Published in final edited form as:

Expert Rev Cardiovasc Ther. 2010 March ; 8(3): 373–391. doi:10.1586/erc.10.17.

Diabetic cardiomyopathy: signaling defects and therapeutic approaches

Joseph S Dobrin and

Cardiovascular Research Center, Mount Sinai School of Medicine, New York, NY, USA

Djamel Lebeche[†]

Cardiovascular Research Center, Mount Sinai School of Medicine, Atran Building AB5–10, One Gustave L. Levy Place, Box 1030, New York, NY 10029-16574, USA Fax: +1 212 241 4080

Joseph S Dobrin: joseph.dobrin@mssm.edu; Djamel Lebeche: djamel.lebeche@mssm.edu

Abstract

Diabetes mellitus is the world's fastest growing disease with high morbidity and mortality rates, predominantly as a result of heart failure. A significant number of diabetic patients exhibit diabetic cardiomyopathy; that is, left ventricular dysfunction independent of coronary artery disease or hypertension. The pathogenesis of diabetic cardiomyopathy is complex, and is characterized by dysregulated lipid metabolism, insulin resistance, mitochondrial dysfunction and disturbances in adipokine secretion and signaling. These abnormalities lead to impaired calcium homeostasis, ultimately resulting in lusitropic and inotropic defects. This article discusses the impact of these hallmark factors in diabetic cardiomyopathy, and concludes with a survey of available and emerging therapeutic modalities.

Keywords

adipokines; antihyperglycemic drugs; calcium cycling; diabetic cardiomyopathy; gene therapy; glucotoxicity; insulin resistance; lipotoxicity; mitochondrial dysfunction; obesity; stem cell therapy

Clinicians have long recognized a link between diabetes mellitus and heart disease. Indeed, a number of diabetes-related comorbidities are now known to adversely affect the heart, including coronary atherosclerosis and microangiopathy, hypertension, autonomic dysfunction and neuro-hormonal abnormalities. Since the 1970s, there has been mounting evidence for a diabetic cardiomyopathy in some patients, specifically left ventricular (LV) dysfunction that cannot be attributed to coronary artery disease (CAD), hypertension or other comorbidities. Diabetic cardiomyopathy usually manifests with diastolic dysfunction

[†]Author for correspondence: Cardiovascular Research Center, Mount Sinai School of Medicine, Atran Building AB5–10, One, Gustave L. Levy Place, Box 1030, New York, NY 10029-16574, USA, Fax: +1 212 241 4080, djamel.lebeche@mssm.edu.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

preceding systolic dysfunction, and has been observed in the context of both insulin-dependent Type 1 diabetes mellitus (T1DM) and noninsulin-dependent Type 2 diabetes mellitus (T2DM). Full discussion of all cardiac-related diabetic comorbidities, while important, is beyond the scope of this review. We shall restrict our focus to some of the key intrinsic myocardial molecular changes – dysregulated cardiac lipid metabolism, myocardial insulin resistance, abnormalities in adipokine activity, mitochondrial dysfunction and calcium cycling perturbations that characterize diabetic cardiomyopathy. We will conclude with a review of current and emerging therapeutic options available to clinicians.

Structural & functional alterations in diabetic cardiomyopathy

The Framingham Heart Study was the first to quantify the increased risk of congestive heart failure experienced by patients with diabetes. Diabetic men have twice the risk of age-matched controls, and diabetic women experience a fivefold increased risk. Statistical analysis revealed that this increased risk could not be explained by obesity, hyperlipidemia, hypertension or CAD [1]. At around the same time, Rubler *et al.* found fibrosis, hypertrophy, remodeling and other evidence of congestive heart failure in four diabetic patients without clinically significant CAD [2]. Although there are some structural differences between the cardiomyopathy seen in T1DM compared with T2DM (animals models of the former revealed enhanced cardiac apoptosis and dilatation, whereas models of the latter tended to show hypertrophy [3]), patients with both T1DM and T2DM share a number of characteristic metabolic defects – including insulin resistance and abnormalities of fatty acid (FA) oxidation [4]. Over time, these findings and later ones built a robust picture of a diabetic cardiomyopathy independent of comorbid risk factors.

Clinical presentation of diabetic cardiomyopathy

The deposition of collagen and its gradual organization into irreversible fibrosis are histological hallmarks of diabetic cardiomyopathy [5]. Over time, fibrosis manifests as myocardial stiffness with impairment of relaxation. However, since cardiac biopsies are rarely indicated, diagnosis is most often made by noninvasive imaging – usually by echocardiography. The most common echocardiographic findings are hypertrophy and diastolic dysfunction – the inability of the heart to relax appropriately between contractions. Diastolic dysfunction is one of the earliest observable cardiac changes in diabetic patients, and often presents initially without any other clinical sign of heart disease. Using echocardiography, diastolic dysfunction is characterized by increased isovolumic relaxation time and Doppler flow changes in the timing of LV filling. Very subtle diastolic dysfunction may require tissue Doppler imaging and measurements of strain and strain rate [6]. Echocardiography of asymptomatic diabetic patients often reveals subclinical hypertrophy and impaired relaxation, even before the onset of clinically significant fibrosis [7]. Similar changes have been observed in children with T1DM, who were unlikely to have clinically significant CAD [8]. Although these findings support the diagnosis of diabetic cardiomyopathy, they are not specific to it. To our knowledge, a generally accepted imaging-based definition of diabetic cardiomyopathy does not yet exist. However, we find the following definition recently proposed by Aneja *et al.* After excluding other contributory causes, diabetic cardiomyopathy can be defined as the presence of both of the following:

- Evidence of cardiac hypertrophy determined by conventional echocardiography or MRI;
- Evidence of LV diastolic dysfunction (with or without LV systolic dysfunction), either clinically by transmitral Doppler or tissue Doppler imaging, or evidence of left atrial enlargement, or subclinically by novel imaging techniques or provocative testing (e.g., strain and strain-rate imaging, or stress imaging) [9].

Many related comorbidities ensue as diabetes progresses, including microangiopathy, CAD, hypertension and autonomic neuropathy. The vascular changes often cause localized ischemia and systolic dysfunction that is detectable by conventional echocardiography. For a comprehensive review of these changes, the reader is directed to the excellent discussion by Fang *et al.* [6].

Dysregulated lipid metabolism

In many patients, dysregulated lipid utilization – often occurring in the context of obesity – is an early and significant risk factor for metabolic syndrome, T2DM and related cardiac dysfunction. Increased adiposity results in higher circulating levels of a number of free FAs and triglycerides, and the altered production and release of adipokines, which modulate the metabolism of several organs, including the heart. Both adipokines and hyperlipidemia contribute to dysregulated cardiac lipid metabolism, cardiac insulin resistance and, ultimately, to the development of diabetic cardiomyopathy (Figure 1).

The heart, an extremely metabolically active organ, has a very high density of mitochondria and requires a constant supply of high-energy substrates. In healthy hearts, cardiomyocytes precisely match energetic demands with the amount of available substrates. Approximately 70% of these substrates are comprised of triglycerides and long-chain FAs owing to their unmatched energy density (mol of ATP derived per mol of substrate), with approximately 30% derived from glucose and lactate [10]. The heart is also able to utilize ketone bodies, particularly in cases where they are abundant, as in T1DM.

Acute control of cardiomyocyte FA metabolism occurs largely at the level of import to the mitochondria, and is mediated by AMPK, which regulates the activity of carnitine palmitoyltransferase (CPT)1. When FAs are not abundant, CPT1 is inhibited by malonyl-CoA, which is produced by acetyl-CoA carboxylase (ACC), and broken down by malonyl CoA decarboxylase (MCD) [11,12]. When FAs are present in large quantities, AMPK inhibits ACC, reducing the concentration of malonyl-CoA, alleviating its inhibition of CPT1, and ultimately results in increased β -oxidation [13]. In this way, the healthy cardiomyocyte precisely matches ATP production with FA oxidation.

When cardiomyocytes are exposed to chronically high levels of FAs, their metabolism is regulated in large part by the peroxisome proliferator-activated receptors (PPARs), a family of nuclear receptor transcription factors that, in association with their coactivator, peroxisome proliferator-activated receptor- β cofactor 1 α (PGC-1 α), bind the promoter region of several genes involved in FA metabolism, activating their transcription. PGC-1 α

and PPAR- α , the most abundant PPAR isoform in the heart, regulate genes involved in the transport of FAs into the cell (FA transport protein, FA binding protein and CD36/FA translocase), transport into the mitochondria (MCD and CPT1) and β -oxidation (acyl-CoA dehydrogenases, 3-ketoacyl-CoA thiolases and acyl-CoA oxidase) [14]. FAs, endogenous ligands of PPAR- α , induce a positive feedback loop when present in high concentrations, in which the expression and activity of PPAR- α itself is upregulated. The result is a profound increase in both uptake and oxidation of FAs [15]. In addition, PGC-1 α also fosters the expression of electron transport genes and promotes mitochondrial biogenesis to accommodate the oxidation of abundant FAs [16].

Upregulation of PPAR- α antagonizes the action of insulin, reducing the amount of glucose entering the cell, and inhibiting both glycolysis and mitochondrial pyruvate oxidation [17]. Cardiac knockout of PPAR- α in rodent models reduces the expression of genes involved in FA metabolism, and switches substrate selection to glucose when it is available [18]. Conversely, the overexpression of PPAR- α or PGC-1 α leads to a phenotype similar to diabetic cardiomyopathy, in which both FA uptake and oxidation are increased [16,19]. Interestingly, PPAR- α appears to be downregulated in late diabetes, after the cardiomyocyte has been exposed to high levels of circulating FAs for many years. Concomitantly, PPAR- β , an isoform most abundantly expressed in liver, is upregulated [15]. Although the downregulation of PPAR- α may be compensatory, the isoform switch to PPAR- β promotes lipogenesis, which some see as evidence of a 'second hit' leading to lipotoxicity [15].

Reduced cardiac metabolic flexibility

In hyperlipidemia, dependence on long-chain FAs is increased, and glucose utilization is inhibited. This inhibition may become problematic in cases of hypoxia or ischemia, where glucose oxidation is preferred owing to its greater metabolic efficiency (mol of ATP derived per mol of oxygen consumed). Indeed, in times of stress, nondiabetic hearts switch their predominant substrate to glucose. Diabetic hearts (and hearts of the obese to a lesser extent) are unable to make this metabolic switch owing to inhibition of the glycolytic and glucose oxidation machinery by high intracellular concentrations of nonesterified FAs (NEFAs) [10,20]. As a result, they are more susceptible to ischemic damage. In addition, this metabolic inflexibility has been associated with insulin resistance and reduced mitochondrial oxidative capacity in obese and diabetic *ob/ob* mice [20], and impaired cardiac performance in obese humans [21].

Lipotoxicity

An imbalance between FA uptake and oxidation within a tissue leads to lipid accumulation, and may result in lipotoxicity when these additional FA have a deleterious impact on cellular function. High serum FA concentrations in the obese lead to increased FA uptake in most tissues, including heart [22]. FA oxidation rates do not increase (and may even drop) in skeletal muscle and liver subject to this hyperlipidemic milieu, contributing to insulin resistance and lipotoxicity in these tissues [23–25]. The heart, with its more robust ability to metabolize FAs, responds somewhat differently. Recent studies in humans and rodents have reported increased FA oxidation rates in the obese, the insulin resistant and those with T2DM [10,26]. However, as diabetes progresses, upregulation of oxidation fails to keep pace

with the increase in uptake [15]. In addition, PPAR isoform switching from PPAR- α to PPAR- β leads to cardiac lipogenesis [27]. The result is the production and build up of toxic metabolites (e.g., ceramide from palmitoyl-CoA), which are associated with increased rates of myocardial apoptosis [10,26].

Glucotoxicity

Dysregulated lipid oxidation may also result in glucotoxicity. It is well established that hyperglycemia leads to glycosylation and crosslinking of collagen and other extracellular matrix proteins, leading to myocardial stiffness [28]. There is a reduction in the amount of glucose entering the cell in diabetic cardiomyopathy due to the inhibition of glucose transporter expression and translocation to the plasma membrane. However, the rates of glycolysis and pyruvate oxidation, especially during ischemia [20,29], are reduced even further, largely due to inhibition of insulin's action by PPAR- α . The result is the shunting of an inappropriate amount of glucose metabolism to the hexosamine biosynthesis pathway [4], the production of reactive oxygen species (ROS) and the increased formation of intracellular advanced glycosylation end products (AGEs). AGE formation has been found to form irreversible crosslinks within or between many proteins, including the sarco-endoplasmic reticulum Ca^{2+} -ATPase (SERCA2a) and the Ca^{2+} release channel, ryanodine receptor 2 (RyR2), causing their inactivation and subsequently leading to abnormal cardiac relaxation and contractility [30,31]. Similarly, increased hexosamine biosynthesis reduces SERCA2a expression and function, leading to impaired excitation–contraction coupling and myocardial relaxation [32].

Insulin resistance

Insulin resistance is one of the hallmarks of T2DM in both animal models and humans, and is seen in a number of tissues including the heart [3,4,33,34]. Myocardial insulin resistance occurs when myocytes lose sensitivity to insulin, resulting in an attenuated response to insulin stimulation, and increased insulin secretion by the pancreas in an attempt to compensate. Myocardial insulin resistance was originally thought to occur in T2DM due to chronic exposure to hyperglycemia, but it is now known that insulin resistance often precedes hyperglycemia [35], and occurs in T1DM as well [36]. Although the cellular mechanisms remain to be fully elucidated, lipotoxicity likely plays a significant role.

