Clinical benefits of trimetazidine in diabetic patients with coronary artery disease

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Abstract
The worldwide prevalence of diabetes mellitus, and in particular type 2 or non insulin-dependent diabetes mellitus, which accounts for up to 90% of the diabetic population, is currently increasing. Diabetes mellitus is an independent risk factor for coronary artery disease, the incidence of which in diabetic populations is about 55%. Conventional treatment strategies for diabetic patients with coronary artery disease include pharmacological treatments such as β-blockers, calcium channel blockers, and nitrates, and revascularization therapy such as percutaneous coronary interventions and coronary artery bypass graft surgery. The metabolic approach is an innovative therapeutic strategy for these patients. Trimetazidine, the first of a new class of metabolic agents, the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors, is an effective antianginal agent that shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting long-chain 3-KAT. In different studies, trimetazidine has shown a significant anti-ischemic effect on myocardial ischemia in diabetic patients with stable angina, in addition to producing an improvement in exercise tolerance. It also has favorable effects in patients with diabetes who have silent ischemia. Furthermore, treatment with trimetazidine has led to improvements in left ventricular systolic and diastolic functions, in addition to its protective effect on the vascular endothelium in patients with diabetic ischemic cardiomyopathy. Because of its effect on cardiac metabolism at rest, and its effects on myocardial ischemia and left ventricular function, trimetazidine should always be considered for the treatment of diabetic patients with ischemic heart disease with or without left ventricular dysfunction.

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Introduction
The prevalence of coronary heart disease increases from 2–4% in the general population to as much as 55% among adult patients with diabetes [1]. Diabetes mellitus is an important risk factor for future cardiovascular events in patients with ischemic heart disease, as well as in patients without heart disease [2,3]. Diabetic patients without overt coronary artery disease have a prognosis similar to that of non diabetic patients with coronary disease, whereas diabetic patients with coronary disease have a cardiovascular death rate double that of those without diabetes [4]. In addition, patients with diabetes and coronary heart disease have an increased incidence of heart failure. This is the result of accelerated atherogenesis, with involvement of peripheral coronary segments and altered myocardial metabolism, both of which lead to diffuse hibernation. The different and more diffuse distribution of atherosclerosis in patients with type 2 (non insulin-dependent) diabetes mellitus compared with that in the general population of patients with
coronary artery disease is related, at least in part, to the metabolic derangements of diabetes and to the clustering of different risk factors such as increased blood pressure, central obesity, and altered lipid profile [5]. The clinical presentation, the pathophysiology of myocardial ischemia, and the progression of both atherosclerosis and heart failure in patients with diabetes mellitus are different from those without diabetes. Although angina is the most common presentation of patients with coronary artery disease, patients with type 2 diabetes mellitus have a lower incidence of anginal pains and a higher incidence of silent myocardial ischemia or myocardial infarction than those without diabetes [6,7], and about 30% of diabetic coronary artery disease patients show evidence of silent ischemia, either during daily activity or during provocative tests.

**Cardiac metabolism in diabetic patients with coronary artery disease**

Under normal conditions, the heart is capable of oxidizing different substrates, such as carbohydrates or free fatty acids (FFA), to produce energy. The ability of the heart to switch from one substrate to the other is fundamental to its health, enabling it to adapt to many different factors, such as substrate availability, tissue perfusion, hormonal regulation, and the amount of cardiac work [8]. The normal heart obtains 60–90% of its energy from FFA oxidation and the remainder from glucose and lactate. Although FFA metabolism produces more ATP per gram of substrate, it has a greater requirement for oxygen because it is less efficient.

In type 2 (non insulin-dependent) diabetes mellitus, myocardial glucose transport, glycolysis, and glucose oxidation are all decreased, and a switch to fatty acid oxidation can provide 90–100% of the ATP requirements of the heart. Decreased glucose uptake resulting from insulin deficiency can partly explain the decrease in glucose metabolism, but high concentrations of circulating fatty acids and alterations in the control of fatty acid oxidation appear to be primarily responsible for this switch [9]. However, the fatty acid oxidation is less effective with respect to energy production because it produces less ATP per mole of oxygen used, and therefore more oxygen is required for ATP production when hearts are metabolizing fatty acids than when they utilize glucose. In addition, fatty acids can induce uncoupling of mitochondria, perhaps by upregulation of the expression and activity of uncoupling proteins [8,10]. Finally, the low rate of glucose oxidation results in increased proton production in the heart because of an uncoupling of glycolysis from glucose oxidation [9]. All these factors, together with the accumulation of glucose and fatty acid metabolic intermediates in the cells, contribute to a deterioration in myocardial cell function [8,10]. This decreases the efficiency of the heart muscle, resulting in decrease in cardiac work per molecule of oxygen consumed. Decreased cardiac efficiency exacerbates the imbalance between oxygen supply and demand that occurs during ischemia [9].

