Cardiovascular diseases and diabetes: causes and cures
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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G. D. Lopaschuk
The prevalence of diabetes worldwide has reached epidemic proportions, with the number of type 2 diabetes mellitus (T2DM) patients now exceeding 400 million. This is a major concern, as T2DM patients are at a much higher risk of developing myocardial ischemia and heart failure than nondiabetic individuals. As a result, cardiovascular disease is the major cause of death of T2DM patients. Although initially considered a "vascular disease" with its associated accelerated atherosclerosis, it is now evident that diabetes also directly affects cardiac cellular mechanisms that can contribute to the incidence and severity of heart failure and ischemic heart disease. This creates both problems and opportunities when treating the diabetic patient with cardiovascular disease. The main problem is that the physician must not only treat the heart disease, but also control the diabetes. There is opportunity arising from understanding how diabetes directly affects the cellular mechanisms contributing to heart disease, as this has the potential to reveal new targets and approaches in treating cardiovascular disease in the diabetic. The articles in this issue of Heart and Metabolism address the important problem of cardiovascular disease in the diabetic while addressing both the causes and potential cures for cardiovascular disease in the T2DM patient.

The rapid rise in the incidence of T2DM worldwide is especially evident in the South Asian population where T2DM has increased dramatically in places such as India and China. In their article, Peter Nilsson and Louise Bennet highlight how diabetes is a global concern and the importance of taking a global view in treating diabetes. They also discuss the significant issue of migration and T2DM risk, while emphasizing the importance of public measures to tackle the epidemic in migrant populations. This includes the promotion of healthy lifestyles and improvement of social conditions for these migrant populations.

The risk of developing heart failure positively correlates with the degree of hyperglycemia in the T2DM patient. Although this would imply that lowering blood glucose should decrease cardiovascular risk, this is not always the case. Despite the rapidly expanding list of antihyperglycemic agents used to treat T2DM, many of these agents are not associated with improved cardiovascular outcomes. However, as reviewed by myself in this issue of Heart and Metabolism, recent large clinical outcome trials have provided evidence that some newer antihyperglycemic agents can significantly improve cardiovascular outcomes in the T2DM patient. These clinical studies provide encouraging evidence that certain types of glycemic control may be an important approach to lessening the severity of cardiovascular disease in the T2DM patient.

Management of heart disease in diabetic patients is complex but should follow the same general principles as for patients without diabetes, which includes controlling ischemic symptoms and reducing ischemic burden. The article by Romualdo Belardinelli nicely describes the indications for medical therapy versus coronary revascularization in diabetic patients with both diabetes and ischemic heart disease. Man-
agement issues are also evident in diabetic patients presenting with heart failure. Patients with diabetes are at high risk for developing left ventricular dysfunction and heart failure. The article by Dominic Leung and Melissa Leung describes the need for early comprehensive assessment of cardiac structure and function in diabetics at risk for developing heart disease and the role exercise echocardiography has in this process. Maria Scali also provides an insightful case report as to the need for risk stratification in treating the diabetic with chest pain. A low-cost approach using echocardiography, electrocardiogram changes, and coronary flow reserve provides a versatile approach to treating the diabetic with chest pain. The article by Joao Eduardo Salles provides insights into what the cardiologist needs to know with regard to the new drugs that are now available to control blood glucose in the diabetic, as well as their implications for cardiovascular disease risk.

Diabetes results in some dramatic alterations in energy metabolism in the heart. Diabetes can result in unique changes in cardiac function and metabolism, especially at the level of cardiac energy metabolism. The article by Kim Ho and John Ussher provides an update on what is known about the dramatic switch in energy metabolism from glucose to fatty acid metabolism and the implications of this on cardiac function in the diabetic. These cardiac metabolic changes seen in the diabetic provide an opportunity to treat heart disease in the diabetic using approaches that directly target cardiac energy metabolism. The article by Gabriele Fragasso and colleagues describes how using the metabolic modulator trimetazidine could be one such approach. Inhibition of fatty acid oxidation has emerged as a new approach to treating ischemic heart disease and heart failure. This type of approach may be particularly relevant in the diabetic with heart disease due to the metabolic switch in the heart toward an excessive use of fatty acids.

Cardiovascular disease has now become the number one cause of death worldwide. The rapid global rise in the incidence of T2DM is an important contributor to this grim statistic. Hopefully, this issue of *Heart and Metabolism* will provide some unique perspectives not only on how the diabetic patient with heart disease should be treated, but also for future direction in how the diabetic patient should be managed.

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The growth of type 2 diabetes (T2DM) as a global public health threat has attracted considerable attention over the last 2 decades. Epidemiological studies have predicted that whereas 422 million subjects were affected by diabetes in 2014, the coming decades will see an astonishing 438 million adults affected by 2030 (www.idf.org). A recent review in *The Lancet* concluded that the burden of diabetes, both in terms of prevalence and number of adults affected, has increased faster in low-income and middle-income countries than in high-income countries.1 The tremendous cost of this diabetes epidemic can be counted not only in financial terms as cost of illness, treatment, and disability, but also in terms of the human cost of suffering and a lowered health-related quality of life.

**Contributing factors to the diabetes epidemic**

The increasing burden of T2DM on a global scale is a reflection of a number of contributing factors with considerable health consequences. First of all, the aging of many populations, with an increasing proportion of elderly people, will contribute to the growing number of subjects reaching the age ranges where T2DM becomes more prevalent. Other contributing factors include a wider screening effort in health care and a time trend for lowering the plasma glucose threshold for a diagnosis of T2DM. More detailed glucometabolic studies have been conducted in high-risk migrant populations, eg, from the Middle East. Recently, intervention programs have also been tested to improve lifestyle and reduce the risk of developing T2DM in at-risk individuals. There are many obstacles to success for such programs, which should be tailored not only to the individual in a culture-sensitive way, but also to families and local ethnic communities.

The epidemic of type 2 diabetes mellitus (T2DM) on a global scale is a matter of concern, not only from a public health perspective, but also with consideration of societal costs. The increased call on health care resources to treat and monitor T2DM and its complications could put a heavy burden on national health care systems and financing. An important contributing factor for development of T2DM is lifestyle, reflecting increasing affluence and exposure to increased calorie intake in combination with sedentary lifestyle and less human energy expenditure. More detailed glucometabolic studies have been conducted in high-risk migrant populations, eg, from the Middle East. Recently, intervention programs have also been tested to improve lifestyle and reduce the risk of developing T2DM in at-risk individuals. There are many obstacles to success for such programs, which should be tailored not only to the individual in a culture-sensitive way, but also to families and local ethnic communities. & *Heart Metab.* 2017;73:4-8

**Keywords:** costs; diabetes; global, lifestyle, migration, obesity

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**Abstract**

The epidemic of type 2 diabetes mellitus (T2DM) on a global scale is a matter of concern, not only from a public health perspective, but also with consideration of societal costs. The increased call on health care resources to treat and monitor T2DM and its complications could put a heavy burden on national health care systems and financing. An important contributing factor for development of T2DM is lifestyle, reflecting increasing affluence and exposure to increased calorie intake in combination with sedentary lifestyle and less human energy expenditure. More detailed glucometabolic studies have been conducted in high-risk migrant populations, eg, from the Middle East. Recently, intervention programs have also been tested to improve lifestyle and reduce the risk of developing T2DM in at-risk individuals. There are many obstacles to success for such programs, which should be tailored not only to the individual in a culture-sensitive way, but also to families and local ethnic communities. & *Heart Metab.* 2017;73:4-8

**Keywords:** costs; diabetes; global, lifestyle, migration, obesity
such as India, China, and some countries in the Middle East is a factor and it is related to increasing affluence and a change in diet and calorie-intake composition. At the same time, increased mechanization of the transport system and working conditions has reduced the amount of physical exercise needed on a daily basis. This is further influenced by a passive lifestyle related to sedentary leisure activities, such as watching television or time spent on the computer, so-called “screen time.” The young generation is especially affected, and this is a reason to worry, as the sedentary young individuals of today risk becoming the patients with T2DM of tomorrow. Another contributing risk factor is smoking, now very prevalent in developing countries even though smoking prevalence rates have decreased in many Western countries. Heavy smoking has been associated with increased insulin resistance, β-cell unresponsiveness to secreted insulin, chronic inflammation, and impaired glucose metabolism.4 Furthermore, smoking is often combined with an increased intake of alcohol, at least in cultures and countries with no ban on alcohol. This factor could contribute to the damage of pancreatic function and thus act in synergy with heavy smoking to increase the risk of T2DM. Also, smokers tend to have a spontaneously chosen selected diet, including more coffee, alcohol, sucrose, and saturated fat, but less vitamins, vegetables, and fruits, than nonsmokers.5 This may be influenced by impaired taste bud function or triggering of brain reward systems due to smoking.

The role of obesity in a global perspective

An interesting aspect is that obesity could be a major contributing factor for T2DM, as it is globally increasing, but with different thresholds for diabetes risk. For example, in Asian populations, the risk of type 2 diabetes starts to increase at a lower body mass index (BMI) than in Western populations,6 and this could also be influenced by the fat distribution; there is a relatively more pronounced tendency for abdominal obesity in subjects of Asian origin. Therefore genetic factors could contribute to differential susceptibility to obesity-induced glucometabolic changes.

With globalization, there is an increased flux of people, goods, and work opportunities across borders and regions all around the world. There remain many obstacles to globalization, such as restrictive regulations, laws, and border controls; nevertheless, political and societal changes in the wake of war, famine, and catastrophes has forced millions of refugees and migrants to cross borders and to move from one country or region to another, often far away. So far, this has influenced lifestyle changes, cultural norms, and health behaviors (and will continue to do so). One typical example is the profound change in lifestyle that migrants from the Middle East region experience as they come to live in Western countries. In addition, these immigrants will also face social problems and adverse living and working conditions, as well as social tensions, prejudice, and even racism, factors that could contribute to social stress, isolation, and difficulties in coping with cultural changes during the acculturation process. For some migrants with a cultural background where obesity is seen as a sign of wealth and prosperity and, for women, a sign of fertility, the health messages of leanness and calorie restriction in Western societies is sometimes hard to understand and accept. In addition, some religious beliefs could affect eating habits and the timing of food intake (eg, Ramadan), a factor that is associated with adverse changes in glucose metabolism.7

On the other hand, it should not be overlooked that globalization can also encourage healthy eating as free trade can increase the supply of cheap vegetables, fruits, and seafood. The flux of people visiting other countries could increase exposure to sunshine (vitamin D) and recreation, both of which are health-promoting factors. However, there is also a downside to global trade and traveling, as transportation is energy dependent and contributes to the burden on the environment.