The insulin receptor (IR) and related IGF-1 receptor (IGF-1R) transduce signals through two primary pathways – a mitogenic pathway via MAPKs, and a metabolic pathway via PI3K and the serine–threonine kinase Akt (also known as PKB). Each pathway has its own scaffold proteins that mediate signals from the receptor to downstream effectors. In the mitogenic pathway, this scaffold protein is Shc, which upon binding to the intracellular face of the activated receptor, sets off a cascade that ultimately results in the activation of a number of MAPKs, of which the best characterized is ERK1/2. In the metabolic pathway, IR substrate (IRS)-1 plays a role homologous to that played by Shc, activating PI3K and a number of effectors including Akt. Activated Akt modulates a number of pathways – inhibiting GSK3 β , activating endothelial nitric oxide synthase (eNOS), and promoting the translocation of the glucose transporter (GLUT)4 to the sarcolemma (Figure 2).

Myocardial insulin resistance occurs when myocytes lose sensitivity to insulin, resulting in an attenuated response to insulin stimulation. As several receptors signal through MAPKs, it is difficult to quantify the effects of insulin resistance on the mitogenic pathway. However, several defects in the metabolic pathway have been described, including increased IRS serine phosphorylation [37,38], increased rates of IRS degradation [39], and increased activity of the phosphatases src homology 2 domain containing inositol 5'-phosphatase 2 (SHIP2), phosphatase tensin homolog deleted on chromosome 10 (PTEN) and phosphotyrosine phosphatase 1B (PTP-1B) (Figure 2) [40,41]. The ultimate result is decreased activation of Akt and other downstream effectors. It is also likely that some of the hypertrophy observed in those with T2DM may be ascribed to shunting insulin signaling away from the metabolic pathway and towards the mitogenic pathway.

Although there is not yet agreement on the proximal cause of insulin resistance, there is growing evidence that the accumulation of intracellular lipids – particularly long-chain FAs – plays a critical role. There are at least two lines of evidence supporting this conclusion. First, there is dysregulation of AMPK, a key metabolic switch that regulates glucose and FA oxidation in the heart [42]. In healthy hearts, AMPK activation is antagonized by insulin in a PI3K-dependent manner, resulting in an increase in malonyl CoA concentration and a concomitant decrease in FA oxidation while facilitating glucose oxidation. In the obese and diabetic, elevated FA concentrations have been shown to reduce AMPK's sensitivity to insulin [29], leading to reduced glucose oxidation and increased FA oxidation.

A second line of evidence involves signals mediated by PKC- θ . In skeletal muscle, PKC- θ is activated by fatty acyl-CoA and diacylglycerol in the presence of high intracellular lipids. It phosphorylates and activates I κ B kinase, which phosphorylates serine residues on IRS-1, inhibiting its ability to bind PI3K [43]. PI3K-dependent Akt signaling is compromised, including GLUT4 translocation to the sarcolemma, resulting in a reduction in glucose oxidation. Diabetic hearts have also been shown to accumulate excess nonesterified FAs and triglycerides [17], but this mechanism has not yet been demonstrated in cardiac tissue [3].

Adipokines: emerging modulators of cardiac performance

Adipose tissue was for many decades thought to have modest metabolic potential and effects. It was viewed largely as a repository for surplus lipids that could be mobilized in times of high metabolic demand. It is now known that adipocytes produce and secrete a number of cytokines (adipokines) that interact with most organs in the body, and several play a role in T2DM and insulin resistance. Although a review of all of these adipokines is beyond the scope of this article, we will focus on three that have significant effects on the heart – leptin, adiponectin and resistin.

Leptin

Leptin, a 16-kD protein primarily produced and secreted by white adipose tissue (but also produced in the heart and other tissues), exerts its endorgan effects by binding the abundantly expressed obesity gene receptor (OBR) [44]. Upon leptin binding the OBR, the receptor undergoes homo-oligomerization, and its intracellular tail interacts with JAK2 [45,46]. JAK2 autophosphorylates itself, and phosphorylates the OBR at three tyrosine

residues, including Tyr 985 and Tyr1138 [47,48]. Phosphorylation of Tyr1138 recruits signal transducer and activator of transcription (STAT)3 to the OBR/JAK2 complex and activates it, also via tyrosine phosphorylation. Upon activation, STAT3 dimerizes and translocates to the nucleus to activate the transcription of target genes. One of these effects is to induce negative feedback of leptin signaling via the transcription of the suppressor of cytokine signaling (SOCS)3 [47,49,50], which binds JAK2 and prevents association of further STAT3s [51]. Phosphorylation of the OBR at Tyr985 ultimately leads to the activation of ERK1/2 via src homology 2-containing tyrosine phosphatase (SHP2) [47]. In addition, JAK2 autophosphorylation causes it to activate several kinases, including RhoA/ROCK, p38 MAPK, PI3K, Akt and PKC [52].

Until recently, leptin was thought to exert generally detrimental effects on the heart. There is now increasing evidence that leptin's effects are more diverse than originally appreciated, and some effects may be cardioprotective. The primary cardiac physiological consequence of leptin's action is negative inotropy mediated by endogenously produced nitric oxide [53]. Leptin also exerts a prohypertrophic response in cardiomyocytes, in part via an autocrine or paracrine response to endothelin-1 and angiotensin (Ang) II stimulation [54]. This hypertrophic response appears to be mediated by RhoA/ROCK, and results in increased f-actin polymerization [55]. It also appears to require intact caveolae for receptor endocytosis and signal transduction, resulting in the translocation of p38 to the nucleus and the transcription of hypertrophic genes [56].

Although elevated leptin plasma concentrations are generally predictors of poor outcome in patients with CAD and heart failure [57], leptin may protect against ischemia/reperfusion injury, possibly via ERK1/2 and PI3K-dependant mechanisms [58]. LV dysfunction, hypertrophy and increased mortality seen in leptin-deficient *ob/ob* mice following 4 weeks of coronary ligation can be reversed by the administration of exogenous leptin [59].

Leptin's metabolic effects are also unclear. *In vitro* studies using the HL-1 murine cell line showed increased FA oxidation after 1 h of leptin treatment, but decreased FA oxidation after 24 h [60]. This time course mirrors the phosphorylation of AMPK and its substrate ACC, suggesting that leptin may activate AMPK, leading to FA oxidation. However, in another study using isolated working rat hearts, leptin increased FA oxidation and triglyceride hydrolysis independent of AMPK/ACC activity, leading to a decrease in cardiac efficiency [61]. Leptin's effect on glucose uptake and oxidation is also unclear. Leptin was shown to stimulate glucose uptake in isolated Langendorff perfused rat hearts [62]. However, no effect on basal or insulin-stimulated glucose uptake or oxidation was observed in the HL-1 cell line or in isolated working rat hearts [60,61].

Paradoxically, rodent models suggest leptin may exert anti-lipotoxic and cardioprotective functions. Plasma leptin levels rise in rodent models within 24 h of beginning high-fat diet [63]. Rodents without normal leptin action (e.g., *ob/ob*, *db/db*) have increased lipid accumulation in peripheral tissues, including heart [64]. The Zucker diabetic fatty (ZDF) rat and *ob/ob* mice show impaired contractility. Thus, in the absence of normal leptin action, FA uptake is increased, while oxidation is impaired; the result is lipotoxicity and contractile dysfunction [64,65]. Taken together, these data suggest that, even though leptin causes

hypertrophy and reduced inotropy, it may protect the heart from lipotoxicity and the relatively hypoxic milieu associated with diabetic cardiomyopathy.

Adiponectin

Adiponectin, a 30-kDa protein, is the most abundant adipokine and is essential for adipocyte differentiation. It can exist as oligomers of a 245-amino acid protein, or as globular fragments of 137 amino acids. Oligomers exist as a low-molecular-weight trimer, a mid-molecular-weight hexamer and a high-molecular-weight multimer (12–18-mer). The high-molecular-weight multimer is thought to be the most biologically active [52].

Adiponectin exerts its effects by binding two receptors –AdipoR1 and AdipoR2. The latter is enriched in the liver, and the former is ubiquitously expressed [52]. In humans and rodents, plasma adiponectin concentrations and adiponectin receptor concentrations (both AdipoR1 and AdipoR2) correlate positively with insulin sensitivity, and inversely with hypertension, hyperlipidemia, insulin resistance, metabolic syndrome and T2DM [66–68]. Studies have shown a correlation between depressed adiponectin levels and increased risk of myocardial infarction, CAD and heart failure [69–71], although there does not appear to be a relationship between the magnitude of adiponectin depression and CAD severity [72].

Experimental rodent models have helped clarify our understanding of the mechanisms by which adiponectin exerts its effects. Mice in which adiponectin is knocked out (ADN-K/O) demonstrate increased concentric hypertrophy and elevated mortality following the induction of pressure overload by transverse aortic constriction (TAC) [73]. This effect is reduced if the mice are transfected with an adenoviral adiponectin vector (Ad.ADN) [73]. Significantly, Ad.ADN also attenuates hypertrophy induced by a number of other factors, including Ang II and norepinephrine, and hypertrophy induced by TAC in leptin receptor-deficient (*db/db*) mice [73]. Taken together, these data suggest adiponectin exerts powerful endogenous antihypertrophic properties.

On a molecular level, adiponectin is thought to generally exert its cardioprotective functions by modulating several pathways, including those involving ERK1/2, AMPK, eNOS and inducible nitric oxide synthase (iNOS). ERK1/2 activity is increased in ADN-K/O mice subjected to TAC, and is reduced by treatment with adiponectin [73]. ADN-K/O mice demonstrate larger infarct areas than wild-type controls when subjected to ischemia/reperfusion. These effects are associated with reduced AMPK levels, and reduction in AMPK and eNOS phosphorylation [74]. Treatment with exogenous adiponectin leads to enhanced AMPK phosphorylation, with a reduction in infarct size [75]. Interestingly, ADN-K/O mice exhibited increased iNOS phosphorylation [76]. Karmazyn *et al.* speculate that under physiological conditions, adiponectin may mediate some of its cardio-protective functions by increasing eNOS. Conversely, during ischemic stress adiponectin may reduce pathological nitric oxide overproduction by inhibiting iNOS [77].

Resistin

Resistin, a novel cysteine-rich hormone secreted by adipocytes in rodents, is postulated to be implicated in obesity, T2DM and insulin resistance [78]. Recombinant resistin protein was found to impair insulin action in normal mice and cultured adipocytes, and

immunoneutralization of resistin improved insulin action in mice with diet-induced obesity [78]. Plasma resistin levels were increased in *db/db*, *ob/ob* and diet-induced obese mice [78], although resistin mRNA levels in obese rodents were often found to be decreased [79,80].

Resistin modulates glucose metabolism and insulin signaling in skeletal muscle – regulating the function of IRS-1, Akt1 and GSK-3 β , and decreasing GLUT4 translocation and glucose uptake in response to insulin [81]. Resistin is also regulated by the PPAR- β agonist thiazolidinediones (TZDs). TZD treatment suppressed resistin expression in 3T3-L1 adipocytes and in the white adipose tissue of mice fed a high-fat diet [78], and reduced plasma resistin levels in human patients with T2DM [82], suggesting that resistin may play an important role in the etiology of insulin resistance and diabetes. However, this point is contested as other studies have failed to show any association with insulin resistance [83,84].

Resistin's role in modulating cardiac glucose metabolism, insulin signaling and contractile performance in the diabetic heart is currently unknown. Both T1DM and T2DM hearts express high levels of resistin [85]. Resistin has been reported to impair glucose transport in isolated mice cardiomyocytes [86], and to be upregulated by cyclic stretch and aorta-caval shunt [87] in rodent models, suggesting resistin may affect cardiac function. Adenoviral transduction of resistin in neonatal rat myocytes causes gross hypertrophy with increased expression of hypertrophic genes [85]. It is also associated with activation of the ERK1/2–p38 MAPK pathways, and with increased serine-636 phosphorylation of IRS-1. Adenoviral induction of resistin in adult myocytes reduces contractility, possibly via a reduction in Ca²⁺ transients [85]. It is likely, therefore, that the high level of resistin observed in diabetes contributes to the impairment of cardiac function, possibly through alterations in cardiac metabolism and the induction of myocardial insulin resistance.

Although human resistin shares only 59% amino acid sequence identity with its mouse homolog [78,88], and humans express resistin primarily in macrophages instead of adipocytes, there is emerging evidence that plasma resistin levels correlate with increased risk of cardiovascular disease. For example, plasma resistin levels are elevated in women with coronary heart disease [89]. Plasma resistin concentrations have also been shown to correlate with the severity of heart failure [90]. In addition, the obese [91], those with T2DM [92] and survivors of myocardial infarction displayed elevated circulating resistin levels. In patients with atherothrombotic strokes, increased plasma resistin levels are associated with elevated risk of 5-year mortality [93]. Although these studies do not indicate causal relationships, increasing plasma resistin concentrations appear to be a predictor of poor prognosis in patients with cardiovascular disease, and warrant further investigation.

The aims of most of the studies described earlier have been to discover the effects of adipokines on promoting or retarding the progress from metabolic syndrome to overt T2DM. It is known that levels of leptin, adiponectin and resistin change as patients progress to diabetes. Unfortunately, there is currently a paucity of data on the long-term impact of these adipokines in full-blown T2DM, and further research is necessary to clarify their role.

