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Current Vascular Pharmacology, **2019,** *17,* **1-10**

REVIEW ARTICLE

Diabetes and Heart Failure: Is it Hyperglycemia or Hyperinsulinemia?

Triantafyllos Didangelos[1,*] and Konstantinos Kantartzis[2]

[1]Diabetes Center, 1st Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, ''AHEPA'' Hospital, Thessaloniki, Greece; [2]Department of Internal Medicine IV, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, University of Tübingen and Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany

ARTICLE HISTORY

Received: July 11, 2018
Revised: October 12, 2018
Accepted: October 15, 2018

DOI:
10.2174/1570161117666190408164326

Abstract: The cardiac effects of exogenously administered insulin for the treatment of diabetes (DM) have recently attracted much attention. In particular, it has been questioned whether insulin is the appropriate treatment for patients with type 2 diabetes mellitus and heart failure. While several old and some new studies suggested that insulin treatment has beneficial effects on the heart, recent observational studies indicate associations of insulin treatment with an increased risk of developing or worsening of pre-existing heart failure and higher mortality rates. However, there is actually little evidence that the associations of insulin administration with any adverse outcomes are causal. On the other hand, insulin clearly causes weight gain and may also cause serious episodes of hypoglycemia. Moreover, excess of insulin (hyperinsulinemia), as often seen with the use of injected insulin, seems to predispose to inflammation, hypertension, dyslipidemia, atherosclerosis, heart failure, and arrhythmias. Nevertheless, it should be stressed that most of the data concerning the effects of insulin on cardiac function derive from *in vitro* studies with isolated animal hearts. Therefore, the relevance of the findings of such studies for humans should be considered with caution. In the present review, we summarize the existing data about the potential positive and negative effects of insulin on the heart and attempt to answer the question whether any adverse effects of insulin or the consequences of hyperglycemia are more important and may provide a better explanation of the close association of DM with heart failure.

Keywords: Diabetes, insulin, heart failure, diastolic dysfunction, systolic dysfunction, cardiomyopathy, autonomic neuropathy.

1. INTRODUCTION

The cardiac effects of injected insulin have only recently attracted attention. It is now widely known that insulin could affect cardiac function, morphology, and perfusion either at rest or at stress conditions [1, 2]. Thousands of insulin receptors (10,000 to 100,000) were shown to be located on the surface of each cardiomyocyte [1]. Thus, insulin can probably act directly on the heart muscle. However, it is still a matter of debate whether insulin has predominantly favorable or rather adverse effects on the heart.

Often in routine clinical practice, patients with poorly controlled diabetes mellitus (DM) (mean HbA_{1c} usually around 11% or 97 mmol/mol) are hospitalized for episodes of acute heart failure due to other causes than acute myocardial ischemia. Not rarely, after the initial management and improvement of blood glucose values near to normal range, patients again develop acute pulmonary edema without any other detectable contributing factor, *e.g.* ischemia. From a clinical point of view, it seems that additional diuresis was needed before the achievement of good glycemic control. Poorly controlled DM patients have glycosuria and lose water and electrolytes because of osmotic diuresis. This mechanism protects them from developing pulmonary edema. Upon hospitalization, most physicians will initiate insulin treatment, because it is the most powerful agent to improve fast and effectively, blood glucose levels but may not take into consideration that good glycemic control will lead to decreased diuresis and may not give or increase diuretics. Of note, many of these patients will have an impaired kidney function as a result of the older age and the long-standing DM. Therefore, heart function worsens in parallel with the improvement of the glucose control, resulting in pulmonary edema for the second time.

In line with this clinical observation, Gilbert and Krum noted in a review paper that "from a mechanistic viewpoint, it seems plausible, though by no means certain, that a reduction in plasma glucose, by whatever means, might adversely affect cardiac function" [3]. Some months later, the Empagliflozin

*Address correspondence to this author at the 1st Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, ''AHEPA'' Hospital, St. Kyriakidi str. 1, 54636, Thessaloniki, Greece;
E-mail: didang@med.auth.gr

1570-1611/19 $58.00+.00

Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial [4] provided an additional, though indirect, support for the possible significant benefits to the heart function of osmotic diuresis due to glycosuria in patients with heart failure (HF). In this trial, treatment of patients with poorly controlled type 2 DM (T2DM) and established cardiovascular disease (CVD) with empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which increases glycosuria, resulted in a significantly lower rate of hospitalization for HF compared with patients on placebo [4]. A search of the literature for clinical studies that may have investigated such clinical cases prospectively (measurement of fluid loss before and after the beginning of treatment with insulin, appropriate dose of diuretics taken) yielded no results, obviously because it has been considered unethical to leave patients in such severe condition without the appropriate treatment. In any case, the above described clinical condition, as an example, may be one of the reasons that insulin treatment in patients with T2DM has been considered by some researchers to contribute to the development of, or to worsen, HF [5, 6].