Migration and type 2 diabetes risk

The risk of T2DM in the wake of migration and globalization has been studied in certain populations, for example, in people of South Asian origin moving to London in the UK and adapting a Western lifestyle.8 These subjects are known to be at increased risk for developing features of the metabolic syndrome (eg, abdominal obesity, impaired glucose metabolism, and T2DM). One contributing factor besides genetics could be an individual background of impaired fetal growth and the small-for-gestational-age birth phenotype, as this has been shown to affect the risk of developing T2DM in adult life if combined with un-
healthy lifestyle. Also, diabetes in pregnancy is a growing problem in developing countries, with an impact on health in the offspring, thus reinforcing the importance of early life conditions for understanding the global epidemic of T2DM.

In Sweden today, 1.6 million out of almost 10 million inhabitants are born abroad with the largest non-European immigrant groups represented by immigrants from the Middle East, Africa, and Asia (Statistics Sweden, 2016). Extensive epidemiological research on the risk of T2DM in migrants from the Middle East to Sweden has been carried out. Wändell et al has documented that the prevalence of T2DM is at least doubled in migrants from the Middle East, including Turkey and Iraq, as compared with Swedish-born subjects. This phenomenon is especially pronounced in obese Turkish women, as influenced by parity, sedentary lifestyle, and suboptimal dietary habits, even if smoking is not frequent.

The MEDIM study in Iraqi immigrants

In the MEDIM study (the impact of Migration and Ethnicity on Diabetes in Malmö), conducted in the city of Malmö, Sweden, a number of observational, mechanistic, and intervention studies were undertaken to elucidate mechanisms contributing to the increased risk of impaired glucose metabolism and T2DM in adult migrants from Iraq. The findings from MEDIM, which investigated approximately 1400 Iraqi immigrants and 800 native Swedes via oral glucose tolerance testing (OGTT), shows prevalence rates of T2DM of 12% and 6%, respectively. However, the prevalence of T2DM in urban areas in Iraq reaches 19% and is considerably higher than in rural areas (7.5%). This higher prevalence in Iraqi cities is thought to be a consequence of a less physically active lifestyle, sedentary work, and higher access to calorie-dense foods than in rural life. Such data could indicate that there is no “true” worsening migration effect (ie, that stress and lifestyle change during migration should increase cardiometabolic disease as is shown in other immigrant groups). One reason for this could be that life in an urban area in Sweden presents a relatively healthy environment compared with urban areas in the Middle East, with access to healthy foods, physical activity opportunities, and public health care, in spite of social adversities. Still, the prevalence of T2DM in Iraqis is twice as high as in the native Swedish population, and furthermore, the Iraqi immigrants develop T2DM 6 to 7 years earlier than native Swedes. The high T2DM is thus not fully explained by well-known diabetes-related risk factors, such as unhealthy lifestyle, obesity, family history, or socioeconomic vulnerability that clusters in this population; this indicates that a genetic mechanism may contribute to the increased risk. The Iraqi population displays impaired glucose metabolism with higher glycated hemoglobin (HbA1c) levels and increased insulin resistance, even in the nondiabetic range. Further, for the same BMI level, insulin sensitivity is more impaired in the Iraqi immigrant population (Figure 1). One contributing factor to this insulin resistance could be a higher prevalence of nonalcoholic fatty liver disease (NAFLD), which is found to differ in prevalence across ethnicities. Estimation of NAFLD via index scores has shown that the Iraqi population has a higher prevalence, and that NAFLD indices are more strongly associated with insulin resistance in the Iraqi than in the native Swedish population. This indicates that the liver may play a key role in fat and glucose regulation in this population.

Data from the National Diabetes Register in Sweden shows that although non-Westernized immigrants diagnosed with T2DM are offered more frequent visits to physicians, their glycemic control is worse, and they develop diabetic microvascular complications faster, than native Swedes. Altogether, these data indicate that T2DM in non-Westernized populations progresses faster and is a more complex condition to prevent and manage than T2DM in a native Swedish population.
Diabetes prevention programs in immigrants

Increased knowledge of mechanisms contributing to the increased diabetes risk in non-European immigrants is important for the prevention and treatment of diabetes in these populations. A Cochrane review provides evidence that culturally adapted lifestyle interventions addressing non-Westernized immigrants with T2DM have beneficial effects on glycemic control in the short term (<24 months), but longer studies are needed. In Sweden and Norway, beneficial effects of culturally adapted programs targeting immigrants from Iraq and Pakistan still free from T2DM have shown beneficial effects on cardiometabolic control, indicating that such programs have beneficial preventive effects. The question is how such programs should be organized, since resources addressing preventive actions are not prioritized today. It is highly probable that more proactive primary prevention strategies addressing non-Westernized immigrant populations could save costs spent on diabetes, but would also contribute to a higher quality of life and health equality.

Summary

In summary, the high cost of globalization for the growing epidemic of T2DM is not only counted in terms of health care, but also in terms of human suffering and reduced health-related quality of life. Public health measures to tackle the epidemic should involve both societal changes, such as promotion of healthy lifestyle and improved social conditions for growing populations, and prevention aimed at individuals, families, and local communities. The technological changes on a global scale could promote sedentary lifestyle, but they could also be used to support a healthy lifestyle if consumption of healthy food could be made easier and cheaper. A reduction in smoking and alcohol intake could add to the preventive measures of importance not only to counteract the epidemic of T2DM, but also of other chronic disease conditions. Further studies on mechanisms involved to better understand the transition to T2DM in migrant populations at risk will be of importance to tailor preventive programs. The time is ripe to offer at-risk populations and individuals access to preventive programs to improve lifestyle and glucose metabolism. Such projects are already underway and should be expanded in order to increase the evidence base for effective methods.

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Better glycemic control and cardiovascular outcomes

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Abstract
Diabetics are at high risk of developing cardiovascular disease, which is correlated to the degree of hyperglycemia. However, pharmacological approaches to lowering blood glucose levels in diabetics is not always associated with a decrease in the risk of developing heart failure. In fact, some treatments actually increase the risk of cardiovascular disease. For instance, the use of thiazolidinediones (ie, rosiglitazone and pioglitazone) increases the risk of heart failure development in type 2 diabetes mellitus (T2DM) patients. Older antihyperglycemic medications, such as metformin, also seem to have a reduced risk of adverse cardiovascular outcomes compared with sulfonylureas. Newer agents, such as the glucagon-like protein 1 (GLP-1) receptor agonists, the dipeptidyl peptidase-4 (DPP-4) inhibitors, and the α-glucosidase inhibitors, appear to have neutral effects on cardiovascular outcomes. In contrast, recent trials with sodium-glucose cotransporter 2 (SGLT2) inhibitors (ie, empagliflozin) have demonstrated a dramatic decrease in adverse cardiovascular outcomes. As a result, it is clear that care must be taken in choosing the antihyperglycemic agent to be used in T2DM patients, especially if underlying cardiovascular disease is present. □ Heart Metab. 2017;73:9-12

Keywords: antihyperglycemic agent; cardiovascular outcome; heart failure; type 2 diabetes mellitus

Introduction
The prevalence of diabetes worldwide has rapidly increased in the last 20 years, with the number of type 2 diabetes mellitus (T2DM) patients now exceeding 400 million.1 These diabetic patients are at twice the risk of developing cardiovascular disease, which is the most common cause of death in diabetics.2 The risk of developing heart failure in diabetics is also positively correlated to the degree of hyperglycemia.3,6 As a result, this would imply that lowering blood glucose should decrease cardiovascular risk. However, there is uncertainty in this regard, and lowering glucose levels may not always result in a reduction in the risk of heart failure. It is also becoming clear that the type of pharmacological approach used for lowering blood glucose may have differential effects on cardiovascular risk in the diabetic. In fact, some antihyperglycemic therapies may actually increase the risk of developing heart failure. As a result, the European Medicines Agency and the US Food and Drug Administration implemented regulations in 2008 calling for adequately powered cardiovascular outcomes trials (CVOTs) to evaluate the efficacy and cardiovascular safety of new antihyperglycemic agents. Although many of these CVOTs
are still ongoing, reports from a number of trials are available; in some, antihyperglycemic agents have been reported to increase the risk of developing heart failure; in others, to have neutral effects on heart failure risk or actually lessen heart failure risk. This paper reviews this clinical data.

Blood glucose and heart failure

Poor glycemic control in T2DM is associated with an increased risk of developing heart failure.6,7 This includes poor glycemic control as assessed by increased fasting blood glucose, postprandial blood glucose, glycated hemoglobin (HbA1c) levels, and/or measures of insulin resistance in T2DM patients. Trials such as UKPDS (the United Kingdom Prospective Diabetes Study) also showed a beneficial effect between lowering blood glucose and decreasing heart failure risk in T2DM patients.8 A number of medications have been developed to improve glycemic control in T2DM patients, and these include thiazolidinediones (TZDs), insulin analogs, metformin, sulfonylureas, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like protein 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. However, despite being effective antihyperglycemic agents, these medications have very different effects on heart failure risk in T2DM patients. The reasons for these differences in heart failure risk in T2DM patients taking these medications are not completely clear, although it is clear that it is not related to the degree of glycemic control. However, as the outcomes of more and more CVOTs trials are reported, it is clear that when choosing the type of antihyperglycemic agent to use in T2DM patients, the risk of heart failure development should be carefully considered.

Thiazolidinediones

TZDs are peroxisome proliferator–activated receptor-γ agonists that have insulin-sensitizing actions. Rosiglitazone and pioglitazone are two agents in this class of medications. However, despite favorable antihyperglycemic and blood pressure–lowering actions, both of these agents in CVOTs showed increased risk of heart failure in T2DM patients8,9 (Table I). The reasons for this increase in heart failure risk are not clear, although plasma volume expansion due to increasing renal tubular sodium reabsorption has been proposed. The outcomes of these CVOTs suggests that the use of TZDs should be contraindicated in patients at high risk for heart failure.

Metformin

Metformin is an older antihyperglycemic agent that has not been investigated in larger CVOTs. However, UKPDs demonstrated that metformin reduced the rate of adverse cardiovascular outcomes in T2DM patients with heart failure compared with other antihyperglycemic agents.4 This included a 20% lower death rate than with other antihyperglycemic agents.