Calcium cycling abnormalities in diabetic cardiomyopathy

Calcium homeostasis plays a critical role in cardiomyocyte contractility. During depolarization, calcium enters cardiomyocytes via voltage-gated L-type calcium channels (LTCCs), prompting calcium-induced calcium release (CICR) from RyR2 channels. The subsequent ten- to 100-fold increase in cytosolic calcium allows Ca^{2+} ions to bind troponin C – alleviating the troponin I-induced inhibition of thick (myosin) and thin (actin, tropomyosin and troponin) filaments. Thick and thin filaments form cross-bridges and slide past each other, generating force and shortening the cell. Cytoplasmic calcium levels return to resting (diastolic) levels via resequestration in the sarco-endoplasmic reticulum (SR) by SERCA2a, and by efflux from the cell primarily by the sodium–calcium exchanger (NCX), with a minor contribution from the sarcolemmal calcium ATPase [94]. Resequstration is enhanced when phospholamban (PLB), an endogenous inhibitor of SERCA2a, is phosphorylated by CaMKII, and by PKA following β -adrenergic stimulation by norepinephrine, causing a conformational change in PLB and releasing SERCA2a from inhibition (Figure 3). In rodents, SERCA2a accounts for more than 90% of relaxation flux. However, in rabbits and humans, approximately 70% is resequestered by SERCA2a, with nearly all of the rest effluxing from the cell via NCX [95,96]. Several facets of calcium cycling are dysregulated in diabetic cardiomyopathy, including altered expression and/or activity levels of RyR2, SERCA2a, NCX, LTCC and ATP-regulated potassium (K_{ATP}) channels, and a reduction in myofilament calcium sensitivity.

Reduction in RyR2 expression and function is seen in animal models of both T1DM and T2DM cardiomyopathy [97,98]. Although decreased RyR2 expression may contribute to a reduction in systolic calcium flux, RyR2 hyperphosphorylation at numerous sites is a greater determinant of this flux, at least in streptozotocin (STZ)-induced T1DM.

Hyperphosphorylation of RyR2 is PKA dependent and occurs in the context of chronic β -adrenergic stimulation seen in heart failure and late diabetic cardiomyopathy [99,100]. Even after secondary downregulation of the β -adrenergic system, RyR2 remains hyperphosphorylated due to depletion of the protein phosphatases PP1 and PP2a [101,102]. As a result of RyR2 hyperphosphorylation, RyR2 is unable to associate with calstabin2, a molecule that stabilizes the closed conformation of the receptor. The result is a dyssynchronous diastolic leak, depleting SR calcium stores and increasing cytosolic diastolic Ca^{2+} concentrations [100,103].

This reduction in SR calcium stores is exacerbated in diabetic hearts by a reduction in SERCA2a activity – slowing diastolic relaxation, reducing the amount of calcium resequestered in the SR following each contraction and further reducing the amplitude of subsequent systolic contractions [104]. Cardiac SERCA2a expression is reduced in STZ-induced T1DM [105] and in some models of T2DM [106]. However, unlike nondiabetic models of heart failure, the expression of PLB is increased two- to fourfold in STZ-induced T1DM [105], and is also increased in most models of T2DM [107]. In addition, the phosphorylation state of PLB is reduced in most diabetic models, increasing PLB's inhibition of SERCA2a [97]. Indeed, the observed decline in SERCA2a activity can be explained primarily by a decreased ratio of SERCA2a to dephosphorylated PLB. A direct link to the insulin metabolic pathway was recently demonstrated when Akt was shown to be

capable of directly phosphorylating PLB at the CaMKII phosphorylation site (thr17) [108]. Thus, part of the reduction in PLB phosphorylation state in diabetes may be ascribed to attenuated Akt activity.

Significantly, the reduced SERCA2a:dephosphorylated PLB ratio is seen even in rodent models in which SERCA2a expression is unchanged [109], and calcium homeostasis and contractility improves when SERCA2a is overexpressed [110]. del Monte *et al.* observed similar findings in human LV cardiomyocytes isolated from heart failure patients at the time of transplant surgery [111], although these studies have not yet been replicated in patients with diabetic cardiomyopathy. Taken together, these data strongly suggest that diabetes causes an impairment of cardiac calcium cycling, and the restoration of physiological ratios of SERCA2a and PLB can ameliorate this defect.

In heart failure, NCX activity increases in inverse proportion to SERCA2a activity, resulting in a nearly equal contribution to calcium relaxation flux [101]. In this regard, one may conceive of NCX as playing a compensatory role – providing a safety valve to reduce pathologically elevated cytosolic calcium. In cardio-myocytes overexpressing NCX, both diastolic and systolic calcium levels are significantly lower than in control myocytes [112]. Similar findings have been observed in the *db/db* mouse model of T2DM cardiomyopathy [98]. However, models of T1DM generally show the opposite – with decreased expression and activity of NCX [113]. It is unclear what aspect of the hyperglycemic and hypoinsulinemic milieu of T1DM impedes NCX's compensatory function seen in other models of heart failure.

Prolongation of ventricular action potentials is an early and consistent finding in diabetic hearts. Since calcium entry via voltage-dependent LTCCs is one of the earliest steps in the cardiac action potential cycle, it is attractive to hypothesize that L-type calcium current (I_{Ca-L}) passing through LTCCs is altered. Unfortunately, results of animal studies do not consistently support this hypothesis. Expression of LTCCs at cardiomyocyte plasma membranes in a mouse model of T1DM is reduced slightly [114], and changes in protein kinase activity (increased PKC, decreased PKA) modulate the function of this and other ion channels in diabetic hearts, including I_{to} (transient outward potassium current) (Figure 3). However, the consequence of altered LTCC expression and function are not clear. I_{Ca-L} is usually reduced in models of T1DM, but only after several months of hyperglycemia [115,116]. Since overt heart failure is often present by this point, it is unclear if the diabetes or the heart failure is responsible for the reduction in I_{Ca-L} . In any event, I_{Ca-L} is altered less significantly than I_{to} , which is depressed within days of T1DM induction in experimental models [117], and likely contributes significantly more than I_{Ca-L} to the increased action potential duration (APD) [114,118].

High concentrations of intracellular long-chain FAs may also alter the kinetics of K_{ATP} channels by depressing the amplitude of the cardiac action potential. In isolated guinea-pig ventricular myocytes, long-chain acyl-CoA esters have been shown to reduce the ATP sensitivity of these channels, facilitating their opening [119]. One result is hyperpolarization, and a likely reduction in the amplitude of subsequent action potentials. Liu *et al.* hypothesize

that this may lead to a reduction in trans-sarcolemmal Ca^{2+} influx with a concomitant reduction in myocardial contractility [119].

In addition to a reduction in the amplitude of calcium transients, there is increasing evidence that diabetic cardiomyopathy reduces myofilament calcium sensitivity, contributing to slower cross-bridge cycling in animal models [120] and diabetic humans [121]. There are at least two likely explanations for this. First, hyperglycemia and increased serum and cardiomyocyte levels of Ang II, both features of diabetic cardiomyopathy, can cause an increased activation of several isoforms of PKC in the heart. PKC-mediated phosphorylation of troponin I and troponin T is associated with reduced myofilament calcium sensitivity in diabetic human hearts by reducing the activity of the actinomyosin Mg^{2+} -ATPase, ultimately resulting in impaired cross-bridge formation and cycling (Figure 3) [120–122]. A second explanation involves abnormal actin and myosin isozyme expression – a facet of the cardiac fetal gene-expression program activated when the heart is exposed to long-term stress, as it is in diabetic cardiomyopathy. This program includes the increased expression of α -skeletal actin and β -myosin heavy chain, with a concomitant reduction in the expression of α -myosin heavy chain [123]. Although initially adaptive (fetal isozymes are more efficient in relatively hypoxic environments associated with hypertrophy), their reduced sensitivity to calcium ultimately results in a heart unable to maintain the structure and function necessary to support the body's needs [124].

Mitochondrial dysfunction in diabetic cardiomyopathy

As discussed previously, hyperglycemia leads to enhanced ROS generation, and mitochondria appear to be the major source [125]. In fact, mitochondria appear to be both a source and a target of ROS, and increased mitochondrial-generated ROS has been linked to mitochondrial dysfunction [125–127]. There is also growing evidence that this mitochondrial dysfunction may be a relevant intermediate mechanism contributing to the pathophysiology of diabetic cardiomyopathy (Figure 1).

Cardiac mitochondria consist of three spatially and morphologically distinct subpopulations termed subsarcolemmal, interfibrillar and perinuclear mitochondria that are located adjacent to the plasma membrane, between the contractile apparatus or in close proximity to the nucleus, respectively [128,129]. In addition to their spatial and morphological differences, these mitochondrial sub-populations differ in structure, bioenergetics function and mitochondrial-dependent signaling pathways [128,130–132]. As a consequence, they appear to respond differently to physiological stimuli, such as obesity, exercise, oxidative stress and apoptosis [128,130–134]. The intermyofibrillar mitochondria provide energy primarily to support muscle contraction, whereas subsarcolemmal mitochondria provide ATP for membrane-related processes, including signal transduction, ion exchange, substrate transport and substrate activation [135]. Furthermore, subsarcolemmal mitochondria have been postulated to be important for FA oxidation, glucose transport and propagation of insulin signaling [135]. Although the majority of mitochondrial research examining the impact of diabetes on mitochondrial function has been performed on total mitochondria, recent evidence indicates that individual subpopulations behave differently in response to diabetes induction. Subsarcolemmal mitochondria electron transport chain activity was reduced in

muscle from T2DM patients [133]. T1DM appears to affect the interfibrillar mitochondria subpopulation more than the subsarcolemmal mitochondria, as indicated by increased ROS damage and greater morphological changes [136].

Diabetes also induces changes in mitochondrial function, affecting high-energy phosphate availability, Ca^{2+} homeostasis and metabolic regulation. Mitochondria play a critical role in energy production, and diabetic cardiomyopathy is characterized by a mismatch between energy supply and demand. Energy derived from key ATP production reactions have been shown to be decreased in both human and experimental models of heart failure. These include oxidative phosphorylation, glycolysis and turnover of high-energy phosphates catalyzed by creatine kinase – with the exception of the myofibrillar isoform [137,138]. Cardiac muscle contains a large amount of phosphocreatine and creatine kinase, which acts as an energy reserve system, especially during high workloads. A decrease in creatine kinase, either pharmacologically or genetically, decreases the ability of cardiac muscle to increase contractile performance [137,138]. We and others have also shown that the phosphocreatine: ATP ratio is decreased in rodent models of heart failure [139] and in T2DM diabetic patients [140], possibly as a result of mitochondrial dysfunction.

Recently, a prominent role of mitochondria in the regulation of Ca^{2+} homeostasis has emerged. Mitochondria appear to control not only their intra-organelle Ca^{2+} concentration, but they also dynamically interact with the cytosol and intracellular Ca^{2+} handling machineries (i.e., ER/SR and the nucleus) to shape the cellular Ca^{2+} signaling network. Although not the focus of this article, here we briefly discuss the coupling of mitochondrial metabolism and Ca^{2+} . The reader is referred to more comprehensive and focused reviews on the subject published elsewhere [141,142].

Intramitochondrial calcium levels are thought to mediate the link between energy supply and demand in the heart [143,144]. Therefore, a link between decreased energy efficiency (generally observed in human and experimental animals with obesity and diabetes) and Ca^{2+} regulation may be related to impaired mitochondrial calcium handling, which may compromise myocardial bioenergetics and contribute to the development of cardiac dysfunction. Recent evidence suggests that there is dynamic exchange of calcium between the mitochondria and the cytosol, and mitochondrial Ca^{2+} uptake is believed to increase mitochondrial ATP production [145]. Mitochondria, owing to their capacity to accumulate, buffer and release Ca^{2+} , can also influence the cytosolic calcium concentration. However, when the intramitochondrial calcium concentration exceeds the buffering capacity of the mitochondria, as in heart failure, irreversible swelling occurs, leading to mitochondrial dysfunction and contractile impairment.

In addition, there is evidence that impaired calcium handling may be due to a limited thermodynamic driving force for SERCA2a. Increasing extracellular calcium in a Langendorff perfused heart increased contractile performance in a normal heart, but not in creatine kinase-inhibited hearts [137,138,146]. This suggests that failure to increase SR Ca^{2+} stores during inotropic stimulation in hearts with low thermodynamic driving force blocks the heart from recruiting its contractile reserve. Indeed, abnormal cardiac function normalizes after overexpression of SERCA2a in a STZ-induced diabetic heart [110].

Therapeutic approaches

Although there are currently no treatments developed specifically for the prevention or management of diabetic cardiomyopathy, antagonism of the renin–angiotensin–aldosterone system with angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and aldosterone antagonists has proven beneficial at preventing or slowing the progression of myocardial dysfunction associated with the disease. ACE inhibitors and aldosterone antagonists have been shown to prevent hypertrophy and inhibit collagen deposition and myocardial fibrosis [147–149]. Candesartan, an ARB, has been shown to reduce collagen synthesis and promote its degradation in asymptomatic diabetic patients, leading to an improvement in echocardiographic parameters of diastolic dysfunction [148]. However, it is unclear if any of these treatments is capable of causing regression of fibrosis or hypertrophy in patients in more advanced stages of diabetic cardiomyopathy.

In the absence of specific therapies for diabetic cardiomyopathy, treatment has focused on addressing early signs of the disease – namely hyperglycemia and hyperlipidemia. Insulin has been the mainstay treatment for T1DM for several decades. There are now several formulations of insulin – both long and short acting – that, if taken appropriately, have proven effective at managing hyperglycemia and reducing the risk of cardiovascular events in T1DM. A number of drugs are currently available to treat T2DM, and most are quite effective at reducing hyperglycemia and/or hyperlipidemia. However, the majority do not improve – or may even exacerbate – the risk of cardiovascular events. The section that follows will review the cardiovascular effects of current and new therapies that are emerging to treat the hyperglycemia and hyperlipidemia seen in T2DM.