2. DIABETES, ANTIDIABETIC DRUGS AND HF

HF and its management are an important and seriously growing health problem worldwide. About 1/3 of patients with HF have also DM [7, 8], suggesting that DM is one of the main causes of HF in the general population. Hyperglycemia, hypertension, obesity and dyslipidemia are disorders that often occur either alone or in various combinations in patients with DM and that substantially increase the risk of diastolic or/and systolic left ventricular dysfunction, which ultimately leads to HF. HF has been reported to be the earliest, the most common and the most serious of the cardiovascular disorders in patients with DM and one of the main causes of increased mortality in those patients [9]. HF has also been characterized as a "frequent, forgotten and often fatal complication" of DM [10]. In addition to the very poor outcomes, HF in DM is associated with very high health care expenses [11, 12].

2.1. Data from Epidemiological Studies

In an echocardiographic study in young patients with type 1 DM (T1DM), left ventricular diastolic dysfunction (LVDD) was more common and occurred earlier in the course of DM than left ventricular systolic dysfunction (LVSD) [13]. In the same study, the duration of DM was one of the most significant factors for increasing the frequency of both LVDD and LVSD [13]. After 25 years of duration of T1DM, LVDD was present in 80% and LVSD in 50% of the patients [13]. In a Swedish observational study, among 20,985 patients with T1DM (mean age: 38.6 years) every 1% increase in HbA_{1c} above 6.5% was associated with a 30% increase in the risk of HF, independent of other risk factors including hypertension, obesity and smoking [14]. These studies included exclusively T1DM patients, and therefore highlight the pure effect of hyperglycemia on cardiac function, in contrast to studies in type 2 diabetes (T2DM), where hyperinsulinemia and other co-morbidities often exist and may act as confounding factors.

In another cohort study, 25,958 men and 22,900 women with predominantly T2DM and no history of HF were followed for a median of 2.2 years. After adjustment for age, sex, race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, use of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, type and duration of DM, and incidence of interim myocardial infarction, each 1% increase in HbA_{1c} was associated with an 8% increase in the risk of HF [15]. An HbA_{1c} ≥10% compared with HbA_{1c} <7%, was associated with a 1.56-fold greater risk of HF [15]. In the Framingham Heart Study, patients with DM had a significantly higher (2-8-fold) risk for developing HF compared with those without DM. Among patients with DM 19% developed symptoms of HF [16]. In the prospective large multicenter United Kingdom Prospective Diabetes Study (UKPDS) study, in patients with T2DM, each 1% decrease in HbA_{1c} was associated with a 16% reduction in the risk of HF [17]. Of particular interest, 2/3 of the patients who developed HF in the Multi-Ethnic Study of Atherosclerosis (MESA) community-based study (6,814 people with no ischemic heart disease followed-up for 4 years) had a normal ejection fraction (EF) [18]. Last, in the Strong Heart Study, DM was independently associated with diastolic dysfunction. The association was stronger when glycemic control was poor [19]. The severity of diastolic dysfunction was similar to the well-known impaired relaxation of the left ventricle associated with hypertension [19]. The combination of DM (type 1 or 2) and hypertension led to more severe LVDD than either condition alone [19].

2.2. Prognosis of HF in DM

Two very interesting recent studies on the prognosis of HF in patients with DM were published. The first one reported on the prognosis of patients with acute HF. A total of 1,810 patients participated in this study; 384 patients (21%) had DM [20]. Patients with new-onset as well as with decompensated chronic HF were included, but patients admitted to the Intensive Coronary Care Unit for acute HF caused by an acute coronary syndrome without any evidence of sustained systolic or diastolic dysfunction were excluded. The 10-year outcome (a composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation) in patients with DM was significantly worse than in those without DM [87 *vs* 76%; adjusted hazard ratio 1.17, 95% confidence interval (CI) 1.02-1.33]. Of note, the long-term prognosis over the last 30 years improved in both groups as a result of improved treatment of HF. This improvement in long-term prognosis was comparable in patients with and without diabetes [20].

The second was the Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (STENO-2) study and its extension. In that study, researchers compared conventional multifactorial management of patients with T2DM and microalbuminuria to intensified multifactorial intervention targeting known modifiable risk factors with individualized lifestyle intervention and tailored multi-pharmacological treatment at a specialized DM clinic [21, 22]. After 3.8 years of intervention, patients who received intensified treatment showed a reduction in the risk of microvascular complications of around 50% [21]; after 7.8 years of intervention, a 53% reduction in the risk of CVD

endpoints was seen in the arm that was allocated to intensified intervention [22]. At this time point, the structured treatment of patients in the intensive-therapy group stopped and the trial continued as an observational follow-up study [23]. After 13.3 years of follow-up, the risks of death from any cause, of death from CVD causes and of CVD events were still about 50% lower in the patients originally allocated to the intensive-therapy group [23]. This year, analyses of the data of 21.2 years follow-up were published. The patients treated with the intensified, multifactorial intervention for the initial 7.8 years exhibited a markedly (about 70%) lower risk of hospitalization for HF [24] and a substantial increase in lifespan (by a median of 7.9 years), matched by the time free from CVD events [25]. This is a "legacy" effect.

Taken together, both the epidemiological data and the large studies on the long-term prognosis of HF in patients with DM clearly show that in patients with DM, both type 1 and 2, cardiac dysfunction is common, occurs early and has a poor prognosis. Glycemic control is a major determinant of the severity, prognosis and the final outcome, *i.e*. mortality rates. As shown in the STENO-2 study, early diagnosis and intensive management of both hyperglycemia and cardiac dysfunction are required in order to reduce the cardiovascular events due to HF.