<table>
<thead>
<tr>
<th>Antihyperglycemic agent</th>
<th>Heart failure risk</th>
<th>Hypoglycemia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (rosiglitazone, pioglitazone)</td>
<td>Increased</td>
<td>Low</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decreased compared with sulfonylureas</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonylureas (tolbutamide, glibenclamide)</td>
<td>Increased compared with metformin</td>
<td>Higher</td>
</tr>
<tr>
<td>GLP-1 receptor agonists (lixisenatide, liraglutide)</td>
<td>Neutral</td>
<td>Low</td>
</tr>
<tr>
<td>DPP-4 inhibitors (saxagliptin, sitagliptin)</td>
<td>Increased with saxagliptin</td>
<td>Low</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (acarbose)</td>
<td>Increased compared with DPP-4 inhibitors</td>
<td>Low</td>
</tr>
<tr>
<td>SGLT2 inhibitors (empagliflozin)</td>
<td>Decreased</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table I Classes of antihyperglycemic agents and associated risks of developing heart failure and hypoglycemia in type 2 diabetes mellitus patients.

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like protein-1; SGLT2, sodium-glucose cotransporter 2.
Better glycemic control and cardiovascular outcomes

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are oral antihyperglycemic agents that increase incretin levels (GLP-1 and gastric inhibitory polypeptide [GIP]) by blocking their degradation by DPP-4; they therefore increase insulin secretion and inhibit glucagon release. Saxagliptin and sitagliptin are two representative DPP-4 inhibitors. The first major CVOT with DPP-4 inhibitors that was reported was with saxagliptin, which examined 16,492 patients with T2DM and a history of cardiovascular disease over a 2.1-year period. Although there was no difference in cardiovascular death, myocardial infarction, or stroke seen in the saxagliptin-treated patients, a significant increase in hospitalization for heart failure was observed. In addition, an increased risk for hypoglycemic events was observed. In contrast, a recently completed CVOT (involving 14,671 patients) that examined sitagliptin in T2DM patients with cardiovascular disease showed that sitagliptin was noninferior to placebo for the primary composite cardiovascular outcomes, and no difference in hospitalization rates for heart failure was observed. As a result, DPP-4 inhibitors have proven cardiovascular safety in T2DM patients, although caution should be used with saxagliptin in heart failure patients.

α-Glucosidase inhibitors

α-Glucosidase inhibitors, which include acarbose, have antihyperglycemic actions by preventing carbohydrate digestion in the small intestine. Although a large CVOT has not been performed with acarbose in T2DM patients, a meta-analysis of smaller randomized clinical trials did not show any differences in heart failure outcomes. However, a recent study comparing add-on therapy with acarbose added to a combined dual therapy with metformin and sulfonylurea showed that the risk of stroke and all-cause mortality was higher with DPP-4 inhibitor add-on therapy.

Sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors are antihyperglycemic agents that act by preventing glucose reabsorption in proximal tubules of the kidney. Three representative SGLT2 inhibitors include empagliflozin, canagliflozin, and dapagliflozin. Of these, only empagliflozin has been investigated in a complete and major CVOT, the EM-
PA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes). Empagliflozin was examined in high-risk patients with diabetes and established cardiovascular disease over a 3-year treatment period. The CVOT reported a dramatic 35% to 40% relative reduction in cardiovascular death and all-cause mortality in empagliflozin-treated patients. A dramatic decrease in hospitalization for heart failure was also observed. This has generated considerable excitement, although the mechanisms for the beneficial effects of empagliflozin have not been unequivocally determined. Possible mechanisms for this benefit include a decrease in diuresis and plasma volume, a decrease in body weight, or an increased cardiac efficiency in use of fuel. Although major CVOTs have yet to be reported for other SGLT2 inhibitors, the dramatic benefit on cardiovascular outcomes with empagliflozin and the low risk for hypoglycemic events has resulted in empagliflozin presently being evaluated for heart failure treatment even in the absence of diabetes.

Summary

Although hyperglycemia is an important contributor to increased cardiovascular risk in diabetics, not all antihyperglycemic approaches in T2DM patients have similar effects on heart failure risk. Some pharmacological approaches can actually increase heart failure risk, whereas some have neutral effects. In contrast, some approaches, such as SGLT2 inhibition, may actually significantly decrease the risk of developing heart failure in T2DM.

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Treating myocardial ischemia in diabetics: drugs, surgery, and stents

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Abstract
Diabetes mellitus (T2DM) is a chronic, progressively worsening disease associated with a variety of complications. Management of T2DM should take into account that coronary artery disease may be silent for many years in diabetic patients, and so both primary and secondary prevention must be a priority in the treatment of such disease. The management of chronic stable angina in patients with T2DM follows the same principles as those for patients without diabetes mellitus—controlling ischemic symptoms and reducing ischemic burden. To this end, treatment consists of medications combined with lifestyle modifications, the three main interventions being smoking cessation, regular moderate aerobic exercise, and correct nutrition. This article focuses on antianginal/anti-ischemic medications and myocardial revascularization procedures. Guidelines suggest use of β-blockers or calcium antagonists as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, and trimetazidine should be considered when first-line medications cannot be used or are insufficient. On the basis of findings from BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease), and recent meta-analyses, coronary artery bypass grafting is considered the preferred coronary revascularization procedure in patients with T2DM and multivessel disease when reduction in clinical events is the main goal of treatment. ■ Heart Metab. 2017;73:13-17

Keywords: chronic angina; diabetes mellitus; therapeutic strategy

Introduction
Diabetes mellitus is a chronic, progressively worsening disease associated with a variety of complications. Over the last 2 decades, the decline in heart disease mortality in Western countries has not been paralleled by a similar trend in patients with diabetes mellitus. A reduction in cardiovascular risk factors and improvement in the treatment of heart diseases seem to be less effective in the diabetic population. Type 2 diabetes mellitus (T2DM) is an independent risk factor for atherosclerosis and future coronary artery disease. Diabetes mellitus is associated with a higher risk of coronary events and a two-to-fivefold increased risk of death.1 Many patients with T2DM (from 17% to 59%, according to clinical studies) have silent myocardial ischemia on electrocardiography (ECG) stress testing, and a silent acute coronary syndrome occurs in 40% of cases. Management of T2DM should take into account that coronary artery disease is frequently silent for many years in diabetic patients. Thus, primary, as well as...
secondary, prevention must be a priority in the treat-
ment of such disease.2

The management of chronic stable angina in pa-
tients with T2DM follows the same principles as those
for patients without diabetes mellitus, namely, con-
trolling ischemic symptoms and reducing ischemic
burden.3,4 These objectives are reached by combin-
ing medications with lifestyle modifications based on
three main interventions: smoking cessation, regular
moderate aerobic exercise, and correct nutrition.
Here, we focus on antianginal/anti-ischemic medica-
tions and myocardial revascularization.

Medications

To date, few specific trials have been published on the
efficacy of antianginal agents in the diabetic population,
and most information derives from subgroup analyses.

β-Blockers

Ischemic symptoms can be controlled by β-blockers. Large
trials have shown that β-blockers are more ef-
efactive in diabetic patients with myocardial infarction
than in nondiabetic patients.5 For instance, in the
Göteborg Metoprolol trial, diabetic patients with myo-
cardial infarction had a significantly greater relative
risk reduction at 3 months than nondiabetic patients
(58% vs 36% reduction; P<0.05). This trend was con-
firmed at 1-year follow-up.6 β-Blockers are effective in
reducing angina pectoris, increasing ischemic thresh-
old during exercise, and improving work tolerance
by reducing heart rate and double pressure product
and myocardial oxygen (O₂) consumption at any work
rate. β-Blockers are effective in hypertension, which
is frequently associated with diabetic patients. They
also prevent acute myocardial infarction and sudden
death in diabetic patients with no previous myocardial
infarction. These benefits overcome the negative ef-
efect of β-blockers on glycemic control and suggest
the use of these medications in diabetic patients with
stable angina. However, side effects, such as fatigue,
depression, bradycardia, and sexual dysfunction may
limit their use. Lipophilic agents, such as metoprolol,
should be preferred in patients with renal dysfunction.

Calcium antagonists

The three major classes of calcium antagonists (CA)
are the dihydropyridines (nifedipine, amlodipine, and
felodipine), the phenylalkylamines (verapamil), and
the modified benzothiazepines (diltiazem). They improve
the balance of O₂ supply and demand and dilate
blood vessels with a consequent reduction in blood
pressure. These effects may explain the increasing use
of CA in diabetics, especially those with concomitant
hypertension, either as monotherapy or in combina-
tion with other agents.7 Although some studies have
shown a greater clinical efficacy of β-blockers, there
are at present no significant differences in the rate of
death or myocardial infarction as compared with CA.8
However, their long-term administration has not been
shown to improve survival in post–myocardial infarction
patients. CAs are appropriate initial therapy in patients
with contraindications to β-blockers or in combination
when β-blockade monotherapy is unsuccessful.

Long-acting nitrates

Long-acting nitrates are widely used for preventing
angina attacks in patients with stable angina with or
without diabetes mellitus. They are potent vessel di-
lators, and this effect is predominant in the venous
circulation, with subsequent reduction in preload,
myocardial wall tension, and O₂ demand. This effect
depends on the conversion of nitrates to nitric oxide,
which activates guanylate cyclase to produce cyclic
guanosine monophosphate (cGMP) and smooth
muscle relaxation. Nitrate tolerance is less frequent
when a daily interval is maintained. The antianginal
effect appears to be greater when nitrates are com-
bined with CA and/or β-blockers.8

Ranolazine

Ranolazine was recently approved as antianginal
medication in stable angina.9 Its efficacy depends on

Abbreviations

BARI 2D: Bypass Angioplasty Revascularization In-
vestigation 2 Diabetes [trial]; CA: calcium antagonist;
CABG: coronary artery bypass grafting; FREEDOM: Fu-
ture REvascularization Evaluation in patients with Dia-
betes mellitus; Optimal Management of multivessel
disease; OMT: optimal medical therapy; PCI: percuta-
neous coronary intervention; T2DM: type 2 diabetes
mellitus
two mechanisms, a metabolic effect of inhibition of fatty acid β-oxidation and a reduction in calcium overload in ischemic myocytes through inhibition of the late inward sodium current. A recent trial showed that a dose of 1000 mg twice a day for 8 weeks significantly reduced the number of weekly angina attacks by 13% (P=0.008) and weekly sublingual nitroglycerin use by 23.5% (P=0.003) as compared with placebo. Because of its effect in prolongation of the QT interval, ranolazine is contraindicated in patients with long-QT syndrome or in combination with other QT-prolonging drugs, such as amiodarone, sotalol, and other noncardiovascular active agents.