Current pharmacotherapies

Sulfonylureas & meglitinides—Sulfonylureas are the first class of insulin secretagogues, and even though they have been available since the early 1960s, they remain the first-line therapy for a number of patients with T2DM. Sulfonylureas bind and inhibit K_{ATP} at the pancreatic- β islet cell plasma membrane, prolonging depolarization and resulting in increased insulin secretion. First-generation sulfonylureas, such as tolbutamide, have been shown to bind cardiac K_{ATP} channels (even though they exhibit some structural differences from pancreatic isoforms). They may oppose the likely effects of high intracellular long-chain FA concentrations in prolonging hyperpolarization in the obese and diabetic, and may help to normalize cardiac APD and contractility. As such, they may be beneficial for obese and diabetic patients without ischemic heart disease. However, caution should be used in patients with known ischemic heart disease, as these agents have been shown to produce arrhythmia, reduce coronary blood flow and increase infarct size, and impair the recovery of contractile function following ischemia in animal studies [150,151]. Glimepiride, a newer and more pancreas-specific sulfonylurea, appears not to interact with cardiac K_{ATP} channels, and may be a better choice for this population [152].

The meglitinides, such as nateglinide and repaglinide, are a newer class of faster and shorter acting insulin secretagogues that, like sulfonylureas, also act by closing islet cell potassium channels. Owing to their more rapid metabolism, they are only taken preprandially, and are less likely than sulfonylureas to cause overshoot hypoglycemia [153]. They also have more

modest effects on glycosylated hemoglobin (Hg_{A1c}), and few if any effects on lipid metabolism [154]. As with sulfonylureas, increased coronary events have been observed in meglitinide-treated patients with ischemic heart disease, and caution should be exercised when considering this pharmaceutical class when designing a treatment regimen for this group.

Biguanides—Biguanides, a class of drugs of which metformin is the only drug still on the market in most countries, act by inhibiting hepatic gluconeogenesis, increasing glucose uptake in heart and skeletal muscle, and reducing glucose absorption from the gut. Metformin improves both lipid and glucose metabolism, reducing Hg_{A1c} without weight gain [154]. Furthermore, metformin has been associated with less cardiovascular morbidity and mortality in heart failure patients when compared with sulfonylureas [155]. Metformin, however, may not be an ideal choice for patients with cardiovascular disease – for at least three reasons. First, many patients on metformin experience malabsorption of folate and vitamin B12, with a concomitant increase in plasma homocysteine levels [156]. This is likely to raise the risk of atherothrombotic events by interfering with normal platelet, clotting factor and endothelial function. Second, there is at least a theoretical risk of lactic acidosis – especially for patients with heart failure or those who have recently experienced a myocardial infarction. Two other drugs in this class, phenformin and buformin, were withdrawn from most markets in the 1970s owing to an increased risk of lactic acidosis and cardiovascular mortality [154,157]. However, a recent rodent study concluded that metformin is actually cardioprotective in ischemic heart failure – via the activation of AMPK and its downstream mediators, eNOS and PGC-1 α [158]. Finally, metformin's rate of renal clearance is reduced when given with nifedipine or furosemide – two drugs commonly prescribed to patients with hypertension and heart failure [154]. Adjustments must be made for patients with renal insufficiency to keep metformin plasma levels in a therapeutic range.

Thiazolidinediones—Thiazolidinediones (also known as glitazones), such as rosiglitazone and troglitazone, are PPAR- β agonists and act primarily in adipose tissue to increase the storage of triglycerides there, reducing their concentration in the circulation, with a concomitant increase in insulin sensitivity in the heart and other tissues. Although this class is much less effective than sulfonylureas at lowering Hg_{A1c} , it is more effective at lowering plasma triglycerides (by 10–20% on average), and modestly increasing high-density lipoprotein concentrations. However, TZDs also raise low-density lipoproteins [159], and a recent rodent study indicates that PPAR- β overexpression in heart leads to myocardial lipogenesis, although this effect has not yet been corroborated in humans [27]. TZDs also cause a decrease in both atrial natriuretic peptide and brain natriuretic peptide levels, potentially resulting in increased volume status. Combined with increased TZD-associated VEGF expression, this may increase vascular permeability and the propensity to develop edema. As a consequence, TZDs are contraindicated in heart failure patients classified as New York Heart Association class III and above. In addition, TZDs caused weight gain secondary to hyperphagia in a number of patients by lowering leptin levels [160]. A recent meta-analysis of rosiglitazone found a significantly increased risk of myocardial infarction, and a borderline significantly increased risk of all-cause cardiovascular mortality [161]. Internal US FDA reports released on 19 February 2010 indicate that 6000 myocardial

infarctions and 3600 cases of heart failure could be avoided annually in the USA if patients currently taking rosiglitazone were switched to pioglitazone. As a consequence, the agency is currently considering removing rosiglitazone from the market [162].

Fibrates—Fibrates, such as fenofibrate and ciprofibrate, are PPAR- α agonists that act directly on the heart and other tissues that metabolize a large amount of FAs to increase the expression of proteins involved in FA uptake and β -oxidation. As a result, circulating FA levels are reduced with generally beneficial systemic effects. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study observed a reduction in total cardiovascular disease events (the study's secondary end point), but not a statistically significant reduction in major coronary events (the primary end point) [163]. However, in ischemic heart disease fibrates may do more harm than good. As noted previously, rodent models overexpressing PPAR- α demonstrate a phenotype similar to diabetic cardiomyopathy [19]. Dewald *et al.* argue that the downregulation of PPAR- α may be a compensatory adaptation to protect the heart from lipotoxicity [164], and long-term PPAR- α agonism may have the opposite effect. However, this point is contested, and Saunders *et al.* argue reduced PPAR- α activity and isoform switching to PPAR- β in late-stage diabetic cardiomyopathy is a larger determinant of lipotoxicity [15]. In their view, long-term PPAR- α agonism should restore the heart's ability to oxidize FAs, limiting lipotoxicity. The results of the FIELD study, although not conclusive, do not contradict this view.

Novel pharmacotherapies

Early-stage clinical trials are being conducted on compounds that may directly target myocardial fibrosis – one of the hallmarks of diabetic cardiomyopathy. One of these involves pyridoxamine, which is being investigated for its ability to inhibit the formation of advanced glycosylated end products (AGEs). The development of safe and effective AGE crosslink breakers would also be a significant advance. Trials of an AGE crosslink breaker, alanine aminotransferase 711, appeared promising in the early 2000s, but did not advance beyond Phase II trials.

The unsatisfactory cardiovascular risk profile of a number of existing antihyperglycemic and antihyperlipidemic therapies has led to the investigation of novel compounds for these indications. Among the most promising are agonists of multiple PPAR isoforms, incretin mimetics and dipeptidyl peptidase (DPP)-4 antagonists. Although there are theoretical reasons to believe these drugs may have fewer cardiovascular side effects, robust outcomes data do not yet exist.

Agonists of multiple PPAR isoforms—Since PPAR- β reduces circulating FAs by sequestering them in adipose tissue, and PPAR- α improves β -oxidation in end organs, it is reasonable to hypothesize that they may act synergistically. Indeed, pharmaceutical companies have recently invested great sums to develop a number of dual PPAR agonists (known as glitizars). Unfortunately, none has advanced beyond Phase III clinical trials owing to safety concerns, including cardiovascular events, hepatotoxicity and neoplasia. Interestingly, bezafibrate, a pan-PPAR agonist, has been available since the 1980s and has proven effective at reducing many of the cardiovascular risk factors associated with T2DM –

increasing plasma high-density lipoprotein and adiponectin levels, improving insulin sensitivity in a number of tissues, lowering plasma levels of glucose and triglycerides, and attenuating the progression of insulin resistance to overt T2DM [165,166]. As a result, patients with metabolic syndrome treated with bezafibrate have experienced a significant reduction in myocardial infarctions and other cardiovascular events, and fewer have progressed to full-blown T2DM [167].

There are two significant differences between bezafibrate and the newer glitazars. First, bezafibrate is a much less potent PPAR ligand than the glitazars. More potent and sustained agonism, particularly of PPAR- β , may lead to lipotoxicity if FA uptake exceeds β -oxidation, or if metabolites get shunted to an alternative pathway leading to the build-up of ceramide and other toxic lipids. Second, bezafibrate activates not only PPAR- α and PPAR- β , but also PPAR- β and PPAR- δ . Although our understanding of these isoforms is limited, PPAR- δ agonists have been shown to reduce obesity and normalize a number of metabolic parameters in rodent models [154,168]. The development of somewhat less potent dual PPAR- α and PPAR- β agonists may prove more effective than either fibrates or thiazolidinediones alone, with greater safety than the current crop of glitazones. Alternatively, somewhat more potent pan-PPAR agonists may prove more beneficial than bezafibrate and with a similar safety profile.

Incretin mimetics—Incretins are gastrointestinal hormones that are released postprandially and potentiate insulin secretion from the pancreas. They are also thought to exert cytoprotective and antiapoptotic effects on pancreatic β islet cells – significant effects since β -cell depletion is a defining pathology of T1DM and also occurs late in the progression of T2DM. Incretins were discovered in the 1960s following the observation that more insulin is secreted in response to an oral glucose load than to intravenous delivery of an equivalent amount of glucose [169]. Glucagon-like peptide (GLP)-1 is one such incretin, and its secretion and activity are impaired in T2DM. Glucagon and GLP-1 are released during periods of hypoglycemia, stimulating hepatic glycogenolysis and the release of glucose into the circulation. They also promote insulin secretion to help drive this glucose into the heart, skeletal muscle and other insulin-responsive tissues, inhibit further glucagon secretion, and normalize fasting plasma glucose levels. They are thought to exert their cytoprotective and antiapoptotic effects on pancreatic β islet cells by reducing endoplasmic reticulum stress due to the overproduction or misfolding of insulin [170].

Glucagon-like peptide-1 itself has a very short half-life (1 h) and is thus unsuitable in its endogenous form as a pharmaceutical agent. Longer acting formulations based on GLP-1 have been developed and have proven effective at slowing the rate of glucose entering the bloodstream. They are also as effective as sulfonylureas and metformin at reducing hyperglycemia [171]. Exenatide, the first of this class of drugs (approved by the US FDA in 2005), is available in twice-daily injections, and an extended-release preparation is currently in clinical trials. Liraglutide, another extended release formulation, has been on the market in the EU since July 2009, and is under review by the FDA. Albiglutide and taspoglutide are additional long-acting incretin mimetics currently in clinical trials.

Long-term studies on cardiovascular risks and benefits of incretin mimetics have not yet been carried out. Intriguingly, rodent studies have demonstrated the presence of GLP-1 receptors on cardiomyocytes [172], and the exogenous administration of GLP-1 has positive inotropic effects – significantly increasing cardiac output by reducing LV end-diastolic volume and increasing stroke volume [173]. Similar results have been observed in a small cohort of human subjects [174], but further data are required to delineate more clearly cardiac risks and benefits.

Dipeptidyl peptidase-4 antagonists—Dipeptidyl peptidase-4 cleaves a number of proteins at alanine and proline residues. The incretins GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are targets of DPP-4. DPP-4 inhibitors, such as sitagliptin or vildagliptin, preserve GLP-1 and GIP levels and, thus, function similarly to incretin mimetics by potentiating insulin secretion and inhibiting glucagon release. One advantage of DPP-4 inhibitors is that they are administered orally, versus subcutaneous injection for the incretin mimetics. Since they allow insulin and glucagon levels to normalize rapidly following blood glucose normalization, they are less likely to cause overshoot hypoglycemia that can be seen with the administration of insulin and some other antihyperglycemic agents [154]. In addition, both incretin mimetics and DPP-4 antagonists do not contribute to the weight gain seen with insulin and insulin secretagogues, and are thus likely to reduce obesity and adipokine release [154]. However, sitagliptin use is associated with a 34% increase in relative risk of all-cause infections [175]. There are currently no long-term cardiovascular event data for DPP-4 inhibitors.

Genetic & cellular therapies

The limited efficacy of current drugs in preventing the progression to heart failure in patients with diabetic cardiomyopathy has spurred the investigation of novel approaches including gene- and cell-based therapeutic strategies. Genetic correction (through vector-based gene transfer) of abnormalities in cardiac excitation–contraction coupling and insulin signaling are emerging as a potential targets in the treatment of heart failure. These interventions are specifically aimed at blocking the underlying remodeling processes, which drive pathological myocardial cellular changes in heart failure. These include manipulating *SERCA2a*, *NCX* and *Akt* expression, RyR stabilization, CaMKII inhibition, PI3K activation, and stimulation of glucose oxidation [176–178]. Ongoing clinical trials transfecting *SERCA2a* in patients with advanced heart failure are currently underway [179]. Other genes are likely to be targeted soon in human trials. However, design of appropriate delivery methods, limited packaging capacity and expression efficiency, inconsistencies in bioactivity and purity between vector stocks, potential off-target effects, and biosafety risks (including the generation of a replication-competent virus, toxicity due to viral gene products and insertional mutagenesis when integrated vectors are used) remain significant challenges.

Considerable effort is also being directed towards the potential of cardiac cell repair therapy [180–184]. Current efforts to enhance the regenerative capacity of the mammalian myocardium follow two directions: transplantation of embryonic stem (ES) cells, and the stimulation of the endogenous proliferative potential of differentiated cardiomyocytes.