2.3. Randomized Controlled Trials

Some of the antidiabetic drugs, e.g. thiazolidinediones and dipeptidyl-peptidase-4 inhibitors, may cause or/and precipitate cardiac dysfunction and are relatively 'contraindicated' in HF [26-28], while others, e.g. glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors, have a beneficial effect on the cardiac function, as reported in large international multicenter studies [4, 29].

PROactive and EMPA-REG were large international, randomized, controlled, double- blind trials, that were designed to show the effects of certain antidiabetic drugs on cardiovascular outcomes, but also provide some interesting insights into the association of diabetes with HF. PROactive was a prospective, randomized controlled trial in 5238 patients with poorly controlled (HbA1c 7.8%) type 2 diabetes and established cardiovascular disease, i.e. at particularly high risk for macrovascular events. An absolute reduction in HbA1c, 0.8% in the pioglitazone group and 0.3% in the placebo group, was achieved [27]. EMPA-REG was a multicenter, prospective, randomized controlled trial with a similar design, i.e. in 7020 patients with poorly controlled (HbA1c 8.0%) type 2 diabetes and established cardiovascular disease. HbA1c fell by 0.36% in empagliflozin group and 0.24% in placebo [4]. In both studies in the placebo group the frequency of episodes of heart failure began to increase already from the first six months of follow-up (Figs. **1**, **2**), which points out to a rapid worsening of cardiac function in such high risk patients and underlines the major clinical importance of managing heart failure early and intensively enough. Of note, the curves during follow-up are very similar in figures 1 and 2, indicating that the continuous increase of the incidence of heart failure is independent of the specific treatment, even though the rate of increase was higher in PROactive in the pioglitazone group and in EMPA-REG in the placebo group [4, 27].

PROactive and EMPA-REG convincingly showed that under pioglitazone cardiac function further deteriorates, whereas empagliflozin treatment results to a significant improvement of the clinical outcome, including the incidence of episodes of heart failure, which is a very hard clinical end point. Although several mechanisms may contribute to the favorable clinical outcome under empagliflozin [30-33], the main reason for the opposite results in the pioglitazone and empagliflozin groups is their different effects on cardiac preload. Thiazolidinediones are known to lead to a roughly 3% decrease in hematocrit, whereas inhibitors of the sodium-glucose cotransporters-2 result in a roughly 3% increase in hematocrit value, which is suggestive of volume contraction. Fluid overload is a key precipitating factor for heart failure deterioration, and it is therefore why diuretics are routine therapy in heart failure. Accordingly, any drug leading to volume expansion, such as the thiazolidinediones, could adversely affect cardiac function, while drugs causing volume

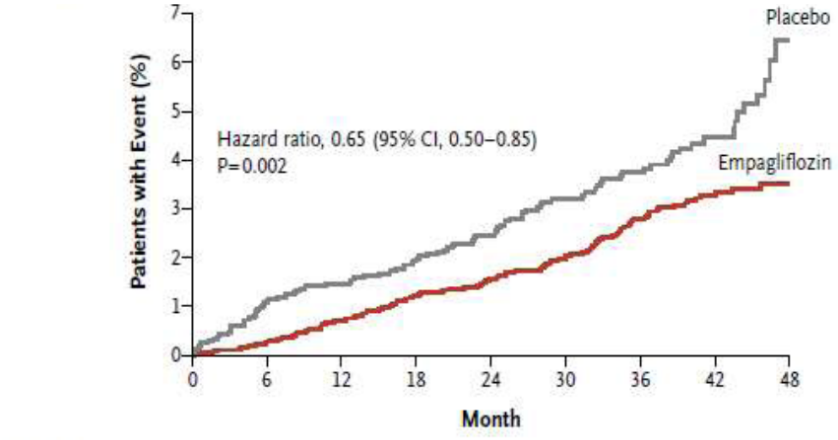

Fig. (1). Hospitalization for heart failure in the EMPA-REG OUTCOME study (from reference [5] with permission).

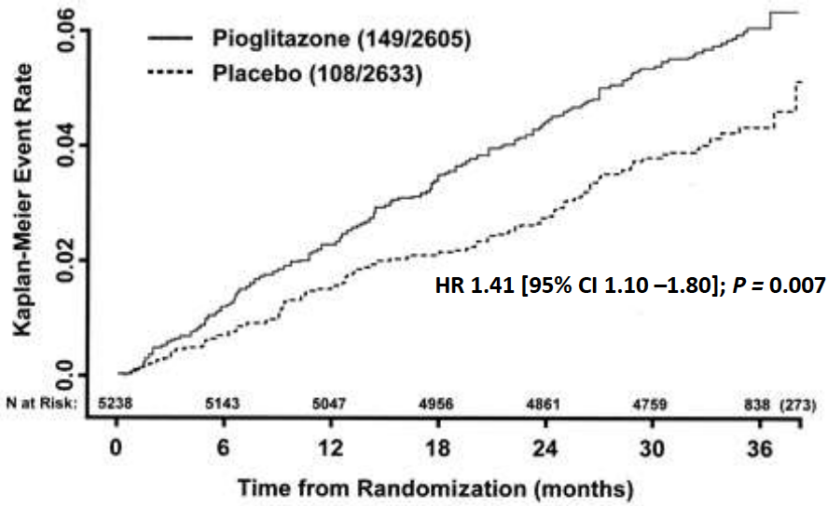

Fig. (2). Pioglitazone use and time to serious heart failure in patients with T2DM and preexisting cardiovascular disease. Data from the PROactive Study (PROactive 08) (from reference [30] with permission). HR, hazard ratio; CI, confidence interval.