**Ivabradine**

Ivabradine decreases heart rate by a selective inhibitory effect on funny-current (If) channels of the sinoatrial node, without any effect on glucose metabolism or adrenergic activity. It has been approved in Europe for the treatment of patients with stable angina with or without diabetes who do not tolerate β-blockers or in those who are inadequately controlled with an optimal dose of a β-blocker.

**Nicorandil**

Nicorandil dilates peripheral and coronary vessels through its action as an adenosine triphosphate (ATP)-sensitive potassium-channel opener and nitric oxide donor. As a result, nicorandil reduces preload and afterload and vasodilates coronary arteries. Its anti-ischemic efficacy has been demonstrated in a trial studying 5126 patients with stable angina, with a significant improvement in outcome owing to a reduction in major coronary events in patients. However, in that study, less than 10% of patients had diabetes mellitus.

**Trimetazidine**

Trimetazidine is a piperazine derivative with antiangiinal efficacy. Trimetazidine at doses of 20 mg three times a day or 35 mg twice a day improves the ischemic threshold during exercise and reduces the number of angina attacks and sublingual nitroglycerin use as compared with placebo. This beneficial effect is related to inhibition of β-oxidation requiring five times more O2 than glucose oxidation, which is consequently accelerated. This results in a more efficient ATP production by ischemic myocytes and a subsequent greater contractility, translating into better left ventricular function. Trimetazidine has no effect on glucose homeostasis, and its efficacy is predominant in diabetic patients with reduced left ventricular efficiency.

In summary, guidelines suggest use of β-blocker or CAs combined as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, trimetazidine, ivabradine, and long-acting nitrates should be con-

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**Table I** Medications to treat stable angina in patients with type 2 diabetes mellitus.

**Abbreviations:** ATP, adenosine triphosphate; CV, cardiovascular; GI, gastrointestinal; Na, sodium; NO, nitric oxide; O2, oxygen
Coronary revascularization

In patients with T2DM and stable angina, the therapeu•tic strategy should focus on combining improve•ment in functional capacity and quality of life with re•duction in cardiovascular events and life prolongation. These objectives are obtained with a combination of medications, lifestyle changes, and reduction in re•versible cardiovascular risk factors. Revascularization approaches should be considered when optimal medical therapy (OMT) alone is insufficient to control symptoms and a patient is at-risk of cardiovascular events due to the severity and extent of coronary artery disease. Recommendations for percutaneous coronary intervention (PCI; a nonsurgical intervention that may involve stent implantation) or coronary artery bypass grafting (CABG; a surgical intervention) should be based on both the severity and extent of inducible myocardial ischemia, the severity of symp•toms and their control by pharmacological and non•pharmacological tools, and functional deterioration. On the basis of the BARI trial (Bypass Angioplasty Revascularization Investigation) results, patients with T2DM treated with percutaneous transluminal coronary angioplasty (PTCA) had a 5-year mortality of 35% vs 19% for those who underwent CABG (P=0.003). At 10 years, the superior•ity of CABG was more evident. On the basis of the findings from BARI 2D (BARI 2 Diabetes), FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Opti•mal Management of multivessel disease), and recent meta-analyses, CABG is considered the preferred coronary revascularization procedure when patients with T2DM and multivessel coronary artery disease when reduction in clinical events is the main goal of treat•ment. In patients with angina not considered at high risk, survival is similar for surgery, PCI, and OMT. In patients with single-vessel disease in whom revas•cularization is necessary, PCI is preferable to CABG.

Conclusion

The management of chronic stable angina in patients with T2DM follows the same principles as those for patients without diabetes mellitus, namely, controlling ischemic symptoms and reducing ischemic burden. These objectives are reached through the combina•tion of medications and lifestyle modifications, the three main interventions being smoking cessation, regular moderate aerobic exercise, and correct nu•trition. According to guidelines, a combination of β-blockers and CAs should be considered as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, trimetazidine, ivabradine, and long-acting nitrates should be considered when first-line medica•tions cannot be used or are insufficient. Revasculariza•tion approaches should be considered when OMT alone is insufficient to control symptoms and a patient is at-risk of cardiovascular events due to severity and extent of coronary artery disease. Recommendations for PCI or CABG should be based on both the severity and extent of inducible myocardial ischemia, the severity of symptoms and their control by pharmacological and nonpharmaco•logical tools, and functional deterioration.

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Early detection of left ventricular dysfunction in diabetes

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Abstract
Patients with type 2 diabetes are at risk of developing left ventricular (LV) dysfunction and heart failure. Symptoms associated with LV dysfunction in these patients, especially in the early stages, may be minimal or attributed to other noncardiac factors. LV dysfunction in diabetes is multifactorial, but there is evidence of the specific entity of diabetic cardiomyopathy. Although a direct relationship between glycemic control and LV function has not been firmly established, there is increasing evidence to suggest that poor glycemic control is associated with LV dysfunction and that improving glycemic control improves LV function. A high index of suspicion is necessary in managing these patients. Echocardiography is a noninvasive, widely available imaging tool that provides comprehensive assessment of cardiac structure and function. Exercise echocardiography allows detection of coronary disease and assessment of LV diastolic reserve. A multifaceted approach targeting all vascular risk factors in the management of LV dysfunction in these patients is essential. A specific treatment for diabetic cardiomyopathy is still lacking, but optimizing glycemic control and aldosterone antagonism may be beneficial, and trials are currently underway. Early detection of LV dysfunction allows identification of at-risk patients and timely intervention, which could ultimately improve patient outcome in this condition, which is associated with significant morbidity and mortality. ■ Heart Metab. 2017;73:18-23

Keywords: cardiomyopathy; diabetes; echocardiography

Introduction
The prevalence of obesity is skyrocketing in both developing and developed countries. This is accompanied by a corresponding increase in the prevalence of type 2 diabetes. Patients with type 2 diabetes have a high prevalence of heart failure, both undiagnosed and diagnosed, and left ventricular (LV) dysfunction. In these patients, although LV dysfunction and heart failure may be attributed to common comorbidities, such as hypertension, obesity, and coronary disease, there is evidence for the distinct clinical entity of diabetic cardiomyopathy. The spectrum of the disease may range from LV diastolic dysfunction in the early stage to systolic dysfunction and overt LV dysfunction and advanced heart failure. The diagnosis of heart failure and LV dysfunction in these patients is often delayed. LV diastolic and systolic dysfunction may be subclinical, and early symptoms of exercise intolerance may be subtle and attributed to lack of physical fitness. Nevertheless, early detection of LV dysfunction in these high-risk...
Evaluation of a 66-year-old man with type 2 diabetes who complained of dyspnea on exertion found left ventricular (LV) hypertrophy, but normal LV ejection fraction. LV global longitudinal strain (GLS) was impaired at -13.2% (Panel A). The patient had grade 1 diastolic dysfunction with a mitral E/A ratio <0.5 at rest (Panel B) and a septal e' velocity of 6 cm/s (Panel C).

**Abbreviations:** 4-ch, 4-chamber view; ANT_SEPT, anteroseptal; APLAX, apical long axis view; AVC_AUTO, aortic valve closure detected automatically; GLPS_A4C, global longitudinal peak strain, apical 4-chamber view; GLPS_LAX, global longitudinal peak strain, apical long axis view; HR, heart rate; HR_ApLAX, heart rate during acquisition of the apical long axis view; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.
patients is important; timely, aggressive, multifaceted management is the key to ameliorating the otherwise devastating consequences of diabetic heart disease.

**Echocardiography in detection of left ventricular dysfunction**

Echocardiography is a versatile, noninvasive, and widely available imaging tool for the assessment of LV structure and function and has been most commonly used in the detection of LV dysfunction. LV ejection fraction is an insensitive marker for early detection of LV dysfunction. Mitral E- and A-wave, and tissue Doppler e'-wave velocities are measures of LV diastolic function. An elevated mitral E/e' velocity ratio is a reliable marker of elevated LV filling pressures, commonly seen in patients with LV dysfunction and heart failure. Echocardiographic strain deformation imaging allows a sensitive, angle-independent, and site-specific assessment of LV systolic function, and assessment of LV global longitudinal strain is superior to ejection fraction in the detection of early diabetic heart disease. Moreover, LV global longitudinal strain has incremental prognostic value over ejection fraction in a wide range of cardiovascular diseases. Exercise echocardiography is a well-accepted, accurate, and noninvasive test for inducible ischemia, allowing detection of coronary artery disease. It also allows assessment of LV filling pressures at rest and after exercise. As an example, Figure 1 and Figure 2 depict an exercise echocardiographic evaluation of a type 2 diabetes patient with dyspnea on exertion.

**Left ventricular dysfunction in diabetes**

The Strong Heart Study demonstrated that heart failure was very prevalent in patients with diabetes despite normal ejection fraction. Fang et al found subclinical LV systolic and diastolic dysfunction in a large proportion of patients with type 2 diabetes without ischemia or hypertrophy. Compared with age-matched controls, asymptomatic patients with type 2 diabetes had impaired LV longitudinal systolic, as well as diastolic, function. In a recent study of 105 patients with poorly controlled type 2 diabetes, we found that these patients have impaired LV diastolic and systolic function and elevated LV filling pressures despite normal LV ejection fraction and LV mass.

The underlying pathophysiological mechanisms of diabetic cardiomyopathy are multifactorial and may include microvascular disease, endothelial dysfunction, autonomic dysfunction, hyperglycemia, hyperinsulinemia, insulin resistance and other metabolic disturbances, myocardial interstitial fibrosis, and myocardial steatosis. Obesity, common in patients with diabetes, may also lead to LV dysfunction. We have demonstrated impaired coronary microvascular function in patients with diabetes in the absence of epicardial coronary stenosis. As cardiac extracellular matrix plays an active role in modulating cardiac function, myocardial fibrosis has been suggested as one of the important mechanisms of LV dysfunction in diabetes.