Although the stem cell approach has made significant progress, several challenges remain, including proper ES cell identification, isolation, *in vitro* propagation and transplantation [185,186]. Initial clinical data from patients who received stem cell therapy (~1000 patients worldwide) indicate modest improvement in cardiac function and acceptable safety profile [184].

The recent breakthrough to generate induced pluripotent stem (iPS) cells from somatic tissue through nuclear reprogramming to an embryonic state has generated great excitement and renewed interest in stem cell research and therapeutic applications. This new technology raises the possibility for establishing patient-specific human ES-like stem cells, which would carry the same genetic background as the patients. Already a number of patient-specific iPS cell human disease models have been generated, including amyotrophic lateral sclerosis and Parkinson's disease [187]. Likewise, human iPS cells have been shown to generate functional cardiomyocytes that exhibit properties similar to ES cell-derived cardiomyocytes [188,189]. Diabetic cardiomyopathy-specific pluripotent cells capable of differentiation into cardiomyocytes could undoubtedly provide new insights into disease pathophysiology by permitting *in vitro* analysis in a human system, specific to the underlying genetic make-up of the patient. However, whether iPS cell-derived cardiomyocytes exhibit physiological and biochemical characteristics seen in native cardiomyocytes remains to be determined.

Recent studies suggest that mammalian cardiomyocytes retain the latent potential to proliferate. Cell cycle activity in the region bordering a myocardial infarction increases transiently tenfold [190]. This has stimulated interest in developing therapeutic approaches to increase cardiomyocyte proliferation to enhance cardiac repair. Activating the cardiomyocyte cell cycle with simian virus 40 large T antigen, cyclin A2, cyclin D2 and dominant-negative p53 and p193 increases cardiomyocyte proliferation and reduces infarct scar size [191–195].

Using extracellular factors to induce endogenous cardiomyocytes to proliferate also shows promise. A large body of recent evidence suggests that the mechanism of effect is paracrine in nature, as paracrine factors secreted by transplanted cells may be responsible for their therapeutic benefits [196]. Administration of FGF with a concurrent inhibition of p38 MAPK increases cardiomyocyte cycling, reduces infarct scar size and improves function [197,198]. Periostin, through the activation of the integrins/PI3K axis, and neuregulin-1 signaling through ErbB4 have been shown to induce the proliferation of differentiated cardiomyocytes, resulting in structural and functional improvements after myocardial infarction [199,200]. Although cell-based therapies may hold a great promise for the treatment of heart failure, additional research is necessary to clarify the mechanisms by which they exert their effects.

Exercise

While there still isn't a magic bullet to treat diabetic cardiomyopathy, it has long been known that regular aerobic exercise improves the prognosis for patients with cardiovascular disease [201]. Those with diabetic cardiomyopathy are no exception. Conversely, those patients who do not get regular exercise experience higher risks of cardiovascular morbidity and mortality [202]. Exercise improves insulin and glucose sensitivity in insulin-resistant

humans and animals [203], likely by increasing expression of *AMPK*, *PGC-1 α* and other genes involved in mitochondrial biogenesis [204,205]. Mitochondrial density, size and oxidative capacity increase in both skeletal muscle and the heart as a result, improving glucose and FA metabolism [38,205]. Thus, by improving mitochondrial biogenesis and function, exercise may delay the progression of diabetic cardiomyopathy and improve the prognosis of patients with the disease.

Conclusion

Diabetic cardiomyopathy is a complex and multifactorial disease characterized by dysregulated cardiac lipid metabolism, insulin resistance, altered response to adipokines and mitochondrial dysfunction. These defects interact with each other and contribute to impaired calcium homeostasis, ultimately leading to ventricular contractile dysfunction independent of exogenous factors such as CAD or hypertension. Although a number of current therapies effectively treat hyperglycemia and hyperlipidemia – key markers of diabetes – many have adverse cardiovascular effects, and none directly target the cardiac manifestations of diabetes. It is possible that newer compounds such as agonists of multiple PPAR isoforms, incretin mimetics and DPP-4 antagonists may offer similar benefits with fewer cardiovascular side effects. Gene and cell therapies are currently being developed to directly target molecules involved in the pathogenesis of diabetic cardiomyopathy. Clinical trials of these new modalities are currently underway, including those that deliver *SERCA2a* to patients with advanced heart failure. Gene and cell therapies aimed at a number of other targets associated with diabetic cardiomyopathy are in development and may increase the treatment options available to clinicians in the coming years.

Expert commentary & five-year view

Despite significant progress over the last few decades, many gaps remain in our understanding of the pathogenesis of diabetic cardiomyopathy. Cardiac insulin resistance plays a critical role and is influenced by dysregulated lipid metabolism, adipokine production and mitochondrial dysfunction. The resulting impairment to calcium homeostasis leads to the inotropic and lusitropic defects that characterize the clinical presentation of the disease. Less well established are the precise ways in which these axes mutually reinforce or antagonize each other. The recent discovery that Akt can directly phosphorylate the *SERCA2a* regulatory protein PLB highlights a direct interaction between the insulin metabolic pathway and calcium-handling pathways. Over the next several years, investigators will undoubtedly shed more light on these inter-relationships. It is also likely we will have a clearer picture of the cardiovascular role of a number of adipokines – in particular the conditions under which leptin may be cardioprotective versus cardiotoxic, and the mechanisms by which resistin exerts its metabolic and calcium modulatory effects. It is also conceivable that other adipokines such as apelin, visfatin and chemerin may prove to have significant effects on the heart.

Current therapies effectively treat hyperglycemia and hyperlipidemia – but many have adverse cardiovascular effects. It is possible that newer compounds such as agonists of multiple PPAR isoforms, incretin mimetics and DPP-4 antagonists may offer similar benefits

with fewer cardiovascular side effects. Gene and cell therapies are currently being developed to address cases where pharmacotherapies are unlikely to succeed. Gene therapy clinical trials are currently underway, including those that deliver SERCA2a to patients with advanced heart failure. Over the next several years we are likely to gain a more robust understanding of appropriate delivery methods – improving expression efficiency and efficacy, which should reduce the likelihood of cardiotoxicity and the potential for off-target effects. Cell-based therapies, especially those that stimulate the heart's endogenous regenerative capacity, and those engineered from iPS cells, may allow for the development of personalized therapies, and are likely to play an increasingly prominent role in the years to come.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation*. 1979; 59(1):8–13. [PubMed: 758126]
- 2•. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol*. 1972; 30(6):595–602. First investigation that had reported the existence of diabetic cardiomyopathy independent of coronary artery disease, hypertension or other comorbidities. [PubMed: 4263660]
3. Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. *Circ Res*. 2006; 98(5):596–605. [PubMed: 16543510]
- 4••. Davidoff AJ. Convergence of glucose- and fatty acid-induced abnormal myocardial excitation–contraction coupling and insulin signalling. *Clin Exp Pharmacol Physiol*. 2006; 33(1–2):152–158. Explores the role of fatty acids, glucose and its metabolites as regulators of myocardial excitation–contraction coupling and insulin resistance. The emerging role of cytoplasmic and nuclear O-linked glycosylation in cardiac biology is discussed. [PubMed: 16445715]
5. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. *Circ Res*. 2000; 87(12):1123–1132. [PubMed: 11110769]
6. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev*. 2004; 25(4):543–567. [PubMed: 15294881]
7. Carugo S, Giannattasio C, Calchera I, et al. Progression of functional and structural cardiac alterations in young normotensive uncomplicated patients with Type 1 diabetes mellitus. *J Hypertens*. 2001; 19(9):1675–1680. [PubMed: 11564989]
8. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE. Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. *Cardiology*. 2002; 98(1–2):33–39. [PubMed: 12373045]
9. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. *Am J Med*. 2008; 121(9):748–757. [PubMed: 18724960]
10. An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2006; 291(4):H1489–H1506. [PubMed: 16751293]
11. Lopaschuk GD, Belke DD, Gamble J, Itoi T, Schonekess BO. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta*. 1994; 1213(3):263–276. [PubMed: 8049240]
12. Goodwin GW, Taegtmeyer H. Regulation of fatty acid oxidation of the heart by MCD and ACC during contractile stimulation. *Am J Physiol*. 1999; 277(4 Pt 1):E772–E777. [PubMed: 10516138]

13. Kudo N, Barr AJ, Barr RL, Desai S, Lopaschuk GD. High rates of fatty acid oxidation during reperfusion of ischemic hearts are associated with a decrease in malonyl-CoA levels due to an increase in 5'-AMP-activated protein kinase inhibition of acetyl-CoA carboxylase. *J Biol Chem.* 1995; 270(29):17513–17520. [PubMed: 7615556]
14. Moller DE. New drug targets for Type 2 diabetes and the metabolic syndrome. *Nature.* 2001; 414(6865):821–827. [PubMed: 11742415]
15. Saunders J, Mathewkutty S, Drazner MH, McGuire DK. Cardiomyopathy in Type 2 diabetes: update on pathophysiological mechanisms. *Herz.* 2008; 33(3):184–190. [PubMed: 18568312]
16. Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor β coactivator-1 promotes cardiac mitochondrial biogenesis. *J Clin Invest.* 2000; 106(7):847–856. [PubMed: 11018072]
17. Lopaschuk GD, Folmes CD, Stanley WC. Cardiac energy metabolism in obesity. *Circ Res.* 2007; 101(4):335–347. Interesting review that discusses the effects of obesity and adipokines on cardiac metabolism, cardiac function and insulin signaling. [PubMed: 17702980]
18. Leone TC, Weinheimer CJ, Kelly DP. A critical role for the peroxisome proliferator-activated receptor α (PPAR α) in the cellular fasting response: the PPAR α -null mouse as a model of fatty acid oxidation disorders. *Proc Natl Acad Sci USA.* 1999; 96(13):7473–7478. [PubMed: 10377439]
19. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPAR α overexpression mimics that caused by diabetes mellitus. *J Clin Invest.* 2002; 109(1):121–130. [PubMed: 11781357]
20. Boudina S, Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED. Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. *Circulation.* 2005; 112(17):2686–2695. [PubMed: 16246967]
21. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation.* 2004; 109(18):2191–2196. [PubMed: 15123530]
22. Lee Y, Naseem RH, Duplomb L, et al. Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. *Proc Natl Acad Sci USA.* 2004; 101(37):13624–13629. [PubMed: 15347805]
23. Lowell BB, Shulman GI. Mitochondrial dysfunction and Type 2 diabetes. *Science.* 2005; 307(5708):384–387. [PubMed: 15662004]
24. Savage DB, Petersen KF, Shulman GI. Mechanisms of insulin resistance in humans and possible links with inflammation. *Hypertension.* 2005; 45(5):828–833. [PubMed: 15824195]
25. Unger RH. Lipotoxic diseases. *Annu Rev Med.* 2002; 53:319–336. [PubMed: 11818477]
26. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci USA.* 2000; 97(4):1784–1789. [PubMed: 10677535]
27. Son NH, Park TS, Yamashita H, et al. Cardiomyocyte expression of PPAR β leads to cardiac dysfunction in mice. *J Clin Invest.* 2007; 117(10):2791–2801. [PubMed: 17823655]
28. Susic D, Varagic J, Ahn J, Frohlich ED. Collagen cross-link breakers: a beginning of a new era in the treatment of cardiovascular changes associated with aging, diabetes, and hypertension. *Curr Drug Targets Cardiovasc Haematol Disord.* 2004; 4(1):97–101. [PubMed: 15032654]
29. Folmes CD, Clanachan AS, Lopaschuk GD. Fatty acids attenuate insulin regulation of 5'-AMP-activated protein kinase and insulin cardioprotection after ischemia. *Circ Res.* 2006; 99(1):61–68. [PubMed: 16741157]
30. Bidasee KR, Nallani K, Yu Y, et al. Chronic diabetes increases advanced glycation end products on cardiac ryanodine receptors/ calcium-release channels. *Diabetes.* 2003; 52(7):1825–1836. [PubMed: 12829653]
31. Bidasee KR, Zhang Y, Shao CH, et al. Diabetes increases formation of advanced glycation end products on Sarco(endo) plasmic reticulum Ca^{2+} -ATPase. *Diabetes.* 2004; 53(2):463–473. [PubMed: 14747299]
32. Fulop N, Marchase RB, Chatham JC. Role of protein O-linked N-acetyl-glucosamine in mediating cell function and survival in the cardiovascular system. *Cardiovasc Res.* 2007; 73(2):288–297. [PubMed: 16970929]