reduction, such as SGLT2 inhibitors, are expected to have a beneficial effect. Particularly in patients with pre-existing left ventricular diastolic dysfunction (LVDD) even a small increase of end- diastolic volume may lead to acute heart failure and of pulmonary edema. Besides an increase in pulmonary vascular pressure and pulmonary congestion, LVDD leads also to a restriction of cardiac output and arterial hypotension, especially under stress conditions. In addition, it has been shown that in diabetic patients increased left ventricular filling pressure significantly lowers myocardial perfusion, even in the absence of coronary stenosis [34].

There were also other studies that essentially confirmed the observed in the PROactive and EMPA-REG effects of thiazolidinediones and SGLT2 inhibitors, respectively, on the cardiac function. In two studies, which investigated the effect of rosiglitazone and pioglitazone compared with placebo for one year in patients with type 2 diabetes and reduced ejection fraction, treatment was associated with an increased risk of heart failure during follow-up [35, 36]. In contrast, in the large CANVAS trial, canagliflozin showed similar to empagliflozin favorable effects in heart failure [37].

2.4. Pathophysiology

In addition to ischemic heart disease, hypertension and nephropathy, diabetic cardiomyopathy and cardiovascular autonomic neuropathy (CAN) are underlying mechanisms which result in and explain the poor prognosis of HF in patients with DM [38, 39].

Early heart disease associated with DM may only involve abnormalities in heart muscle function (without ischemia or neuropathy). This disorder is termed “diabetic cardiomyopathy”. Diabetic cardiomyopathy is initially characterized by myocardial fibrosis, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical HF. Hyperglycemia directly activates a fibrogenic program, leading to accumulation of advanced glycation end-products (AGEs) that cross-link extracellular matrix proteins and transduce fibrogenic signals through reactive oxygen species (ROS) generation or through activation of AGEs receptor (RAGE)-mediated pathways. DM-associated interstitial fibrosis is associated with accumulation of type I and III collagen, involves both left and right ventricle, and has been described in both type 1 and T2DM. Cardiomyocytes may play a critical role in DM-associated cardiac fibrosis through several distinct mechanisms. DM and metabolic dysfunction may exert toxic effects on cardiomyocytes, eventually leading to irreversible injury and cell death. Fibrosis in diabetic patients may reflect the replacement of dead cardiomyocytes with fibrous tissue, rather than direct activation of fibroblasts or immune cells. Furthermore, hyperglycemia may promote a fibrogenic phenotype in cardiomyocytes, inducing synthesis and release of growth factors and cytokines that induce fibroblast proliferation and activation [1]. Moreover, mitochondrial dysfunction, oxidative stress, reduced nitric oxide bioavailability, impaired mitochondrial and cardiomyocyte calcium handling, inflammation, renin-angiotensin–aldosterone system activation, endoplasmic reticulum stress, microvascular dysfunction have all been implicated in the development and progression of diabetic cardiomyopathy (Fig. **3**). Molecular mechanisms linked to the underlying pathophysiological changes include abnormalities in adenosine monophosphate (AMP) - activated protein kinase, peroxisome proliferator-activated receptors, O-linked N-acetylglucosamine, protein kinase C, microRNA and exosome pathways. The diabetic environment promotes myocardial fatty acid oxidation while decreasing myocardial glucose metabolism. That energy substrates shift is accompanied by increased ROS production and augmented uncoupling proteins (UCPs) expression. Taken together, DM increases oxidative stress, lipid peroxidation products and oxygen consumption, in parallel reducing ATP generation and ATP/consumed O_2 ratio. All those effects lead to marked reduced myocardial efficiency. In addition, DM is associated with lipid accumulation in the myocardium [40-43]. Diabetic patients also show a characteristic alteration of the microvascular architecture, which is characterized by abnormal capillary permeability, the formation of micro-aneurysms, subendothelial matrix deposition and perivascular fibrosis [44]. All these mechanisms eventu-