Although hyperglycemia is the primary metabolic disturbance in diabetes, the relationship between glycemic control and cardiac function is unclear. Some studies have shown poor glycemic control to be associated with abnormal LV relaxation, elevated filling pressures, and impaired systolic contraction. Patients who had poorly controlled diabetes in the Strong Heart Study were found to have abnormal LV relaxation. In 120 patients with type 2 diabetes, peak systolic strain was independently associated with glycated hemoglobin (HbA₁c) levels, whereas septal e’ velocities were related more to age and hypertension and not to glycemic control. However, a number of other studies have demonstrated no association between glycemic control and ventricular function. The relationship between prevailing glycemic control and LV function may be more complicated and affected by multiple factors, including duration of diabetes, presence and control of other vascular risk factors, medications, body weight, and others that are known to have an impact on LV function.

**Impact of improving glycemic control on left ventricular function**

A few studies have examined the effect that improved glycemic control has on LV function. von Bibra et al showed that intensive glycemic control with insulin improved LV diastolic, but not systolic, function. However, others did not demonstrate improvements, despite better glycemic control. Most of these studies examined improved glycemic control over short periods of time, which may not have been sufficient to effect any detectable changes in LV function. We
Fig. 2 Evaluation of a 66-year-old man with type 2 diabetes who complained of dyspnea on exertion (see also Fig. 1) found a dilated left atrium (Panel A), with a maximum left atrial volume of 51 mL/m². On exercise echocardiography, no inducible ischemia was found. Immediately after exercise, the mitral E/A ratio reversed and became >1 (Panel B). The septal e’ velocity decreased to 5 cm/s, leading to a significantly higher E/e’ ratio, this indicates elevated LV filling pressures and limited LV diastolic reserve, explaining the exertional dyspnea.

Abbreviations: A2C, apical 2-chamber; A-L, area-length; LAEDV, left atrial end diastolic volume; LAAd, left atrial area; LALd, left atrial longitudinal dimension.
recruited 105 patients with suboptimally controlled type 2 diabetes; during a 12-month follow-up period, we optimized treatment aimed to improve their metabolic control. Improved glycemic control led to improvement in LV diastolic and systolic function, and both the magnitude of the improvement and the final glycemic control affected LV function at follow-up. Worsened glycemic control actually led to further deterioration of LV systolic function. Patients with diabetes are often overweight and obesity itself is also linked to LV dysfunction. In support of this concept, weight loss has been shown to lead to improved LV function. The impact of improving glycemic control on LV function may be mediated through the beneficial effects of weight loss on LV function. However, in another study, we demonstrated that both improved glycemic control and weight loss had incremental additive benefits on LV function.

Effort intolerance in diabetes

Early stages of LV dysfunction in diabetes may be associated with little or no symptoms. Effort intolerance is usually the first manifestation. Unfortunately, effort intolerance may be attributed to body weight or lack of physical fitness. Coronary artery disease may be another underlying cause. Evaluation of LV function at rest may not be adequate in patients with diabetes. Therefore, examining the response of the left ventricle to exercise may yield further diagnostic information. Diastolic reserve is the ability of LV filling pressures to remain normal with exercise and tachycardia. Impaired diastolic reserve is seen in the early stages of LV diastolic dysfunction in diabetes. Patients with diabetes have an impaired diastolic reserve, and elevated LV filling pressures with exercise manifest an exertional dyspnea even without inducible myocardial ischemia. Exercise echocardiography, by allowing assessment of LV diastolic reserve, is a useful tool to unmask diastolic and systolic dysfunction to evaluate patients with exertional dyspnea. Improving glycemic control is also associated with an improvement in exercise tolerance in these patients.

Treatment of left ventricular dysfunction in diabetes

Treatment of LV dysfunction in diabetes requires a multifaceted approach. Early detection of LV dysfunction in these patients allows identification of at-risk patients and early intervention. As these patients often have multiple comorbidities, a comprehensive approach to the management of all vascular risk factors is essential. Aggressive blood pressure lowering, treating hypercholesterolemia to target, and optimization of body weight are all important parts of management. Optimization of glycemic control may also lead to improvement in LV systolic and diastolic function and exercise tolerance.

A specific therapeutic agent for diabetic cardiomyopathy is still lacking. Aldosterone antagonism, which reduces cardiac extracellular matrix turnover, improves symptoms and outcomes in advanced systolic heart failure and after acute myocardial infarction. Aldosterone antagonism has also been shown to improve LV function in dilated and hypertensive cardiomyopathy and metabolic syndrome with regression in markers of myocardial fibrosis. Trials evaluating the impact of specific aldosterone antagonism on LV systolic and diastolic function in patients with type 2 diabetes are ongoing.

Conclusions

LV dysfunction and heart failure are prevalent in patients with diabetes. Hypertension, coronary artery disease, and obesity are common comorbidities and may also cause LV dysfunction. Diabetic cardiomyopathy is considered a distinct entity. LV dysfunction in these patients may be associated with little or no symptoms, with exertional dyspnea a common, though nonspecific, symptom. LV function is linked to glycemic control, and early detection of LV dysfunction is important. Echocardiography, combined with exercise testing, allows comprehensive assessment of LV morphology, systolic and diastolic function at rest and after stress, and exclusion of coronary artery disease. A multifaceted approach targeting all vascular risk factors in the management of LV dysfunction in these patients is essential. A specific treatment for diabetic cardiomyopathy is still lacking, but aldosterone antagonists may be beneficial. Timely intervention may improve patient outcome for such a condition, which is associated with significant morbidity and mortality.

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Clinical benefits of targeting cardiac cells directly with trimetazidine in patients with coronary disease and diabetes

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Abstract
Patients with coronary artery disease (CAD) and diabetes have a cardiovascular death rate double that of nondiabetic patients with CAD. Accelerated atherogenesis mediated by altered cellular metabolism is the likely cause of this association. In fact, ischemic metabolic changes, which occur as a consequence of the mismatch between blood supply and cardiac metabolic requirements, are heightened by the metabolic changes inherent to diabetes itself. Increased utilization of free fatty acid and the reduced utilization of glucose as a source of energy during stress and ischemia are responsible for the increased susceptibility of the diabetic heart to myocardial ischemia and to a greater decrease in myocardial performance for given amounts of ischemia than observed for nondiabetic hearts. In this context, a therapeutic approach aimed at improving cardiac metabolism through manipulations of the use of metabolic substrates should result in an improvement in myocardial ischemia. Trimetazidine, by acting directly at the cardiac-cell level, partially inhibits fatty acid oxidation, improves global cardiac metabolism, and, as a consequence, increases cardiac resistance to ischemia and reduces the decline of left ventricular function due to chronic underperfusion and repetitive episodes of myocardial ischemia. Therefore, modulation of myocardial metabolism represents a key target in patients with CAD and diabetes. Because of its effect on cardiac metabolism and its well-established beneficial effects on myocardial ischemia and left ventricular function, trimetazidine should be considered an essential treatment for diabetic patients with ischemic heart disease. ■ Heart Metab. 2017;73:24-28

Keywords: CAD; diabetes; myocardial metabolism; trimetazidine

Introduction
Type 2 diabetes mellitus is an important predictor of future cardiovascular events, regardless of the presence or absence of coronary disease.1,2 Diabetic patients without overt coronary artery disease (CAD) have a prognosis similar to nondiabetic patients with CAD, and coronary disease patients with diabetes have a cardiovascular death rate double that of nondiabetic patients with CAD.3,4 Glucose-metabolism impairment and the insulin resistance syndrome are, per se, crucial factors in the accelerated development
of atherosclerosis and the clinical evolution of the ensuing cardiac diseases. Altered glucose metabolism exerts its detrimental cardiovascular effects at two levels: (i) on vascular wall function and (ii) on regulation of cell energy metabolism.

Direct vascular and muscular effects of deranged glucose metabolism

The direct vascular effects of type 2 diabetes are known to be mediated by endothelial dysfunction. Additionally, when the endothelium is damaged, the balance between vasoactive substances—which can either cause vasoconstriction (via endothelin-1 [ET-1] and thromboxane A2) or vasodilation (via nitric oxide and other prostaglandins, such as prostacyclin)—can shift toward a greater production of vasoconstrictor agents, triggering a vicious circle and further promoting atherosclerosis. Acute hyperglycemia may itself impair endothelial-derived vasodilation. In fact, the inability to increase myocardial blood flow appears independently related to long-term blood glucose control, indicating that hyperglycemia itself is of considerable importance for impaired vascular function. Additionally, the impairment of insulin action in type 2 diabetes has also been found in both cardiac and skeletal muscle. Heart and arm skeletal muscle glucose uptake are inversely related to free fatty acid (FFA) levels in the serum and increased FFA flux from adipose tissue to nonadipose tissue, resulting from abnormalities in fat metabolism, and participate in and amplify many of the fundamental metabolic derangements that are characteristic of the insulin resistance syndrome and type 2 diabetes. Previous findings also suggest that elevated FFA levels not only impair glucose uptake in heart and skeletal muscles but also cause alterations in the metabolism of vascular endothelium, leading to premature cardiovascular disease.

Specific effects of glucose derangement on cellular metabolic efficiency

Since glucose is a major energy substrate in the body, its deranged utilization in the diabetic heart may be particularly deleterious. Increasing FFA oxidation in the heart decreases glucose oxidation, whereas increasing glucose oxidation inhibits FFA oxidation. In fact, FFA oxidation is a less efficient source of energy than glucose oxidation (with regard to adenosine triphosphate [ATP] produced per oxygen [O2] molecules consumed), and this helps explain why elevated FFA oxidation rates reduce cardiac efficiency.

Direct effects of ischemia on myocardial metabolism

Apart from diabetes, myocardial ischemia per se results in major cardiac metabolic consequences, basically making ischemia a metabolic problem. The healthy heart derives most of its energy from the FFA pathway, which accounts for approximately two-thirds of energy production (ATP), the other source of energy being derived from glucose oxidation and lactate. In hypoxic conditions, myocardial cells respond to mild-to-moderate ischemia by accelerating glucose uptake in order to generate sufficient ATP for the maintenance of ionic gradients and calcium homeostasis, as glycolysis requires less O2 per mole of ATP generated than does FFA oxidation. On the other hand, severe ischemia rapidly induces an imbalance between the requirement of cardiac tissue for O2 and coronary blood supply, resulting in functional, metabolic, and morphological alteration of the myocardium. At a cellular level, glucose uptake is decreased, and conversion to lactate is increased; lactate uptake by the heart is switched to lactate production, and pyruvate is mostly transformed into lactate, thereby increasing cell acidosis and resulting in less ATP production. These metabolic changes lead to disruption of cell homeostasis, alterations in membrane structure, and ultimately, cell death.

