomyopathy is multifactorial, metabolic derangements probably have a central role

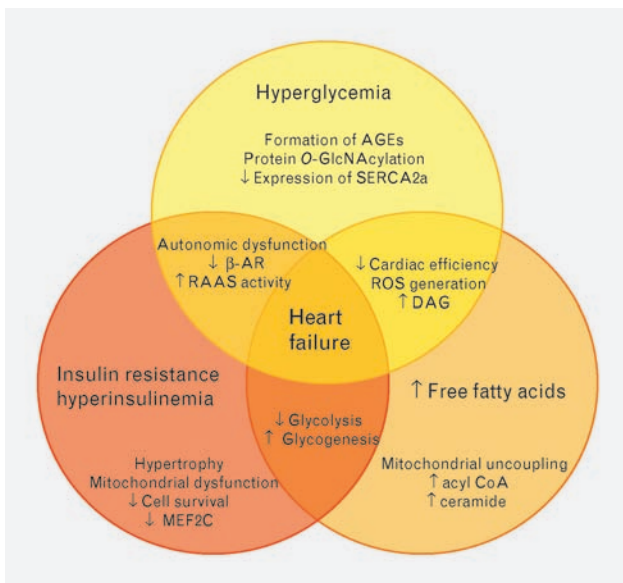


Figure 2. Potential mechanisms linking the metabolic derangements found in diabetic cardiomyopathy to the development of non ischemic heart failure. AGEs, advanced glycation end products; β-AR, β-adrenergic receptor; DAG, diacylglycerol; MEF2C, myocyte enhancer factor 2C; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SERCA2a, sarcoplasmic reticulum calcium ATPase.

in the disease (Figure 2). There is evidence that non ischemic heart failure in diabetes can develop independently of other comorbidities. High concentrations of substrates, and the development of insulin resistance, have pro-aging effects on cardiac structure and function. Most of the above has, however, been determined in genetic models of cardiomyopathy, and in animal models of untreated insulin- and non-insulin-dependent diabetes. The demonstration of a causal link between heart failure and diabetic cardiomyopathy in humans is hampered by a lack of consensus on how to diagnose and treat this entity at the subclinical level. Recent clinical trials aiming at tight glycemic control in patients with diabetes have ended with disappointing results, because the pathophysiology of heart failure in diabetes is still not understood.

*See glossary for definition of these terms.

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