33. Abel ED. Myocardial insulin resistance and cardiac complications of diabetes. *Curr Drug Targets Immune Endocr Metabol Disord*. 2005; 5(2):219–226. [PubMed: 16089356]
34. Ouwens DM, Diamant M. Myocardial insulin action and the contribution of insulin resistance to the pathogenesis of diabetic cardiomyopathy. *Arch Physiol Biochem*. 2007; 113(2):76–86. Excellent review of current concepts of insulin signaling and excitation–contraction coupling. [PubMed: 17558606]
35. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol*. 2008; 51(2):93–102. [PubMed: 18191731]
36. Pang TT, Narendran P. Addressing insulin resistance in Type 1 diabetes. *Diabet Med*. 2008; 25(9):1015–1024. [PubMed: 19183305]
37. Zick Y. Ser/Thr phosphorylation of IRS proteins: a molecular basis for insulin resistance. *Sci STKE*. 2005; 2005(268):pe4. [PubMed: 15671481]
38. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res*. 2008; 102(4):401–414. [PubMed: 18309108]
39. Zhande R, Mitchell JJ, Wu J, Sun XJ. Molecular mechanism of insulin-induced degradation of insulin receptor substrate 1. *Mol Cell Biol*. 2002; 22(4):1016–1026. [PubMed: 11809794]
40. Egawa K, Maegawa H, Shimizu S, et al. Protein-tyrosine phosphatase-1B negatively regulates insulin signaling in I6 myocytes and Fao hepatoma cells. *J Biol Chem*. 2001; 276(13):10207–10211. [PubMed: 11136729]
41. Vinciguerra M, Foti M. PTEN and SHIP2 phosphoinositide phosphatases as negative regulators of insulin signalling. *Arch Physiol Biochem*. 2006; 112(2):89–104. [PubMed: 16931451]
42. Hardie DG, Carling D, Carlson M. The AMP-activated/SNF1 protein kinase subfamily: metabolic sensors of the eukaryotic cell? *Annu Rev Biochem*. 1998; 67:821–855. [PubMed: 9759505]
43. Kim JK, Fillmore JJ, Sunshine MJ, et al. PKC- θ knockout mice are protected from fat-induced insulin resistance. *J Clin Invest*. 2004; 114(6):823–827. [PubMed: 15372106]
44. Purdham DM, Zou MX, Rajapurohitam V, Karmazyn M. Rat heart is a site of leptin production and action. *Am J Physiol Heart Circ Physiol*. 2004; 287(6):H2877–H2884. [PubMed: 15284063]
45. Kloeck C, Haq AK, Dunn SL, Lavery HJ, Banks AS, Myers MG Jr. Regulation of JAK kinases by intracellular leptin receptor sequences. *J Biol Chem*. 2002; 277(44):41547–41555. [PubMed: 12196522]
46. White DW, Kuropatwinski KK, Devos R, Baumann H, Tartaglia LA. Leptin receptor (OB-R) signaling. Cytoplasmic domain mutational analysis and evidence for receptor homo-oligomerization. *J Biol Chem*. 1997; 272(7):4065–4071. [PubMed: 9020115]
47. Banks AS, Davis SM, Bates SH, Myers MG Jr. Activation of downstream signals by the long form of the leptin receptor. *J Biol Chem*. 2000; 275(19):14563–14572. [PubMed: 10799542]
48. Eyckerman S, Broekaert D, Verhee A, Vandekerckhove J, Tavernier J. Identification of the Y985 and Y1077 motifs as SOCS3 recruitment sites in the murine leptin receptor. *FEBS Lett*. 2000; 486(1):33–37. [PubMed: 11108838]
49. Munzberg H, Bjornholm M, Bates SH, Myers MG Jr. Leptin receptor action and mechanisms of leptin resistance. *Cell Mol Life Sci*. 2005; 62(6):642–652. [PubMed: 15770417]
50. Bates SH, Myers MG. The role of leptin-->STAT3 signaling in neuroendocrine function: an integrative perspective. *J Mol Med*. 2004; 82(1):12–20. [PubMed: 14557860]
51. Dunn SL, Bjornholm M, Bates SH, Chen Z, Seifert M, Myers MG Jr. Feedback inhibition of leptin receptor/JAK2 signaling via Tyr1138 of the leptin receptor and suppressor of cytokine signaling 3. *Mol Endocrinol*. 2005; 19(4):925–938. [PubMed: 15604114]
52. Karmazyn M, Kilic A, Javadov S. The role of NHE-1 in myocardial hypertrophy and remodelling. *J Mol Cell Cardiol*. 2008; 44(4):647–653. [PubMed: 18329039]
53. Nickola MW, Wold LE, Colligan PB, Wang GJ, Samson WK, Ren J. Leptin attenuates cardiac contraction in rat ventricular myocytes. Role of NO. *Hypertension*. 2000; 36(4):501–505. [PubMed: 11040226]
54. Rajapurohitam V, Javadov S, Purdham DM, Kirshenbaum LA, Karmazyn M. An autocrine role for leptin in mediating the cardiomyocyte hypertrophic effects of angiotensin II and endothelin-1. *J Mol Cell Cardiol*. 2006; 41(2):265–274. [PubMed: 16806260]

55. Zeidan A, Javadov S, Karmazyn M. Essential role of Rho/ROCK-dependent processes and actin dynamics in mediating leptin-induced hypertrophy in rat neonatal ventricular myocytes. *Cardiovasc Res*. 2006; 72(1):101–111. [PubMed: 16901475]
56. Zeidan A, Javadov S, Chakrabarti S, Karmazyn M. Leptin-induced cardiomyocyte hypertrophy involves selective caveolae and RhoA/ROCK-dependent p38 MAPK translocation to nuclei. *Cardiovasc Res*. 2008; 77(1):64–72. [PubMed: 18006472]
57. Karmazyn M, Purdham DM, Rajapurohitam V, Zeidan A. Leptin as a cardiac hypertrophic factor: a potential target for therapeutics. *Trends Cardiovasc Med*. 2007; 17(6):206–211. [PubMed: 17662916]
58. Smith CC, Mocanu MM, Davidson SM, Wynne AM, Simpkin JC, Yellon DM. Leptin, the obesity-associated hormone, exhibits direct cardioprotective effects. *Br J Pharmacol*. 2006; 149(1):5–13. [PubMed: 16847434]
59. McGaffin KR, Sun CK, Rager JJ, et al. Leptin signalling reduces the severity of cardiac dysfunction and remodelling after chronic ischaemic injury. *Cardiovasc Res*. 2008; 77(1):54–63. [PubMed: 18006469]
60. Palanivel R, Eguchi M, Shuralyova I, Coe I, Sweeney G. Distinct effects of short- and long-term leptin treatment on glucose and fatty acid uptake and metabolism in HL-1 cardiomyocytes. *Metabolism*. 2006; 55(8):1067–1075. [PubMed: 16839843]
61. Atkinson LL, Fischer MA, Lopaschuk GD. Leptin activates cardiac fatty acid oxidation independent of changes in the AMP-activated protein kinase–acetyl-CoA carboxylase–malonyl-CoA axis. *J Biol Chem*. 2002; 277(33):29424–29430. [PubMed: 12058043]
62. Haap M, Houdali B, Maerker E, et al. Insulin-like effect of low-dose leptin on glucose transport in Langendorff rat hearts. *Exp Clin Endocrinol Diabetes*. 2003; 111(3):139–145. [PubMed: 12784187]
63. Lee Y, Wang MY, Kakuma T, et al. Liporegulation in diet-induced obesity. The antisteatotic role of hyperleptinemia. *J Biol Chem*. 2001; 276(8):5629–5635. [PubMed: 11096093]
64. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology*. 2003; 144(8):3483–3490. [PubMed: 12865329]
65. Young ME, Guthrie PH, Razeghi P, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes*. 2002; 51(8):2587–2595. [PubMed: 12145175]
66. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and Type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001; 86(5):1930–1935. [PubMed: 11344187]
67. Mohan V, Deepa R, Pradeepa R, et al. Association of low adiponectin levels with the metabolic syndrome – the Chennai Urban Rural Epidemiology Study (CURES-4). *Metabolism*. 2005; 54(4):476–481. [PubMed: 15798954]
68. Iwashima Y, Katsuya T, Ishikawa K, et al. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension*. 2004; 43(6):1318–1323. [PubMed: 15123570]
69. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA*. 2004; 291(14):1730–1737. [PubMed: 15082700]
70. Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB. Adiponectin and future coronary heart disease events among men with Type 2 diabetes. *Diabetes*. 2005; 54(2):534–539. [PubMed: 15677512]
71. Takano H, Obata JE, Kodama Y, et al. Adiponectin is released from the heart in patients with heart failure. *Int J Cardiol*. 2009; 132(2):221–226. [PubMed: 18192035]
72. Lawlor DA, Davey Smith G, Ebrahim S, Thompson C, Sattar N. Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. *J Clin Endocrinol Metab*. 2005; 90(10):5677–5683. [PubMed: 16076942]
73. Shibata R, Ouchi N, Ito M, et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat Med*. 2004; 10(12):1384–1389. [PubMed: 15558058]
74. Liao Y, Takashima S, Maeda N, et al. Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovasc Res*. 2005; 67(4):705–713. [PubMed: 15907819]

75. Shibata R, Sato K, Pimentel DR, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med.* 2005; 11(10): 1096–1103. [PubMed: 16155579]
76. Tao L, Gao E, Jiao X, et al. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. *Circulation.* 2007; 115(11):1408–1416. [PubMed: 17339545]
77. Karmazyn M, Purdham DM, Rajapurohitam V, Zeidan A. Signaling mechanisms underlying the metabolic and other effects of adipokines on the heart. *Cardiovasc Res.* 2008; 79(2):279–286. [PubMed: 18474523]
78. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature.* 2001; 409(6818):307–312. [PubMed: 11201732]
79. Rajala MW, Lin Y, Ranalletta M, et al. Cell type-specific expression and coregulation of murine resistin and resistin-like molecule- α in adipose tissue. *Mol Endocrinol.* 2002; 16(8):1920–1930. [PubMed: 12145345]
80. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. *Trends Endocrinol Metab.* 2002; 13(1):18–23. [PubMed: 11750858]
81. Palanivel R, Maida A, Liu Y, Sweeney G. Regulation of insulin signalling, glucose uptake and metabolism in rat skeletal muscle cells upon prolonged exposure to resistin. *Diabetologia.* 2006; 49(1):183–190. [PubMed: 16341686]
82. Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA. Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated Type II diabetic patients. *Int J Obes Relat Metab Disord.* 2004; 28(6):783–789. [PubMed: 15024400]
83. Heilbronn LK, Rood J, Janderoova L, et al. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *J Clin Endocrinol Metab.* 2004; 89(4):1844–1848. [PubMed: 15070954]
84. Lee JH, Chan JL, Yiannakouris N, et al. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab.* 2003; 88(10):4848–4856. [PubMed: 14557464]
85. Kim M, Oh JK, Sakata S, et al. Role of resistin in cardiac contractility and hypertrophy. *J Mol Cell Cardiol.* 2008; 45(2):270–280. [PubMed: 18597775]
86. Graveleau C, Zaha VG, Mohajer A, et al. Mouse and human resistins impair glucose transport in primary mouse cardiomyocytes, and oligomerization is required for this biological action. *J Biol Chem.* 2005; 280(36):31679–31685. [PubMed: 15983036]
87. Wang BW, Hung HF, Chang H, Kuan P, Shyu KG. Mechanical stretch enhances the expression of resistin gene in cultured cardiomyocytes via tumor necrosis factor- α . *Am J Physiol Heart Circ Physiol.* 2007; 293(4):H2305–H2312. [PubMed: 17573461]
88. Ghosh S, Singh AK, Aruna B, Mukhopadhyay S, Ehtesham NZ. The genomic organization of mouse resistin reveals major differences from the human resistin: functional implications. *Gene.* 2003; 305(1):27–34. [PubMed: 12594039]
89. Pischon T, Bamberger CM, Kratzsch J, et al. Association of plasma resistin levels with coronary heart disease in women. *Obes Res.* 2005; 13(10):1764–1771. [PubMed: 16286524]
90. Takeishi Y, Niizeki T, Arimoto T, et al. Serum resistin is associated with high risk in patients with congestive heart failure – a novel link between metabolic signals and heart failure. *Circ J.* 2007; 71(4):460–464. [PubMed: 17384443]
91. Burnett MS, Devaney JM, Adenika RJ, Lindsay R, Howard BV. Cross-sectional associations of resistin, coronary heart disease, and insulin resistance. *J Clin Endocrinol Metab.* 2006; 91(1):64–68. [PubMed: 16249281]
92. McTernan PG, Fisher FM, Valsamakis G, et al. Resistin and Type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. *J Clin Endocrinol Metab.* 2003; 88(12):6098–6106. [PubMed: 14671216]