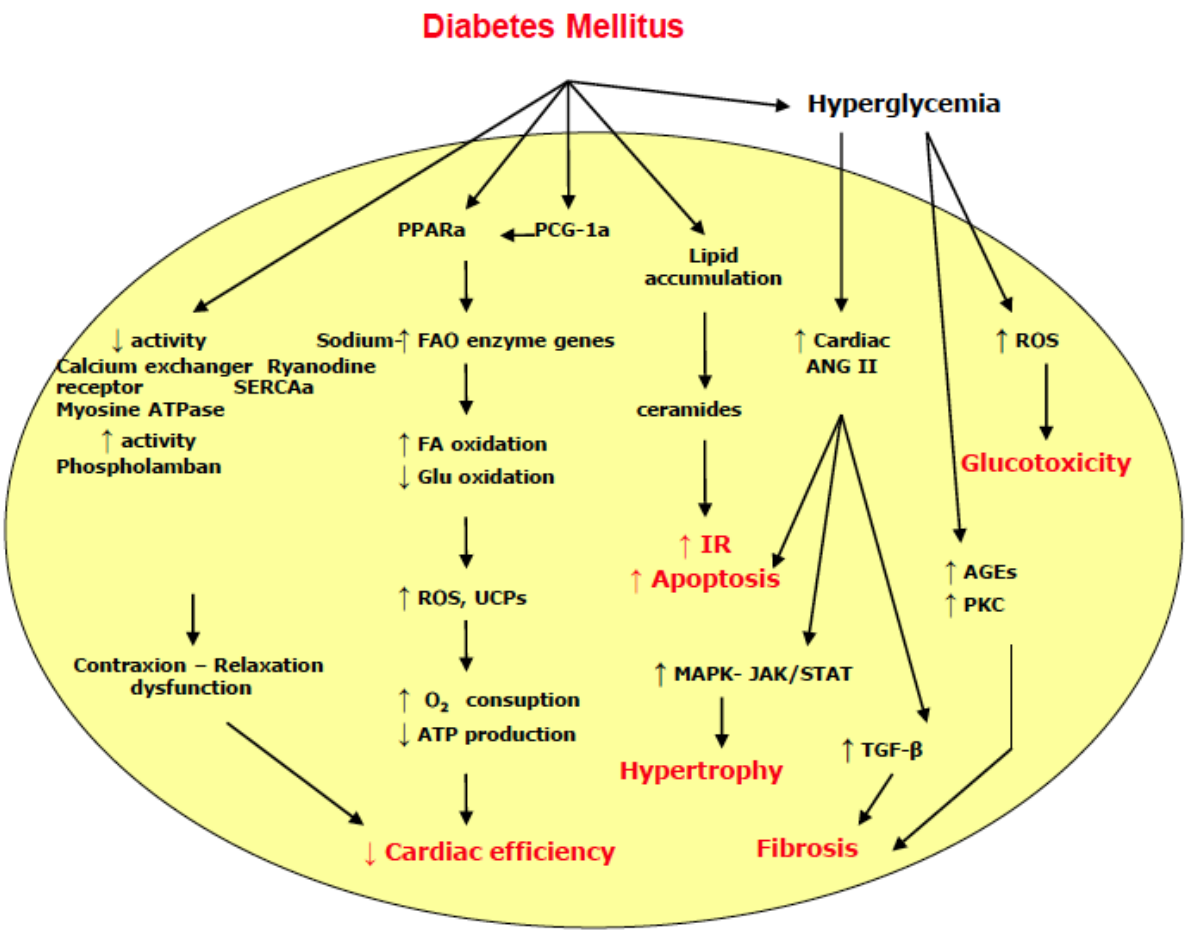

Fig. (3). Proposed mechanisms involved in the pathogenesis of diabetic cardiomyopathy. PKC, Protein kinase C; PPAR-α, Peroxisome proliferator-activated receptor-α; PCG-1a, Peroxisome proliferator-activated receptor-γ activator 1; AGEs, Advanced Glycosylated Endproducts; ROS, Reactive oxygen species; IR insulin resistance; TGF-β, Transforming growth factor beta; FAO, Fatty Acids Oxidation; ANG, Angiotensin; SERCAa, Sarcoendoplasmic reticulum calcium transport ATPase; UCPs, Uncoupling Proteins; MAPK, mitogen-activated protein kinase; JAK/STAT, Janus kinase/signal transducers and activators of transcription.

ally lead to the disturbed contraction and relaxation which characterizes the function of diabetic cardiomyocytes.

Cardiovascular diabetic autonomic neuropathy is a complication related to poorly controlled DM and includes abnormalities in heart rate control, vascular hemodynamics, and cardiac structure and function. In a recent study, we used radionuclide ventriculography to estimate left ventricular dysfunction (LVD) and observed in well-characterized patients with T2DM without hypertension and ischemic heart disease that the severity of autonomic dysfunction is associated with the severity of LVDD [38].

An early characteristic of cardiac autonomic neuropathy is the reduction of parasympathetic activity with an imbalance towards relatively higher sympathetic nervous system (SNS) activity. In this regard, activation of the SNS enhances adrenergic receptor signaling that promotes cardiac hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis and impaired function [45,46]. Autonomic nervous system imbalance in the diabetic population is an important predictor of cardiovascular events. Recently, a crosstalk by means of various nerve growth factors (NGF), between cardiomyocyte and cardiac sympathetic nerves was shown. Axon growth, denervation and functional alternation of sympathetic nerves have all been described in HF [47]. Moreover, in a randomized, double-blind, placebo-controlled, parallel study in 40 patients with T2DM on insulin treatment, rosiglitazone was found to increase vascular leakage in insulin-treated patients with T2DM with autonomic neuropathy. Autonomic neuropathy did not exaggerate rosiglitazone-induced fluid retention. Therefore, the authors concluded that autonomic neuropathy should be considered as a risk factor for thiazolidinedione-induced edema [48].