Therefore, adverse cardiac effects of diabetes are consequent to vascular and muscle metabolic mechanisms. In these contexts, lowering elevated plasma FFA levels or reducing FFA utilization by the cells could decrease the heart’s reliance on fatty acids.

Metabolic therapeutic approach in coronary diabetic patients: the role of trimetazidine

The possibility of modifying cardiac metabolic substrate preferences of the diabetic heart is particularly attractive. Specifically, increasing the rate of glucose oxidation at the expense of FFA oxidation could help improve diabetic cardiac function.

Abbreviations

CAD: coronary artery disease; ET-1: endothelin-1; FFA: free fatty acid

Heart Metab. (2017) 73:24-28
metabolism and, accordingly, reducing FFA oxidation, is a very attractive therapeutical approach. Trimetazidine shifts energy production from FFA to glucose oxidation and preserves cellular energy by increasing myocardial high-energy phosphate intracellular levels (Figure 1). On this basis, several clinical studies have demonstrated the beneficial effects of trimetazidine in patients with CAD, and it is currently indicated by the European Society of Cardiology for the treatment of angina pectoris. Trimetazidine appears particularly effective in the presence of hyperglycemia and hyperinsulinemia, which are often observed in insulin-resistance states. For these reasons, trimetazidine has been very effective in diabetic patients with CAD and left ventricular dysfunction. In a subsequent study performed in a large cohort of patients with type 2 diabetes mellitus and CAD, trimetazidine—by acting directly at the cardiac-cell level—on top of conventional medical treatment decreased the incidence of angina episodes and the ischemic response in the exercise test with excellent tolerability.

A subsequent 24-hour ambulatory-electrocardiography-monitoring study confirmed that in patients with diabetes and chronic stable angina, the addition of trimetazidine to standard medical therapy reduces the number of episodes of ST-segment depression, the episodes of silent ischemia, and total ischemic burden.

Finally, since glucose metabolism derangement is the greatest risk factor for restenosis after percutaneous myocardial revascularization, optimal medical management of these patients would appear mandatory. In this context, it was very recently shown that adjunctive therapy with trimetazidine after drug-eluting–stent implantation in elderly multivessel-CAD patients with diabetes can have a beneficial effect on recurrent angina pectoris, as well as on left ventricular function. Thus, trimetazidine treatment in coronary diabetic patients undergoing percutaneous interventions appears particularly useful.

**Specific effects of trimetazidine in the diabetic-ischemic patient**

As previously stated, trimetazidine facilitates myocardial utilization of glucose instead of FFAs, which in the context of malfunctioning myocardial cells appears to be beneficial. These effects are probably operative on both cardiac and skeletal muscle; therefore, the effects of trimetazidine on glucose metabolism could be dependent on improved cardiac efficiency and improved peripheral glucose extraction and utilization. In fact, trimetazidine has also been shown to reduce ET-1 release (Figure 2), which is associated with a reduction in endothelin-1 release and forearm release of endothelin-1 after hyperinsulinemic-euglycemic clamp in type 2 diabetic patients with cardiomyopathy.

![Fig. 1](image1.png)

*Fig. 1 In vivo 31P-magnetic resonance spectroscopy evaluating the effects of 3 months’ therapy with trimetazidine on the left ventricular cardiac phosphocreatine-to–adenosine triphosphate (PCr/ATP) ratio in patients with heart failure (a). The histogram shows an important trimetazidine-induced improvement in cellular energy reserve, as evidenced by the significant increase in PCr/ATP compared with placebo. As a reference comparison, after trimetazidine, PCr/ATP levels are similar to that observed in a control population (b). Abbreviation: PCr/ATP, ratio of phosphocreatine to adenosine triphosphate; TMZ, trimetazidine.*


![Fig. 2](image2.png)

*Fig. 2 Endothelin-1 in the basal state (left) and at the end of the euglycemic clamp studies (right) in 15 type 2 diabetic patients with cardiomyopathy after 15 days of trimetazidine (red bars) and after 15 days of placebo (gray bars). When on trimetazidine, endothelin-1 and forearm release of endothelin-1 after hyperinsulinemic-euglycemic clamp are significantly reduced compared with placebo, indicating improved endothelial function. Values are expressed as mean ± standard error. *P<0.05. Abbreviation: ET-1, endothelin-1; F. ET-1 release, forearm release of endothelin-1; TMZ, trimetazidine.*

with the severity of myocardial ischemia and dysfunction; its levels correlate with prognosis. Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium could influence not only myocardial function but also endothelial function. By decreasing endothelial damage, trimetazidine may inhibit ET-1 release after high- and low-flow ischemia. Additionally, it has been shown that trimetazidine, in the presence of high levels of triglycerides, may improve both myocardial recovery and ET-1 release simply by decreasing the effects of chronic myocardial ischemia. Additionally, it has been shown that trimetazidine, in the presence of high levels of triglycerides, may improve both myocardial recovery and ET-1 release after high- and low-flow ischemia. Considering the known relation between ET-1 concentration and glucose metabolism abnormalities, the observed beneficial effects of trimetazidine on glucose metabolism could also be partly attributed to the reduction in ET-1 levels.

Conclusions

Diabetes mellitus is becoming progressively common. Most diabetic patients will develop cardiovascular complications, of which CAD is one of the most frequent and insidious. In these patients, ischemic heart disease should be aggressively treated. Drugs directly affecting myocardial cell metabolism could be particularly useful. Trimetazidine, by acting directly at the cardiac-cell level, partially inhibits fatty acid oxidation, improves global cardiac metabolism, and as a consequence increases cardiac resistance to ischemia and reduces the decline of left ventricular function due to chronic underperfusion and repetitive episodes of myocardial ischemia. Therefore, modulation of myocardial metabolism should be a key target in patients with CAD and diabetes. Because of its effect on cardiac metabolism and its well-established beneficial effects on myocardial ischemia and left ventricular function, trimetazidine should always be considered an essential treatment for diabetic patients with ischemic heart disease.

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Managing chest pain in a diabetic patient

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Abstract
Coronary artery disease is the leading cause of mortality in patients with diabetes. We present the case of a 61-year-old diabetic male patient with a previous history of percutaneous coronary intervention on the left circumflex coronary artery and who came to our outpatient clinic because of persistence of chest pain and limited exercise tolerance. The patient underwent stress echocardiography (stress echo), which was negative for inducible regional wall motion abnormalities but positive for left anterior descending coronary flow velocity reserve (1.7; normal values are above 2.0). The patient was intolerant to β-blockers and was started on ivabradine 5 mg twice daily plus trimetazidine 20 mg three times a day. After 1 month of therapy, the patient was reevaluated, and we observed a marked improvement in symptoms and a coronary flow velocity reserve of 2.1. With versatile use of stress echo, noninvasive risk stratification in diabetic patients can be obtained efficiently, at low cost, and without cumulative damage from radiation exposure, allowing a comprehensive assessment of wall motion, symptoms, electrocardiogram changes, and coronary flow velocity reserve. The latter was markedly improved by the combination of ivabradine plus trimetazidine.

Keywords: B-lines; risk; stress-echo

The risk of myocardial infarction and cardiac death is two- to fourfold higher in diabetic than in nondiabetic patients; the latest European Society of Cardiology guidelines recommend the use of noninvasive testing for risk stratification of patients with known or suspected coronary artery disease, which should be performed according to clinical needs and clinical judgment and not meant as a general recommendation to be followed in all patients. Stress echocardiography (stress echo) is certainly an attractive option owing to its widespread availability, low cost, and radiation-free nature, but the problem remains that the negative predictive value of the test is lower in diabetics than in nondiabetic patients. Recent new evidence has emerged that a better negative predictive value can be obtained if we augment regional wall motion analysis with new parameters, such as assessment of left ventricular contractile reserve, left anterior descending coronary flow reserve, and/or B-lines during lung ultrasound. In particular, coronary flow velocity has long-term prognostic value in diabetics, and a reduction in coronary flow velocity is associated with higher long-term mortality even in patients with normal regional wall motion. The case presented here is of a diabetic patient with negative stress echo by wall
motion criteria but reduced coronary flow reserve that improved after initiation of therapy with ivabradine and trimetazidine.

**Case report**

We present the case of a 61-year-old diabetic male patient with persistent chest pain and dyspnea after a percutaneous coronary revascularization (3 years earlier) with drug-eluting stent implantation on the proximal left circumflex coronary artery. The patient was referred to the outpatient clinic because of the persistence of symptoms. While under standard anti-ischemic therapy, the patient underwent stress echo (with dipyridamole) testing; the results were negative for wall motion abnormalities, but the chest pain was reproduced and was associated with a 2-mm ST-segment depression on the anterior leads. After that, the coronary flow velocity reserve on the mid-distal left anterior descending coronary artery (calculated as stress/rest ratio of peak diastolic velocity) was assessed, yielding a value of 1.7 (normal values >2.0). Pharmacologic treatment was modified with the introduction of ivabradine (5 mg twice daily) plus trimetazidine (20 mg thrice daily), and the patient was reevaluated after 1 month. Quality of life was substantially ameliorated with the disappearance of chest pain. The stress echo test was repeated, confirming the absence of regional wall motion abnormalities, now without symptom or ST-segment changes and showing an increase in the coronary flow velocity reserve from 1.7 to 2.1 (Figure 1).

![Fig. 1 The conceptual approach to dual imaging with vasodilator stress echo (with dipyridamole). The left upper panel shows the schematic representation of a normal epicardial coronary artery perfusing a normally contracting myocardium (square box). In the left lower panel, the standard two-dimensional (2D) stress echo (the end-systolic frames of the 2D short axis view) shows normal wall motion, consistent with the absence of critical coronary stenosis after revascularization. In the right upper panel, the damaged microcirculation (red circles) is schematically shown. The patient, on ivabradine, had a coronary flow velocity reserve within normal limits (2.1) during high-dose dipyridamole testing (right lower panels). The right middle panel shows the color Doppler image of coronary flow in the mid-distal left anterior descending artery; the left, the pulsed Doppler tracing at rest; the right, after dipyridamole. The ratio of stress/rest peak diastolic flow velocity is the index of coronary flow velocity reserve. It was 1.7 in a test performed 1 month before, off ivabradine. Abbreviation: CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; cm/s, centimeters per second; IVA, ivabradine.](image-url)
**Discussion**

Diabetic patients often pose challenging diagnostic problems. In ischemic diabetic patients, chest pain may be absent or atypical when present. Provocative tests may be required to associate symptoms with objective signs of myocardial ischemia, such as regional wall dysfunction and/or ischemic electrocardiogram changes.