**Rationale for the use of anti-ischemic metabolic agents in patients with type 2 diabetes mellitus**

The classic treatment of angina involves drugs that affect cardiovascular hemodynamics (β-blockers, calcium channel blockers, and nitrates), thereby reducing myocardial energy demand. Many of these patients with type 2 diabetes are also undergoing myocardial revascularization, with either percutaneous coronary interventions or coronary artery bypass graft surgery. However, these treatment modalities are sometimes incapable of controlling anginal symptoms and halting the disease process, which leads to progressive contractile dysfunction and left ventricular enlargement. Moreover, conventional anti-ischemic agents have systemic hemodynamic effects that reduce patient compliance. In the case of myocardial ischemia, the increase in fatty acid oxidation inhibits the enzyme pyruvate dehydrogenase—an effect that suppresses glucose oxidation. The result of this inhibiting effect is an increase in lactate production and a decrease in intracellular pH in the ischemic cell; this, in turn, leads to impaired myocardial contractile function, as the production of ATP that is required to restore intracellular homeostasis is reduced. The accumulation of fatty acid intermediates during β-oxidation has been shown to induce diastolic left ventricular dysfunction and to lower the threshold for the development of ventricular arrhythmias during myocardial ischemia [11]. Ischemia is always associated with metabolic disturbances that should be addressed specifically, alongside all other factors that contribute to the development of angina. Metabolic consequences of myocardial ischemia are serious, in both the short and the long term, and therefore early and effective treatment is required for this metabolic problem.

**Trimetazidine, the metabolic modulator**

The modulation of fatty acid metabolism can be obtained by drugs that inhibit their oxidation. Trimetazidine (Vastarel MR), the first of a new class of metabolic agents, the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors [12,13], is an effective antianginal agent that shifts cardiac energy metabolism from fatty
acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-KAT [13]. The benefits of increased glycolytic substrate utilization are attributed to several mechanisms. The expected number of moles of ATP produced per mole of oxygen consumed is 12% greater for glucose oxidation than for FFA oxidation, although it is reasonable to believe that improvement in glucose metabolism may increase ATP production by up to 30% [5]. By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with less oxygen consumption [12]. In addition, trimetazidine stimulates the turnover of membrane phospholipids during ischemia and reperfusion, redirecting fatty acids towards phospholipids, and increasing cell tolerance to ischemia-reperfusion damage. The anti-ischemic properties of trimetazidine are independent of hemodynamic changes, and are associated with a greater recovery of mechanical function after ischemia [5]. Metabolic modulators such as trimetazidine are effective in the treatment of myocardial ischemia, whether silent or symptomatic, and in improving left ventricular systolic and diastolic functions in patients with diabetes and coronary artery disease.

**Trimetazidine in patients with diabetes, chronic stable angina, and silent ischemia**

The TRIMetazidine in POLand 1 (TRIMPOL-1) study showed that treatment with trimetazidine for 4 weeks in diabetic patients with chronic stable angina significantly reduced the number of anginal episodes and improved myocardial ischemia and exercise capacity [14]. Rosano and colleagues [15] showed that, in this patient population, the addition of trimetazidine to standard medical treatment reduced the number of episodes of ST-segment depression, the number of episodes of silent ischemia, and the total duration of silent myocardial ischemia over 24 h, and reduced the total ischemic burden. Marazzi and coworkers [16] evaluated the metabolic effect of trimetazidine in patients with diabetes and coronary artery disease. They found that trimetazidine significantly decreased the incidence of silent and symptomatic episodes of myocardial ischemia (by 24%), and the number of episodes and total duration of silent myocardial ischemia over 24 h (by 42% and 37%, respectively) (Figure 1). In the DIETRIC study, which included 580 patients, Rodriguez Padial and colleagues studied the efficacy and tolerability of trimetazidine, combined with regular medical treatment, in diabetic coronary artery disease patients. Trimetazidine reduced the incidence of anginal episodes, improved results in the exercise
tolerance test, and increased the time to ST-segment depression [17].

**Trimetazidine in diabetic patients with ischemic cardiomyopathy**

Partial inhibition of fatty acid oxidation may represent an alternative approach to the treatment of diabetic patients with heart failure. As a result of the preferential promotion of glucose and pyruvate oxidation, trimetazidine improves the activities of the sodium-potassium ATPase and calcium uptake pumps of the sarcoplasmic reticulum that are, respectively, responsible for left ventricular systolic depolarization and diastolic relaxation. In addition, the metabolic effects of trimetazidine translate into a reduced total ischemic burden and a better utilization of metabolic substrates, which translate into greater mechanical efficiency [18–23]. Fragasso and colleagues studied the short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy, and found that the drug improved left ventricular function, symptoms, glucose metabolism, and endothelial function [24]. Another group of investigators studied the effect of trimetazidine on myocardial perfusion and left ventricular systolic function in diabetic patients with ischemic cardiomyopathy and reported that it improved left ventricular systolic function (by 16%) (Figure 2) and functional capacity, despite no change in myocardial perfusion [25]. Rosano et al [15] reported that the addition of trimetazidine to standard treatment caused a significant reduction in left ventricular systolic and diastolic diameters, a significant decrease in left ventricular diastolic–systolic volume index, an improvement in left ventricular systolic and diastolic functions, and a significant decrease in the wall motion score index of chronically dysfunctional
myocardium in patients with type 2 diabetes mellitus, coronary artery disease, and reduced left ventricular function [15]. Monti and colleagues [26] demonstrated that trimetazidine has positive effects on the peripheral vasculature and skeletal muscle metabolism in diabetic patients with ischemic cardiomyopathy. Treatment with trimetazidine for 15 days increased glucose utilization in skeletal muscle, and reduced the release of endothelin-1 compared with placebo, suggesting a protective effect on the vascular endothelium.

Summary

Trimetazidine is the first of an innovative class of metabolic agents. It has been shown that it has beneficial effects in patients with type 2 diabetes mellitus and stable coronary artery disease, improving ischemic episodes whether silent or symptomatic. It also has a favorable effect in improving both left ventricular systolic and diastolic functions in patients with diabetic ischemic cardiomyopathy.

REFERENCES