A critical question is how early in the course of DM all the above mentioned pathogenic mechanisms begin. Unfortunately, this is not known. At an early stage, diabetic cardiomyopathy can be considered as an adaptation to the diabetic metabolism, resulting in functional changes, whereas at a later stage, structural changes appear, for which the myocardium has only a limited capacity to repair. CAN has been described already after two years of poorly controlled T1DM patients and after one year in T2DM patients [49]. Many studies have reported that diabetic patients have LVDD at an early stage of diabetic cardiomyopathy [50]. However, this finding has been questioned, because the techniques used for the evaluation of systolic function are less sensitive than those used for the assessment of diastolic function [51].

More recent studies using speckle echocardiography and magnetic resonance imaging for evaluating strain and strain rate showed subclinical LVSD in addition to diastolic abnormalities in asymptomatic DM patients with a normal left ventricular ejection fraction [51, 52]. Regarding morbidity, hospitalization and mortality, there are no significant differences between diastolic and systolic HF [53].

3. INSULIN AND THE HEART: FRIEND OR FOE?

Insulin promotes glucose uptake and its utilization initially via glycolysis. Insulin, promoting glucose as the main cardiac energy substrate, reduces myocardial O_2 consumption and increases myocardial work efficiency. Moreover, insulin seems to augment cardiomyocyte contraction, while it affects favorably myocardial relaxation, increases ribosomal biogenesis and protein synthesis, stimulates vascular endothelial growth factor (VEGF) and thereby angiogenesis, suppresses apoptosis, promotes cell survival and finally ameliorates both myocardial microcirculation and coronary artery resistance, leading to increased blood perfusion of the myocardium. Thus, insulin acts directly on heart muscle, and this action is mediated principally through the PKB/Akt signal pathway [1]. Under pathological conditions, such as T2DM, myocardial ischemia, and cardiac hypertrophy, insulin signal transduction pathways and action are clearly modified [1, 2]. Fig. (**4**) summarizes the beneficial effects of insulin on myocardial function, morphology and perfusion.

The natural competition which exists between glucose and fatty acid metabolism in the heart is regulated by feedback control and allosteric and transcriptional modulation of key limiting enzymes. Inhibition of these glycolytic enzymes not only controls the flux of a substrate through the glycolytic pathway, but also leads to the diversion of the glycolytic intermediate substrate through pathological pathways, which mediate the onset of diabetic complications [54].

The effects of insulin therapy on myocardial ischemia and reperfusion injury were investigated in a randomized clinical trial in patients with T2DM and coronary artery disease. Insulin seemed to increase blood flow in ischemic myocardial segments [55]. Table **1** summarizes the beneficial insulin effects during myocardial ischemia and reperfusion. However, failure to achieve euglycemia attenuates the beneficial influence of insulin on ischemic myocardium [56]. In addition, insulin administration at doses that maintain the plasma glucose within the normal range, significantly reduces many factors predisposing to atherothrombosis, such as intracellular adhesion molecule-1, chemo-attractive monocyte protein- 1, metalloproteases -2 and -9 and plasminogen activator inhibitor-1 (PAI-1) [2] (Fig. **5**). Accordingly, regarding the effect of hyperinsulinemia, we believe that there two possible clinical situations. The first refers to what happens in poorly controlled DM (despite endogenous hyperinsulinemia or insulin treatment). In the heart tissue, there are increased levels of glucose and insulin, as well as of free fatty acids, the latter as a result of an increased lipolysis due to the poor metabolic control. The competition between glucose and fatty acid metabolism, as defined by the Randle hypothesis and transcriptional regulation of limiting enzymes, results in attenuation of insulin-mediated stimulation of glucose transport and oxidation, and elevations in fatty acid uptake and oxidation [57]. Under these conditions, the heart muscle works inefficiently. The second condition refers to when insulin maintains plasma glucose within the normal range in the heart. Insulin attenuates lipolysis (adipose tissue), proteolysis (muscles) and ketogenesis (liver) [57]. Thereby, free FA, protein and ketone supply to myocardial