93. Efstathiou SP, Tsiakou AG, Tsioulos DI, et al. Prognostic significance of plasma resistin levels in patients with atherothrombotic ischemic stroke. *Clin Chim Acta*. 2007; 378(1–2):78–85. [PubMed: 17173885]
94. Endoh M. Signal transduction and Ca^{2+} signaling in intact myocardium. *J Pharmacol Sci*. 2006; 100(5):525–537. [PubMed: 16799263]
95. Hove-Madsen L, Bers DM. Sarcoplasmic reticulum Ca^{2+} uptake and thapsigargin sensitivity in permeabilized rabbit and rat ventricular myocytes. *Circ Res*. 1993; 73(5):820–828. [PubMed: 8403253]
96. Li L, Chu G, Kranias EG, Bers DM. Cardiac myocyte calcium transport in phospholamban knockout mouse: relaxation and endogenous CaMKII effects. *Am J Physiol*. 1998; 274(4 Pt 2):H1335–H1347. [PubMed: 9575939]
97. Choi KM, Zhong Y, Hoit BD, et al. Defective intracellular Ca^{2+} signaling contributes to cardiomyopathy in Type 1 diabetic rats. *Am J Physiol Heart Circ Physiol*. 2002; 283(4):H1398–H1408. [PubMed: 12234790]
98. Pereira L, Matthes J, Schuster I, et al. Mechanisms of $[\text{Ca}^{2+}]_i$ transient decrease in cardiomyopathy of *db/db* Type 2 diabetic mice. *Diabetes*. 2006; 55(3):608–615. [PubMed: 16505222]
99. Marx SO, Reiken S, Hisamatsu Y, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*. 2000; 101(4):365–376. [PubMed: 10830164]
100. Yaras N, Ugur M, Ozdemir S, et al. Effects of diabetes on ryanodine receptor Ca release channel (RyR2) and Ca^{2+} homeostasis in rat heart. *Diabetes*. 2005; 54(11):3082–3088. [PubMed: 16249429]
101. Lehnart SE, Maier LS, Hasenfuss G. Abnormalities of calcium metabolism and myocardial contractility depression in the failing heart. *Heart Fail Rev*. 2009; 14(4):213–224. [PubMed: 19434491]
102. Reiken S, Gaburjakova M, Guatimosim S, et al. Protein kinase A phosphorylation of the cardiac calcium release channel (ryanodine receptor) in normal and failing hearts. Role of phosphatases and response to isoproterenol. *J Biol Chem*. 2003; 278(1):444–453. [PubMed: 12401811]
103. Marks AR. Ryanodine receptors/calcium release channels in heart failure and sudden cardiac death. *J Mol Cell Cardiol*. 2001; 33(4):615–624. [PubMed: 11273716]
104. Lebeche D, Davidoff AJ, Hajjar RJ. Interplay between impaired calcium regulation and insulin signaling abnormalities in diabetic cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2008; 5(11):715–724. Interesting review that primarily focuses on the hypothesis that impaired Ca^{2+} regulation and insulin signaling contribute to the pathophysiology of diabetic cardiomyopathy. [PubMed: 18813212]
105. Zhong Y, Ahmed S, Grupp IL, Matlib MA. Altered SR protein expression associated with contractile dysfunction in diabetic rat hearts. *Am J Physiol Heart Circ Physiol*. 2001; 281(3):H1137–H1147. [PubMed: 11514280]
106. Sakata S, Lebeche D, Sakata Y, et al. Mechanical and metabolic rescue in a Type II diabetes model of cardiomyopathy by targeted gene transfer. *Mol Ther*. 2006; 13(5):987–996. [PubMed: 16503203]
107. Belke DD, Swanson EA, Dillmann WH. Decreased sarcoplasmic reticulum activity and contractility in diabetic *db/db* mouse heart. *Diabetes*. 2004; 53(12):3201–3208. [PubMed: 15561951]
108. Catalucci D, Latronico MV, Ceci M, et al. Akt increases sarcoplasmic reticulum Ca^{2+} cycling by direct phosphorylation of phospholamban at Thr17. *J Biol Chem*. 2009; 284(41):28180–28187. [PubMed: 19696029]
109. Wold LE, Dutta K, Mason MM, et al. Impaired SERCA function contributes to cardiomyocyte dysfunction in insulin resistant rats. *J Mol Cell Cardiol*. 2005; 39(2):297–307. [PubMed: 15878173]
110. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. Overexpression of the sarcoplasmic reticulum Ca^{2+} -ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes*. 2002; 51(4):1166–1171. [PubMed: 11916940]

111. del Monte F, Harding SE, Schmidt U, et al. Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation*. 1999; 100(23):2308–2311. [PubMed: 10587333]
112. Ranu HK, Terracciano CM, Davia K, et al. Effects of Na⁺/Ca²⁺-exchanger overexpression on excitation–contraction coupling in adult rabbit ventricular myocytes. *J Mol Cell Cardiol*. 2002; 34(4):389–400. [PubMed: 11991729]
113. Hattori Y, Matsuda N, Kimura J, et al. Diminished function and expression of the cardiac Na⁺–Ca²⁺ exchanger in diabetic rats: implication in Ca²⁺ overload. *J Physiol*. 2000; 527(Pt 1):85–94. [PubMed: 10944172]
114. Chattou S, Diacono J, Feuvray D. Decrease in sodium–calcium exchange and calcium currents in diabetic rat ventricular myocytes. *Acta Physiol Scand*. 1999; 166(2):137–144. [PubMed: 10383493]
115. Wang DW, Kiyosue T, Shigematsu S, Arita M. Abnormalities of K⁺ and Ca²⁺ currents in ventricular myocytes from rats with chronic diabetes. *Am J Physiol*. 1995; 269(4 Pt 2):H1288–H1296. [PubMed: 7485560]
116. Lu Z, Jiang YP, Xu XH, Ballou LM, Cohen IS, Lin RZ. Decreased L-type Ca²⁺ current in cardiac myocytes of Type 1 diabetic Akita mice due to reduced phosphatidylinositol 3-kinase signaling. *Diabetes*. 2007; 56(11):2780–2789. [PubMed: 17666471]
117. Shimoni Y, Firek L, Severson D, Giles W. Short-term diabetes alters K⁺ currents in ventricular myocytes. *Circ Res*. 1994; 74(4):620–628. [PubMed: 8137498]
118. Shimoni Y, Liu XF. Role of PKC in autocrine regulation of rat ventricular K⁺ currents by angiotensin and endothelin. *Am J Physiol Heart Circ Physiol*. 2003; 284(4):H1168–H1181. [PubMed: 12626328]
119. Liu GX, Hanley PJ, Ray J, Daut J. Long-chain acyl-coenzyme A esters and fatty acids directly link metabolism to K(ATP) channels in the heart. *Circ Res*. 2001; 88(9):918–924. [PubMed: 11349001]
120. Malhotra A, Sanghi V. Regulation of contractile proteins in diabetic heart. *Cardiovasc Res*. 1997; 34(1):34–40. [PubMed: 9217870]
121. Jweied EE, McKinney RD, Walker LA, et al. Depressed cardiac myofilament function in human diabetes mellitus. *Am J Physiol Heart Circ Physiol*. 2005; 289(6):H2478–H2483. [PubMed: 16085678]
122. Akella AB, Ding XL, Cheng R, Gulati J. Diminished Ca²⁺ sensitivity of skinned cardiac muscle contractility coincident with troponin T-band shifts in the diabetic rat. *Circ Res*. 1995; 76(4):600–606. [PubMed: 7534660]
123. Dillmann WH. Diabetes mellitus induces changes in cardiac myosin of the rat. *Diabetes*. 1980; 29(7):579–582. [PubMed: 6445843]
124. Rajabi M, Kassiotis C, Razeghi P, Taegtmeier H. Return to the fetal gene program protects the stressed heart: a strong hypothesis. *Heart Fail Rev*. 2007; 12(3–4):331–343. [PubMed: 17516164]
125. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. *Toxicol Appl Pharmacol*. 2006; 212(2):167–178. [PubMed: 16490224]
126. Santos DL, Palmeira CM, Seica R, et al. Diabetes and mitochondrial oxidative stress: a study using heart mitochondria from the diabetic Goto–Kakizaki rat. *Mol Cell Biochem*. 2003; 246(1–2):163–170. [PubMed: 12841358]
127. Shen X, Zheng S, Thongboonkerd V, et al. Cardiac mitochondrial damage and biogenesis in a chronic model of Type 1 diabetes. *Am J Physiol Endocrinol Metab*. 2004; 287(5):E896–E905. [PubMed: 15280150]
128. Palmer JW, Tandler B, Hoppel CL. Biochemical properties of subsarcolemmal and interfibrillar mitochondria isolated from rat cardiac muscle. *J Biol Chem*. 1977; 252(23):8731–8739. [PubMed: 925018]
129. Riva A, Tandler B, Loffredo F, Vazquez E, Hoppel C. Structural differences in two biochemically defined populations of cardiac mitochondria. *Am J Physiol Heart Circ Physiol*. 2005; 289(2):H868–H872. [PubMed: 15821034]

130. Adhihetty PJ, Ljubcic V, Menzies KJ, Hood DA. Differential susceptibility of subsarcolemmal and intermyofibrillar mitochondria to apoptotic stimuli. *Am J Physiol Cell Physiol.* 2005; 289(4):C994–C1001. [PubMed: 15901602]
131. Koves TR, Noland RC, Bates AL, Henes ST, Muoio DM, Cortright RN. Subsarcolemmal and intermyofibrillar mitochondria play distinct roles in regulating skeletal muscle fatty acid metabolism. *Am J Physiol Cell Physiol.* 2005; 288(5):C1074–C1082. [PubMed: 15647392]
132. Mollica MP, Lionetti L, Crescenzo R, et al. Heterogeneous bioenergetic behaviour of subsarcolemmal and intermyofibrillar mitochondria in fed and fasted rats. *Cell Mol Life Sci.* 2006; 63(3):358–366. [PubMed: 16416026]
133. Ritov VB, Menshikova EV, He J, Ferrell RE, Goodpaster BH, Kelley DE. Deficiency of subsarcolemmal mitochondria in obesity and Type 2 diabetes. *Diabetes.* 2005; 54(1):8–14. [PubMed: 15616005]
134. Williamson CL, Dabkowski ER, Baseler WA, Croston TL, Alway SE, Hollander JM. Enhanced apoptotic propensity in diabetic cardiac mitochondria: influence of subcellular spatial location. *Am J Physiol Heart Circ Physiol.* 2010; 298(2):H633–H642. [PubMed: 19966057]
135. Hood DA. Invited review: contractile activity-induced mitochondrial biogenesis in skeletal muscle. *J Appl Physiol.* 2001; 90(3):1137–1157. [PubMed: 11181630]
136. Dabkowski ER, Williamson CL, Bukowski VC, et al. Diabetic cardiomyopathy-associated dysfunction in spatially distinct mitochondrial subpopulations. *Am J Physiol Heart Circ Physiol.* 2009; 296(2):H359–H369. [PubMed: 19060128]
137. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation.* 1997; 96(7):2190–2196. [PubMed: 9337189]
138. Spindler M, Saupe KW, Tian R, Ahmed S, Matlib MA, Ingwall JS. Altered creatine kinase enzyme kinetics in diabetic cardiomyopathy. $A^{31}P$ NMR magnetization transfer study of the intact beating rat heart. *J Mol Cell Cardiol.* 1999; 31(12):2175–2189. [PubMed: 10640445]
139. del Monte F, Williams E, Lebeche D, et al. Improvement in survival and cardiac metabolism after gene transfer of sarcoplasmic reticulum Ca^{2+} -ATPase in a rat model of heart failure. *Circulation.* 2001; 104(12):1424–1429. [PubMed: 11560860]
140. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with Type 2 diabetes. *Circulation.* 2003; 107(24):3040–3046. [PubMed: 12810608]
141. Szabadkai G, Duchon MR. Mitochondria: the hub of cellular Ca^{2+} signaling. *Physiology (Bethesda).* 2008; 23:84–94. The authors review the effect of cytosolic Ca^{2+} overload on mitochondrial function, as well as the contribution of mitochondria to Ca^{2+} homeostasis. [PubMed: 18400691]
142. Murgia M, Giorgi C, Pinton P, Rizzuto R. Controlling metabolism and cell death: at the heart of mitochondrial calcium signalling. *J Mol Cell Cardiol.* 2009; 46(6):781–788. [PubMed: 19285982]
143. Balaban RS. Cardiac energy metabolism homeostasis: role of cytosolic calcium. *J Mol Cell Cardiol.* 2002; 34(10):1259–1271. [PubMed: 12392982]
144. Hansford RG, Zorov D. Role of mitochondrial calcium transport in the control of substrate oxidation. *Mol Cell Biochem.* 1998; 184(1–2):359–369. [PubMed: 9746330]
145. Jouaville LS, Pinton P, Bastianutto C, Rutter GA, Rizzuto R. Regulation of mitochondrial ATP synthesis by calcium: evidence for a long-term metabolic priming. *Proc Natl Acad Sci USA.* 1999; 96(24):13807–13812. [PubMed: 10570154]
146. Tian R, Halow JM, Meyer M, et al. Thermodynamic limitation for Ca^{2+} handling contributes to decreased contractile reserve in rat hearts. *Am J Physiol.* 1998; 275(6 Pt 2):H2064–H2071. [PubMed: 9843805]
147. Zaman AK, Fujii S, Goto D, et al. Salutary effects of attenuation of angiotensin II on coronary perivascular fibrosis associated with insulin resistance and obesity. *J Mol Cell Cardiol.* 2004; 37(2):525–535. [PubMed: 15276022]
148. Kawasaki D, Kosugi K, Waki H, Yamamoto K, Tsujino T, Masuyama T. Role of activated renin–angiotensin system in myocardial fibrosis and left ventricular diastolic dysfunction in diabetic