The case we present here was difficult to assess by a standard approach because of the atypicality of symptoms and the absence of transient akinesia during stress. So, we resolved to take advantage of the most recent developments in stress echo imaging, where the classical imaging based on regional wall motion analysis has been augmented by assessment of coronary flow velocity reserve. Regional wall motion abnormalities are influenced by the epicardial coronary artery stenosis, whereas the coronary artery flow velocity reserve is affected by the coronary microcirculation.

Coronary microvascular dysfunction may be effectively targeted by cardiometabolic and hemodynamic agents. Ivabradine has been shown to increase the coronary flow reserve in angina patients—-with and without diabetes—in the poststenotic territory, as well as in areas remote from the epicardial coronary stenosis. Reported increases in flow velocity reserve vary from 2.6 to 3.5 (+30%), probably through a combination of effects, including the increase in diastolic perfusion time, improved isovolumic ventricular relaxation, a reduction in end-diastolic pressure responsible for extravascular resistances, and improved flow through collaterals. This approach is not only pathophysiologically appealing, but also expands the potential of risk stratification because in ischemic patients (and especially in diabetics), many cardiac events can occur independently of the coronary plaque targeted by the stress-induced approach and are linked to microcirculatory disease.

We usually focus solely on coronary stenosis, but the pathophysiological inconsistencies and clinical collateral damage driven by this simplistic approach are well-known. Dual-imaging stress echo allows many different variables to be brought into focus. The cardiovascular hard-event rate of a diabetic patient with negative stress echo by conventional wall motion criteria is 2%, but with the addition of a normal response of coronary flow reserve, the hard-event annual rate drops off to less than 0.5%. It remains to be clarified with prospective randomized studies whether an improvement in coronary flow velocity reserve achieved with drugs such as ivabradine—and/or trimetazidine, also effective through a different cardiometabolic effect in patients still symptomatic on standard therapy—modifies the long-term prognosis in diabetic patients. In particular, the role of trimetazidine in diabetics has a strong pathophysiological rationale, as diabetes also affects the microcirculation, which cannot be treated by revascularization and is the preferred target of trimetazidine treatment. Such treatment may compensate for the deteriorated glucose uptake and utilization in myocardial cells caused by altered insulin levels.

**REFERENCES**


Cardiac energy metabolism in diabetes

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Abstract
Diabetes is a significant risk factor for cardiovascular disease, and ongoing efforts aim to elucidate how diabetes precipitates ventricular dysfunction. Myocardial energy metabolism is intricately regulated because the heart—the most metabolically demanding organ in the body on a per gram basis—must dynamically metabolize a diverse range of fuel sources. However, in type 1 and type 2 diabetes mellitus, increases in myocardial fatty acid oxidation and decreases in myocardial glucose oxidation are observed, and it has been postulated that these metabolic perturbations are key contributors to diabetes-related ventricular dysfunction. With a number of pharmacological tools now available to modulate energy metabolism, targeting the diabetes-induced alterations in myocardial energy metabolism may be a promising strategy to improve ventricular function in diabetic subjects. Such a strategy is widely supported by current evidence in preclinical studies. ■ Heart Metab. 2017;73:33-36

Keywords: energy metabolism; fatty acid oxidation; glucose oxidation; type 1 diabetes; type 2 diabetes

Introduction
As of 2014, it was estimated that there were over 420 million people worldwide living with diabetes, of which 90% was accounted for by type 2 diabetes mellitus (T2DM). Despite having a variety of different drug classes to control hyperglycemia in these individuals, the vast majority of diabetics will eventually die from cardiovascular causes such as myocardial infarction and heart failure (HF).1,2 Hence, there has been and continues to be a strong effort within the scientific and medical community to understand the cardiovascular actions of therapies for treating diabetes, in addition to understanding how diabetes itself increases the risk of developing cardiovascular disease. With regard to the latter, we have now come to appreciate that energy metabolism in the myocardium of an individual with type 1 diabetes mellitus (T1DM) or T2DM is significantly different from that in a healthy individual.2,4 Of particular importance, the healthy heart is a metabolic omnivore with high flexibility that is able to consume a wide variety of substrates according to their availability throughout various physiological states (eg, feeding versus starvation). However, during both T1DM and T2DM, the robust increase in circulating free fatty acids and triglycerides greatly augments fatty acid delivery to the myocardium, making fat the primary fuel choice for the heart’s energy demands, which severely limits its ability to adapt to and use other energy sources (Figure 1). The aims of this
refresher article are to highlight the specific myocardial metabolic alterations observed in patients with T1DM and T2DM, and to describe whether these metabolic alterations can be targeted to improve cardiac function in diabetic subjects.

Myocardial energy metabolism in type 1 diabetes

Because T1DM is often the result of insulin deficiency, many of the alterations in myocardial energy metabolism in a T1DM individual can be attributed to deficient myocardial insulin action. In a healthy insulin-sensitive individual, insulin acts to increase glucose uptake in the heart, leading to increases in both glycolysis and glucose oxidation. Increases in glucose oxidation lead to a corresponding reduction in fatty acid oxidation, a phenomenon first described by Shipp and colleagues in the 1960s, but later given prominence by Philip Randle and colleagues. As such, this reciprocal glucose–fatty acid relationship for oxidative metabolism is commonly referred to as the "Randle Cycle." Insulin also decreases myocardial fatty acid oxidation rates indirectly by inhibiting adipose tissue lipolysis. In addition, insulin directly inhibits myocardial fatty acid oxidation rates by activating acetyl coenzyme A (CoA) carboxylase to increase levels of malonyl CoA, a potent endogenous inhibitor of carnitine palmitoyltransferase-1 (CPT-1), which subsequently inhibits mitochondrial fatty acid uptake. Therefore, in a T1DM individual, myocardial fatty acid oxidation rates are markedly elevated as a result of absent insulin action, whereas glucose oxidation and glycolysis rates are severely diminished. Indeed, studies in rats subjected to experimental T1DM via tail-vein injection of streptozotocin (55 mg/kg) demonstrate that fatty acid oxidation accounts for approximately 95% of total oxidative adenosine triphosphate (ATP) production during isolated aerobic working heart perfusion. Likewise, the Akita mouse (a mouse model of T1DM due to genetic mutation in the insulin 2 [Ins2] gene) demonstrates no changes in glucose oxidation and significant increases in myocardial fatty acid oxidation during isolated aerobic working heart perfusion, though the changes in fatty acid oxidation are not nearly as prominent as those seen in the streptozotocin model of T1DM. Similar findings have been recapitulated in humans, in which positron emission tomography (PET) imaging studies in T1DM subjects with 1-11C-glucose and 1-11C-palmitate revealed reductions in myocardial glucose utilization rates and increases in myocardial fatty acid oxidation rates, respectively.

Myocardial energy metabolism in type 2 diabetes

The myocardial metabolic alterations reported in animal models of obesity and/or T2DM, or in T2DM patients are similar to those observed in a T1DM individual. In mice subjected to chronic high-fat feeding (60% kcal from lard) for 12 weeks to induce experimental obesity, marked reductions in glucose oxidation rates are observed, whereas fatty acid oxidation rates remain largely unaffected. Of interest, severe insulin resistance is observed in this model with regard to insulin’s ability to promote glucose oxidation, such that in the presence of insulin, the vast majority of oxidative energy metabolism is met through the oxidation of fatty acids. In genetic mouse models of T2DM, including both leptin-deficient ob/ob and leptin receptor-deficient db/db mice, marked increases in myocardial fatty acid oxidation and corresponding decreases in glucose oxidation rates are observed during isolated aerobic working heart perfusions. These changes in myocardial energy metabolism are associated with sig-
significant increases in myocardial oxygen consumption rates, but are not matched by an equivalent increase in cardiac work/power, such that the efficiency of contractile function is reduced in both ob/ob and db/db mice. These observations have been recapitulated in a human cohort study of obese women from Petersen and colleagues, whereby PET imaging studies revealed marked increases in fatty acid oxidation rates in obese women, which strongly correlated with the degree of glucose intolerance. Moreover, increasing obesity is inversely associated with cardiac efficiency in these women. Additional PET imaging studies have recorded similar observations, as Rijzewijk and colleagues demonstrated an elevation in myocardial fatty acid oxidation rates and a decline in myocardial glucose uptake in T2DM patients with diastolic dysfunction.

Myocardial energy metabolism alterations in diabetic subjects with heart failure

An important potential confounding factor when assessing the impact of diabetes on myocardial energy metabolism is the comorbidity of HF. Diabetes is a major risk factor for HF, and it is estimated that 30% to 40% of HF patients have some form of diabetes. Because HF is associated with its own distinct myocardial metabolic phenotype, most notably a reduction in fatty acid oxidation rates that appears to correlate with the severity of the decline in ventricular function, careful consideration needs to be taken with interpretation of myocardial energy metabolism profiles in comorbid diabetic/HF individuals.

Optimizing myocardial energy metabolism to improve cardiac function in diabetes

A key question arising from the myocardial metabolic aberrations in diabetic subjects is whether they can be targeted to improve cardiac function in these individuals. Of particular relevance, a number of studies in animal models of obesity and/or diabetes have demonstrated that pharmacological activation of glucose oxidation often improves both cardiac function and contractile efficiency of the heart. For example, isolated working hearts from rats treated with streptozotocin to induce T1DM demonstrate a marked reduction in cardiac function during aerobic perfusion, which is negated by the inclusion of 0.5 mM dichloroacetate (DCA) in the perfusate. DCA is a pharmacological inhibitor of pyruvate dehydrogenase (PDH) kinase, and thereby increases glucose oxidation by preventing phosphorylation-induced inhibition of PDH, the rate-limiting enzyme of glucose oxidation. Likewise, DCA supplementation in the drinking water (final concentration of 1 mM) has also been shown to increase myocardial glucose oxidation rates via a novel 13C hyperpolarized magnetic resonance imaging (MRI) method in a rat model of experimental T2DM (long-term high-fat feeding plus a single low-dose streptozotocin injection), ultimately resulting in an abrogation of diastolic dysfunction. Of interest, inhibiting fatty acid oxidation rates in animal models of experimental obesity/insulin resistance also has beneficial actions on the myocardium. Indeed, mice with a deficiency for malonyl CoA decarboxylase, which decreases fatty acid oxidation rates due to elevating levels of malonyl CoA and subsequent inhibition of CPT-1, demonstrate increases in cardiac efficiency, as well as a marked improvement in insulin-stimulated glucose oxidation rates. In addition, the antianginal agent trimetazidine, which reduces myocardial fatty acid oxidation rates by inhibiting the β-oxidation enzyme, 3-ketoacyl-CoA thiolase, can attenuate diastolic dysfunction in middle-aged mice subjected to experimental obesity/insulin resistance. Similarly, trimetazidine treatment for 6 months in T2DM subjects with idiopathic cardiomyopathy improves both diastolic function and systolic function.