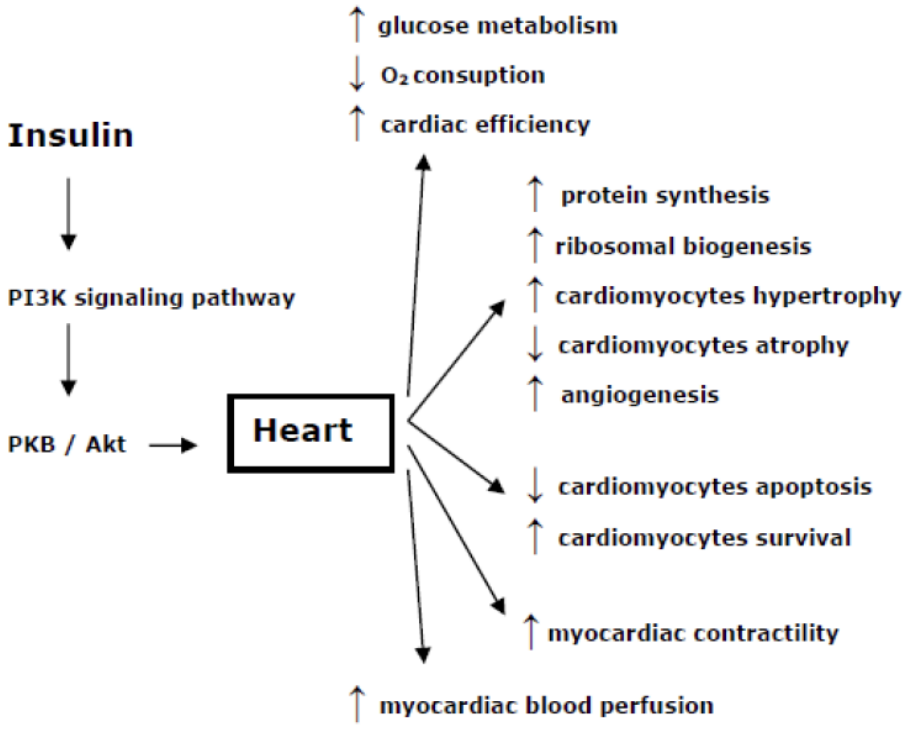

Fig. (4). Presumed actions of insulin in the heart.

Table 1. Beneficial effects of insulin during myocardial ischemia and reperfusion.

1. Lowers fatty acid levels	Increases cardiac efficiency
2. Increases glucose-derived ATP production	
3. Decreases ROS production	
4. Decreases O_2 consumption	
5. Increases the ATP production/O2 consumption ratio	
6. Antagonizes the detrimental effects of AMPK during reperfusion	
7. Prolongs cellular survival	
8. Protects from apoptosis	
9. Has anti-inflammatory properties (↓NFkB, ↓MCP-1, ↓ICAM-1, ↓CRP, ↑IkB)	
10.Exerts anti-thrombotic actions (↓TF, ↓PAI-1)	
11.Increases blood flow in ischemic myocardial segments	

ROS, Reactive oxygen species; AMPK, Adenosine monophosphate-activated protein kinase; NFκB, Nuclear factor kappa B; MCP-1, Monocyte chemoattractant protein-1; ICAM-1, Intracellular adhesion molecule-1; IκB, Inhibitor of kappaB; TF, tissue factor; PAI-1, Plasminogen Activator Inhibitor 1, CRP c-Reactive protein, ATP Adenosine triphosphate, O_2 Oxygen .

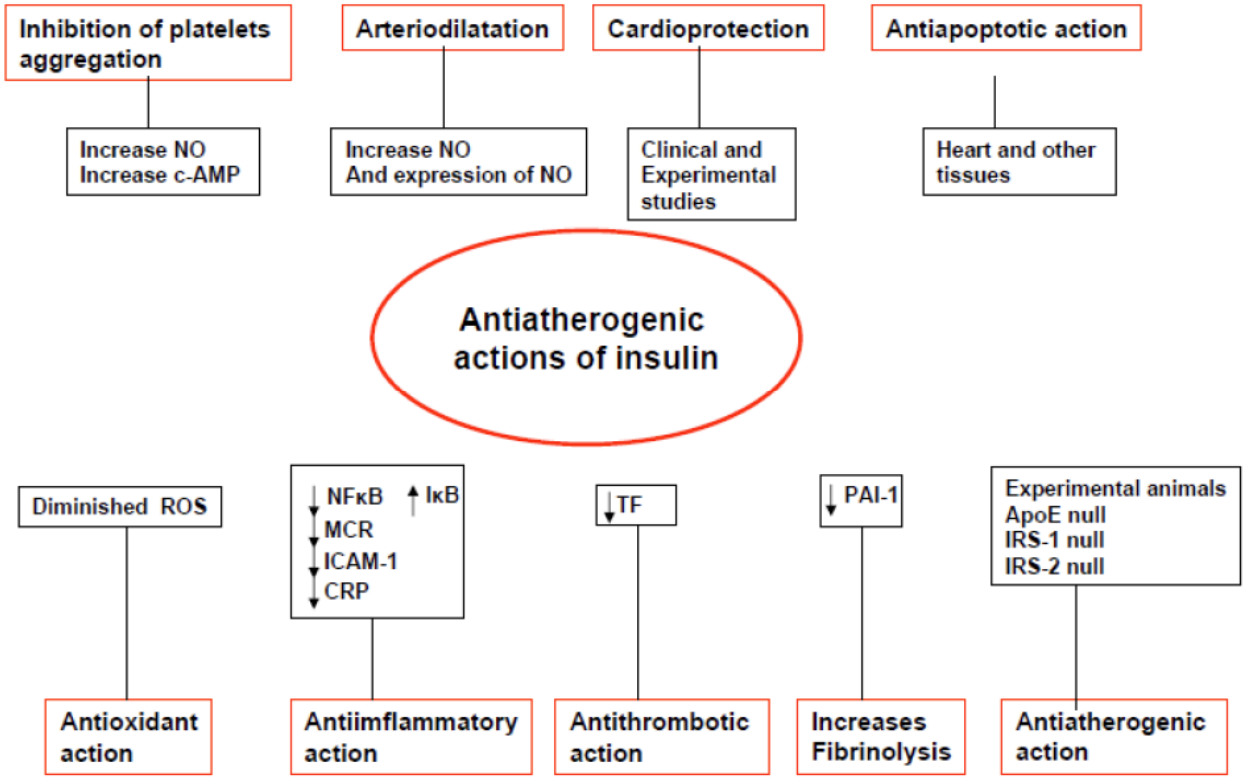

Fig. (5). Antiatheromatic effects of insulin (from [2] with permission). NFκB, Nuclear factor kappa B; MCP-1, Monocyte chemoattractant protein-1; ICAM-1, Intracellular adhesion molecule-1; IκB, Inhibitor of kappaB; TF, tissue factor; PAI-1, Plasminogen Activator Inhibitor 1.

tissue is reduced. In that case, the fatty acids-to-glucose ratio favors glucose uptake and usage. By promoting glucose as the main cardiac energy substrate insulin reduces myocardial O_2 consumption and increases cardiac efficiency (cardiac performance/oxygen consumption) [57].