- patients – reversal by chronic angiotensin II Type 1A receptor blockade. *Circ J*. 2007; 71(4):524–529. [PubMed: 17384453]
149. Orea-Tejeda A, Colin-Ramirez E, Castillo-Martinez L, et al. Aldosterone receptor antagonists induce favorable cardiac remodeling in diastolic heart failure patients. *Rev Invest Clin*. 2007; 59(2):103–107. [PubMed: 17633796]
 150. Duncker DJ, Van Zon NS, Altman JD, Pavek TJ, Bache RJ. Role of K⁺ATP channels in coronary vasodilation during exercise. *Circulation*. 1993; 88(3):1245–1253. [PubMed: 8353886]
 151. Ballagi-Pordany G, Koszeghy A, Koltai MZ, Aranyi Z, Pogatsa G. Divergent cardiac effects of the first and second generation hypoglycemic sulfonylurea compounds. *Diabetes Res Clin Pract*. 1990; 8(2):109–114. [PubMed: 2106423]
 152. Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J*. 1999; 20(6): 439–446. [PubMed: 10213347]
 153. Hu S, Wang S, Dunning BE. Glucose-dependent and glucose-sensitizing insulinotropic effect of nateglinide: comparison to sulfonylureas and repaglinide. *Int J Exp Diabetes Res*. 2001; 2(1):63–72. [PubMed: 12369728]
 154. Fisman EZ, Tenenbaum A. A cardiologic approach to non-insulin antidiabetic pharmacotherapy in patients with heart disease. *Cardiovasc Diabetol*. 2009; 8:38. [PubMed: 19619327]
 155. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabet Med*. 2005; 22(4):497–502. [PubMed: 15787679]
 156. Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. *Diabetologia*. 1983; 24(1):16–18. [PubMed: 6825978]
 157. Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3 Clinical implications of UGDP results. *JAMA*. 1971; 218(9):1400–1410. [PubMed: 4941698]
 158. Gundewar S, Calvert JW, Jha S, et al. Activation of AMP-activated protein kinase by metformin improves left ventricular function and survival in heart failure. *Circ Res*. 2009; 104(3):403–411. [PubMed: 19096023]
 159. DeFronzo RA. Pharmacologic therapy for Type 2 diabetes mellitus. *Ann Intern Med*. 1999; 131(4):281–303. [PubMed: 10454950]
 160. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in Type II diabetes. *J Hum Hypertens*. 2003; 17(1):7–12. [PubMed: 12571611]
 161. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007; 356(24):2457–2471. [PubMed: 17517853]
 162. Harris, G. New York Times. Feb 19. 2010 Research ties diabetes drug to heart woes.
 163. Fazio S. More clinical lessons from the FIELD study. *Cardiovasc Drugs Ther*. 2009; 23(3):235–241. [PubMed: 19160032]
 164. Dewald O, Sharma S, Adroque J, et al. Downregulation of peroxisome proliferator-activated receptor- α gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. *Circulation*. 2005; 112(3):407–415. [PubMed: 16009788]
 165. Tenenbaum A, Fisman EZ, Boyko V, et al. Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. *Arch Intern Med*. 2006; 166(7):737–741. [PubMed: 16606809]
 166. Hiuge A, Tenenbaum A, Maeda N, et al. Effects of peroxisome proliferator-activated receptor ligands, bezafibrate and fenofibrate, on adiponectin level. *Arterioscler Thromb Vasc Biol*. 2007; 27(3):635–641. [PubMed: 17194889]
 167. Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med*. 2005; 165(10):1154–1160. [PubMed: 15911729]

168. Tenenbaum A, Motro M, Fisman EZ. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: thebezafibrate lessons. *Cardiovasc Diabetol*. 2005; 4:14. [PubMed: 16168052]
169. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *J Clin Invest*. 1967; 46(12):1954–1962. [PubMed: 6074000]
170. Burcelin R. The incretins: a link between nutrients and well-being. *Br J Nutr*. 2005; 93(Suppl 1):S147–S156. [PubMed: 15877888]
171. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with Type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005; 28(5):1083–1091. [PubMed: 15855571]
172. Bullock BP, Heller RS, Habener JF. Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. *Endocrinology*. 1996; 137(7):2968–2978. [PubMed: 8770921]
173. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation*. 2004; 110(8):955–961. [PubMed: 15313949]
174. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004; 109(8):962–965. [PubMed: 14981009]
175. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in Type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007; 298(2):194–206. [PubMed: 17622601]
176. Hoshijima M. Gene therapy targeted at calcium handling as an approach to the treatment of heart failure. *Pharmacol Ther*. 2005; 105(3):211–228. [PubMed: 15737405]
177. Zhang R, Khoo MS, Wu Y, et al. Calmodulin kinase II inhibition protects against structural heart disease. *Nat Med*. 2005; 11(4):409–417. [PubMed: 15793582]
178. Kaye DM, Krum H. Drug discovery for heart failure: a new era or the end of the pipeline? *Nat Rev Drug Discov*. 2007; 6(2):127–139. [PubMed: 17268484]
179. Hajjar RJ, Zsebo K, Deckelbaum L, et al. Design of a Phase 1/2 trial of intracoronary administration of AAV1/SERCA2a in patients with heart failure. *J Card Fail*. 2008; 14(5):355–367. Describes the first clinical trial (Phase 1) of gene therapy in subjects with congestive heart failure. [PubMed: 18514926]
180. Dimmeler S, Zeiher AM, Schneider MD. Unchain my heart: the scientific foundations of cardiac repair. *J Clin Invest*. 2005; 115(3):572–583. [PubMed: 15765139]
181. Anversa P, Kajstura J, Leri A. If I can stop one heart from breaking. *Circulation*. 2007; 115(7):829–832. [PubMed: 17309932]
182. Daley GQ, Scadden DT. Prospects for stem cell-based therapy. *Cell*. 2008; 132(4):544–548. [PubMed: 18295571]
183. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. *Nature*. 2008; 451(7181):937–942. [PubMed: 18288183]
184. Gersh BJ, Simari RD, Behfar A, Terzic CM, Terzic A. Cardiac cell repair therapy: a clinical perspective. *Mayo Clin Proc*. 2009; 84(10):876–892. Excellent review on the clinical prospect of using stem cells in cardiac repair. [PubMed: 19797777]
185. Rubart M, Field LJ. Cardiac repair by embryonic stem-derived cells. *Handb Exp Pharmacol*. 2006; (174):73–100.
186. Nadal-Ginard B, Kajstura J, Leri A, Anversa P. Myocyte death, growth, and regeneration in cardiac hypertrophy and failure. *Circ Res*. 2003; 92(2):139–150. [PubMed: 12574141]
187. Soldner F, Hockemeyer D, Beard C, et al. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. *Cell*. 2009; 136(5):964–977. [PubMed: 19269371]
188. Zhang J, Wilson GF, Soerens AG, et al. Functional cardiomyocytes derived from human induced pluripotent stem cells. *Circ Res*. 2009; 104(4):e30–e41. [PubMed: 19213953]
189. Nelson TJ, Martinez-Fernandez A, Yamada S, Perez-Terzic C, Ikeda Y, Terzic A. Repair of acute myocardial infarction by human stemness factors induced pluripotent stem cells. *Circulation*. 2009; 120(5):408–416. [PubMed: 19620500]

190. Soonpaa MH, Field LJ. Survey of studies examining mammalian cardiomyocyte DNA synthesis. *Circ Res.* 1998; 83(1):15–26. [PubMed: 9670914]
191. Katz EB, Steinhilber ME, Delcarpio JB, Daud AI, Claycomb WC, Field LJ. Cardiomyocyte proliferation in mice expressing α -cardiac myosin heavy chain-SV40 T-antigen transgenes. *Am J Physiol.* 1992; 262(6 Pt 2):H1867–H1876. [PubMed: 1377879]
192. Chaudhry HW, Dashoush NH, Tang H, et al. Cyclin A2 mediates cardiomyocyte mitosis in the postmitotic myocardium. *J Biol Chem.* 2004; 279(34):35858–35866. [PubMed: 15159393]
193. Pasumarthi KB, Nakajima H, Nakajima HO, Soonpaa MH, Field LJ. Targeted expression of cyclin D2 results in cardiomyocyte DNA synthesis and infarct regression in transgenic mice. *Circ Res.* 2005; 96(1):110–118. [PubMed: 15576649]
194. Nakajima H, Nakajima HO, Tsai SC, Field LJ. Expression of mutant p193 and p53 permits cardiomyocyte cell cycle reentry after myocardial infarction in transgenic mice. *Circ Res.* 2004; 94(12):1606–1614. [PubMed: 15142950]
195. Woo YJ, Panlilio CM, Cheng RK, et al. Therapeutic delivery of cyclin A2 induces myocardial regeneration and enhances cardiac function in ischemic heart failure. *Circulation.* 2006; 114(1 Suppl):I206–I213. [PubMed: 16820573]
196. Gneccchi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res.* 2008; 103(11):1204–1219. [PubMed: 19028920]
197. Engel FB, Schebesta M, Duong MT, et al. p38 MAP kinase inhibition enables proliferation of adult mammalian cardiomyocytes. *Genes Dev.* 2005; 19(10):1175–1187. [PubMed: 15870258]
198. Engel FB, Hsieh PC, Lee RT, Keating MT. FGF1/p38 MAP kinase inhibitor therapy induces cardiomyocyte mitosis, reduces scarring, and rescues function after myocardial infarction. *Proc Natl Acad Sci USA.* 2006; 103(42):15546–15551. [PubMed: 17032753]
199. Kuhn B, del Monte F, Hajjar RJ, et al. Periostin induces proliferation of differentiated cardiomyocytes and promotes cardiac repair. *Nat Med.* 2007; 13(8):962–969. [PubMed: 17632525]
200. Bersell K, Arab S, Haring B, Kuhn B. Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. *Cell.* 2009; 138(2):257–270. [PubMed: 19632177]
201. Spin JM, Prakash M, Froelicher VF, et al. The prognostic value of exercise testing in elderly men. *Am J Med.* 2002; 112(6):453–459. [PubMed: 11959055]
202. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002; 346(11):793–801. [PubMed: 11893790]
203. Hughes VA, Fiatarone MA, Fielding RA, et al. Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. *Am J Physiol.* 1993; 264(6 Pt 1):E855–E862. [PubMed: 8333511]
204. Toledo FG, Menshikova EV, Ritov VB, et al. Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in Type 2 diabetes. *Diabetes.* 2007; 56(8):2142–2147. [PubMed: 17536063]
205. Constable SH, Favier RJ, McLane JA, Fell RD, Chen M, Holloszy JO. Energy metabolism in contracting rat skeletal muscle: adaptation to exercise training. *Am J Physiol.* 1987; 253(2 Pt 1):C316–C322. [PubMed: 3618765]

Key issues

- Diabetic cardiomyopathy is characterized by left ventricular dysfunction (often with diastolic dysfunction preceding systolic) that cannot be attributed to coronary artery disease or hypertension.
- Dysregulated cardiac lipid metabolism, which contributes to the pathogenesis of both Type 1 and Type 2 diabetes mellitus, stems largely from altered fatty acid oxidation and results in a host of deleterious consequences including lipotoxicity, reduced metabolic flexibility, glucotoxicity and insulin resistance.
- Several adipokines alter the function of the diabetic heart: leptin causes hypertrophy and negative inotropy, but may offer some protection from ischemia, adiponectin generally opposes leptin's activity, and resistin reduces insulin sensitivity and is associated with poor outcomes in atherothrombotic disease.
- The diabetic cardiomyocyte exhibits calcium handling abnormalities on many levels – including altered myofilament sensitivity, and impaired entry and exit of calcium from the sarcolemma and sarcoplasmic reticulum.
- Altered mitochondrial calcium utilization impairs optimal energy production and contributes to contractile deficits.
- Current therapies effectively treat hyperglycemia and hyperlipidemia, but many have adverse cardiovascular effects. Newer compounds such as agonists of multiple PPAR isoforms, incretin mimetics and dipeptidyl dipeptidase-4 antagonists may offer similar benefits, but cardiovascular safety has not yet been established.
- Gene and cell therapies are currently being developed to address cases where pharmacotherapies are unlikely to succeed. Clinical trials are currently underway, including those that deliver sarco-endoplasmic reticulum Ca^{2+} -ATPase to patients with advanced heart failure via an adeno-associated viral vector.

Figure 1. Obesity-induced changes in cardiac function

Illustrates possible links between obesity, insulin resistance and diabetic cardiomyopathy.

Decreased adiponectin levels and augmented levels of nonesterified fatty acids, TNF- α , leptin and resistin (which also increases the secretion of IL-6 and TNF- α) contribute to the onset of insulin resistance, leading to hyperglycemia and mitochondrial dysfunction.

Hyperglycemia increases ROS production, causing mitochondrial dysfunction, which further increases ROS production, and with increased AGE generation, results in cardiac dysfunction (broken arrows indicate that insulin resistance and hyperglycemia can promote cardiac dysfunction through other mechanisms not depicted in the diagram).

AGE: Advanced glycosylated end product; NEFA: Nonesterified fatty acid; ROS: Reactive oxygen species.

Figure 2. Insulin signaling pathway

After insulin binds to its receptor IR, the receptor phosphorylates and activates IRS-1. Akt is activated by PI3K/PDK-1 and, in turn, activates several metabolic pathways, including GLUT4 translocation. Following chronic insulin stimulation, mTOR, through the activation of p70S6K (S6K), inhibits PI3K signaling by promoting reduction in IRS-1 stability and transcription, leading to its de-association from PI3K (negative-feedback regulation). In addition, S6K can phosphorylate IRS-1 on multiple inhibitory sites, promoting its degradation.

aPKC: Atypical protein kinase C; GLUT4: Glucose transporter-4; IR: Insulin receptor; PDK-1: Phosphoinositide-dependent protein kinase 1; PIP₂: Phosphatidylinositol 4,5-bisphosphate; PIP₃: Phosphatidylinositol 3,4,5-triphosphate.

Figure 3. Excitation–contraction abnormalities in diabetic cardiomyopathy

The defects in excitation–contraction coupling manifest as depressed outward K⁺ currents (particularly I_{to}), L-type Ca²⁺ current, Na⁺/Ca²⁺ exchange and sarcoplasmic reticulum Ca²⁺ uptake due to SERCA2a downregulation. In addition, impaired ryanodine receptor function, depressed β-adrenergic receptor signaling and phospholamban phosphorylation all contribute to slowed cytosolic Ca²⁺ release and clearing. Elevated PKC activity and depressed PKA activity in the diabetic heart modulate many of these events.

AngII: Angiotensin II; Ca²⁺: Calcium ion; DAG: Diacyl glycerol; K⁺: Potassium ion; Na⁺: Sodium ion; SERCA2a: Sarco-endoplasmic reticulum Ca²⁺-ATPase.