As mentioned in the previous section, myocardial fatty acid oxidation rates are often impaired in individuals with HF; thus, it may be anticipated that inhibiting myocardial fatty acid oxidation in a comorbid diabetic/HF subject would be undesirable. Nevertheless, treatment with trimetazidine for 3 months has been shown to reduce myocardial fatty acid oxidation rates and improve ventricular function in systolic HF patients with idiopathic dilated cardiomyopathy. Moreover, treatment of optimally medicated chronic HF patients for 8 weeks with perhexiline, a fatty acid oxidation inhibitor that directly antagonizes CPT-1, also leads to significant improvements in ventricular function. Therefore, inhibition of myocardial fatty acid oxidation rates may still be potentially beneficial even in a comorbid diabetic/HF subject.

Summary

It has been strongly established that both T1DM and T2DM lead to significant alterations in myocardial en-
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energy metabolism, most notably an elevation in fatty acid oxidation rates and a reduction in glucose oxidation rates (Figure 1), as determined in preclinical studies. Elevations in myocardial fatty acid oxidation have also been seen in human subjects with T1DM or T2DM, but because methodologies to assess glucose oxidation in vivo are limited, confirmation that glucose oxidation rates are reduced in diabetic patients is lacking. However, the development of the novel $^{13}$C hyperpolarized MRI method to quantify glucose oxidation in vivo has recently been successfully applied to human subjects, suggesting that we may soon have confirmation of reduced myocardial glucose oxidation rates in diabetic subjects. Current evidence from preclinical studies supports the notion that normalizing diabetes-induced alterations in myocardial energy metabolism may be a novel approach to attenuate diabetes-induced ventricular dysfunction. Though human data is lacking, this is a promising area that requires further investigation.

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Type 2 diabetes (T2DM) is related to an increased cardiovascular risk, and the main reason for this is thought to be insulin resistance, which is clinically represented by metabolic syndrome. Hyperglycemia in diabetes—both types 1 and 2—increases cardiovascular risk due to endothelial lesions. Control of all risk factors, including lipids, hypertension, and blood glucose are important to decrease the risk of cardiovascular disease. With particular regard to blood glucose, the UKPDS study (United Kingdom Prospective Diabetes Study) showed that early intensive glycemic control was essential in the reduction in cardiovascular disease. A decrease in mortality observed with glucagon-like peptide-1 (GLP-1) analog use is probably due to a reduction in body weight; findings for empagliflozin still remain unclear. 

Keywords:
presence of ROS is the triggering factor behind development of diabetes complications, both macro and micro, due to endothelial injury.\(^2\)

However, in an approximately 23-year retrospective comparison of patients with type 1 diabetes mellitus (T1DM) and T2DM, diagnosed at the same age (15 and 30 years old), patients with T2DM presented with a higher incidence of macro and microvascular disease and had a higher mortality.\(^3\)

Regarding cardiovascular coronary dysfunction, Bonamichi et al revealed through intravascular ultrasound that hyperglycemia plays an important role in the development of atherosclerotic disease in patients with metabolic syndrome and may lead to a worsening of the pathology.\(^4\)

The control of all risk factors, including lipids, hypertension, and blood glucose, plays an important role in decreasing cardiovascular disease risk. Particularly with blood glucose, the UKPDS study (United Kingdom Prospective Diabetes Study) was effective in demonstrating that early intensive glycemic control is essential to reduce cardiovascular disease.\(^5\) The results of UKPDS 80, a trial that evaluated the same UKPDS outcomes published in 1998, demonstrated that the patients that benefited most in terms of prevention of heart attack and all-cause mortality were the patients in the intensive treatment group.\(^5\)

**Cardiovascular safety of hypoglycemic medications**

Cardiovascular safety studies performed with hypoglycemic medications for T2DM were and are important, not just to evaluate the primary outcomes related to cardiovascular disease, but also to establish and evaluate possible side effects, as well as benefits, of those medications.

With regard to dipeptidyl peptidase-4 (DPP-4) inhibitors, the studies that have been thus far published, such as SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis In Myocardial Infarction),\(^6\) EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care),\(^7\) and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin),\(^8\) have demonstrated cardiovascular safety. However, they have not shown significant decreases in the complications related to T2DM.

The ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) also demonstrated cardiovascular safety with gliclazide use in patients with T2DM and established cardiovascular disease.\(^9\) The results are important for the differentiation of gliclazide from other medications in terms of cardiovascular safety.\(^9\)

After the ADVANCE study, patients were followed-up for approximately 6 years in the ADVANCE-ON (ADVANCE Observational) trial. Glycated hemoglobin in both ADVANCE and ADVANCE-ON studies was established to be an average of 7.4%, suggesting methodological importance, leading us to conclude that the intensive glucose control at baseline was the main difference.\(^9\)

Recently, results of cardiovascular outcomes trials (CVOTs) were published for two classes of medications. Cardiovascular safety of GLP-1 analogs was shown, with a decrease in mortality in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results)\(^10\) and a decrease in major adverse cardiac events (MACE) in the SUSTAIN trial (Trial to Evaluate Outcomes with Sema-glutide in Subjects with Type 2 Diabetes).\(^11\) Sodium-glucose cotransporter-2 (SGLT2) inhibitors were shown to reduce mortality and MACE in the EMPA-REG OUTCOME trial (Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) with empagliflozin, though there was no reduction in cardiovascular events.\(^12\)

We conclude that treatment for cardiovascular disease in patients with T2DM should be sought from the first day of diabetes diagnosis, with intensive glycemic control, lipid control through use of statins, and hypertension control. The decrease in mortality observed with GLP-1 analogs is probably due to a reduction in body weight, whereas the findings of the empagliflozin study remain unclear.

**REFERENCES**


α-Cell
α-Cells are endocrine cells localized within islets of the pancreas, where they secrete the peptide hormone glucagon during times of prolonged fasting/starvation in order to stimulate hepatic glucose production for maintaining normoglycemia. The α-cell makes up approximately 20% of the pancreatic islet-cell population in humans.

Body mass index
Body mass index (BMI) is a formula for measuring an individual’s relative weight based on their mass and height and is calculated by the formula BMI = mass in kilogram/(height in meters)². A healthy BMI is generally considered to be in the range of 18.5 to 24.9, whereas those with BMIs in the 25 to 29.9 range are classified as being overweight, and those with BMIs >30 are classified as obese. Although BMI is frequently used to assess general body mass in patient populations, the BMI does not take into account age, sex, or muscle mass, and it can result in large BMI scores for people that actually have very low body fat percentages, such as body builders.

Carnitine palmitoyl transferase-1
Carnitine palmitoyl transferase-1 (CPT-1) is the rate-limiting enzyme involved in the uptake of fatty acids in the mitochondria. It converts fatty acyl-coenzyme A to fatty acylcarnitine, which is then transported into the mitochondria where it is further metabolized. CPT-1 is a highly regulated enzyme that prevents excess fatty acid from being taken up into the mitochondria.

Endothelin-1
Endothelin-1 is a small peptide produced in a variety of tissues, including endothelial and vascular smooth muscle cells. It acts as a modulator of vasomotor tone, cell proliferation, and hormone production. It is a potent vasoconstrictor.

Glycated hemoglobin
Glycated hemoglobin (HbA₁c) forms from the nonenzymatic coupling of glucose to the major component of adult hemoglobin (ie, HbA α2β2). Glucose, via a complex series of reactions, is coupled to specific valine residues of HbA β chains. HbA₁c levels at a threshold of 6.5% can be used as a diagnostic test indicative of diabetes. HbA₁c levels are reflective of average glycemic control over a period of 2 to 3 months before testing/analysis.

Glycolysis
Glycolysis is the series of biochemical reactions occurring in the cytosolic compartment that converts a glucose molecule into two molecules of pyruvate. In the presence of oxygen (ie, the aerobic setting), pyruvate is transported into the mitochondria and undergoes oxidative decarboxylation, yielding acetyl-CoA. In the absence of oxygen (ie, the anaerobic setting), pyruvate is reduced to lactate by the enzyme lactate dehydrogenase, which generates the nicotinamide adenine dinucleotide (NAD⁺) required to maintain flux through glycolysis.

Incretin
Incretin refers to gastrointestinal peptide hormones released by enteroendocrine cells of the intestinal mucosa in response to the ingestion of food (or oral glucose load). The two major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP). Incretins enhance glucose-stimulated insulin secretion and, thus, are important regulators of glucose homeostasis. In addition, a variety of extraglycemic effects of incretins have been documented, including a slowing of gastric emptying, promotion of satiety, and reductions in food intake.

Insulin
Insulin is a pancreatic peptide hormone secreted from β-cells of the islets of Langerhans in the post-absorptive state. Its major metabolic effects are anabolic in nature, exemplified by the ability of insulin to do the following: increase glucose and amino acid uptake, as well as glycogen and protein synthesis, in muscle; increase glucose uptake and triacylglycerol synthesis in adipose tissue; and increase glucose uptake, glycogen, and triacylglycerol synthesis in the liver.

Leptin
Leptin is a peptide hormone synthesized by adipocytes and plays a key role in the regulation of appetite and energy expenditure. This can occur through direct actions of leptin on the hypothalamus or on peripheral lipid and glucose metabolism.
**Thromboxane $A_2$**
Thromboxane $A_2$ is a product of the cyclooxygenase pathway of arachidonic acid metabolism. In that pathway, cyclooxygenase catalyzes the production of prostaglandin $H_2$ (PGH$_2$) from arachidonic acids; PGH$_2$ can then be used in the formation of a number of different eicosanoid products, including prostaglandins. Metabolism of PGH$_2$ by thromboxane synthase, which is abundant in lung and platelets, results in the production of thromboxane $A_2$. Thromboxane $A_2$ has a variety of biological effects, including vasoconstriction and promotion of platelet aggregation.
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Heart failure in real life