In addition to the, widely accepted actions of insulin in the cardiovascular (CV) system, insulin in excess, *i.e.* in insulin resistance or treatment of DM, has been implicated in sodium renal retention, and therefore in the pathogenesis of edema and hypertension. This issue is still a matter of debate. In the literature, there is a great amount of data supporting the hypothesis of sodium retention by insulin. These data come from correlational analyses in humans, acute insulin infusion studies in humans and animals, and chronic insulin

infusion studies in rats [58-60]. However, several experimental studies using chronic insulin infusion in dogs failed to confirm this hypothesis [61, 62]. Moreover, patients with insulinoma do not develop hypertension [63]. In another study conducted on conscious dogs with kidney mass reduced by 70% in order to increase their susceptibility to hypertensive stimuli, chronic hyperinsulinemia did not increase blood pressure and did not potentiate the hypertensive effects of angiotensin II. Insulin caused transient sodium and potassium retention followed by renal "escape" that was associated with a considerable increase (12-27%) of glomerular filtration rate [62]. We consider that current data are conflicting and not enough to support the sodium retention hypothesis [59, 62, 63]. More studies are needed to clarify if at all and by which mechanisms insulin directly affects renal function and blood pressure in DM.

Assessing any effect of endogenous or exogenous hyperinsulinemia *per se* on long-term CVD outcomes in T2DM is nearly infeasible. This is due to practical and ethical reasons. Insulin treatment is usually applied late in the course of T2DM. Patients are mostly older than 60 years and are likely to have already developed complications. Other comorbidities may also exist. Obviously, such patients are prone to developing HF or other cardiovascular complications independently of insulin or any other treatment [64]. The most common reason for initiating insulin treatment is poor DM control with an HbA_{1c} >8.5% in most instances. Thus, the effects of long-lasting hyperglycemia may prevail over the effects of insulin. In the Study of Once Daily Levemir (SOLVE™), it was an international observational study involving 10 countries and a total of 17,374 participants with T2DM, at the time of initiation of insulin treatment the mean age of patients was 62 years, the mean duration of DM 10 years, and the mean HbA_{1c} 8.9% (standard deviation 1.6%) [64]. SOLVE could not evaluate the effect of insulin on HF because there is significant inertia of starting insulin treatment despite the guidelines [64]

Two studies attempted to assess the effect of insulin treatment on CVD outcomes. In the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, 12,537 patients with impaired fasting glucose, impaired glucose tolerance, or T2DM and CVD risk factors were randomized to insulin or standard care alone [65]. Insulin treatment had a neutral effect (hazard ratio 1.04; 95% confidence interval, 0.97-1.11) on the composite primary outcome death from CVD causes, CVD events and hospitalization for HF [65]. Another small, short-term randomized clinical trial evaluated the effect of insulin in 40 patients with inadequately controlled (HbA_{1c} >7.5%) T2DM and reduced LVSD [66]. The patients were randomized to a group in which 'optimized' DM treatment, including insulin use, was applied and a 'control' group with no optimization of treatment, for 4 months. The primary outcome was defined as changes in the left ventricular contractile reserve capacity from baseline to follow-up. The study showed no impairment of cardiac function and no patients were hospitalized for HF during the study period [66].

CONCLUSION

HF is an early and severe complication of DM. Hyperglycemia is a major pathogenic factor, while endogenous insulin or insulin treatment *per se* does not seem to be largely involved in the pathogenesis of HF. Careful management of HF is mandatory, although it can be very difficult. Appropriate pharmacological treatment combined with good metabolic control seems to offer the best chances for beneficial outcomes. When the right treatment for HF is applied, insulin administration is safe and is the proper means for achieving good glycemic control.

LIST OF ABBREVIATIONS

AMPK	=	Adenosine monophosphate-activated protein kinase
CAD	=	Coronary heart disease
CV	=	Cardiovascular
DPP-4	=	Dipeptidyl peptidase-4
GLP-1	=	Glucagon-like peptide 1
PKC	=	Protein kinase C
PPAR-α	=	Peroxisome proliferator-activated receptor-α
PPAR-γ	=	Peroxisome proliferator-activated receptor-γ
PI3K	=	Phosphoribosyls 3-kinase
RAGE	=	AGE receptor
ROS	=	Reactive oxygen species
RAAS	=	Renin–angiotensin–aldosterone system
ICAM-1	=	Intracellular adhesion molecule-1;
MCP-1	=	Monocyte chemoattractant protein-1;
NFκB	=	Nuclear factor kappa B
PAI-1	=	Plasminogen Activator Inhibitor 1
IRS	=	Insulin receptor substrate
IκB	=	Inhibitor of kappaB
TF	=	Tissue factor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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