Heart Metab. (2017) 73:24-28

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

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

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.[5] Additionally, when the endothelium is damaged, the balance between vasoactive substances—which can either cause vasoconstriction (via endothelin-1 [ET-1] and thromboxane A_2) 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.[6] Acute hyperglycemia may itself impair endothelial-derived vasodilation.[7] In fact, the inability to increase myocardial blood flow appears independently related to long-term blood glucose control,[8] 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[9] and skeletal muscle.[10] 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,[11] 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.[12] 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.[13]

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 [O_2] molecules consumed), and this helps explain why elevated FFA oxidation rates reduce cardiac efficiency.[14]

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 O_2 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 O_2 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.[14]

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

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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*).[15,16] On this basis, several clinical studies

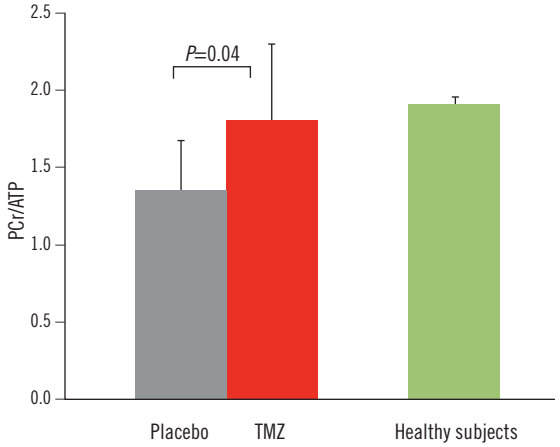

Fig. 1 *In vivo ^{31}P-magnetic resonance spectroscopy evaluating the effects of 3 months' therapy with trimetazidine on the left ventricular cardiac phosphocreatine-to–adenosine triphosphate (PCr/ATP) ratio in patients with heart failure (a). The histogram shows an important trimetazidine-induced improvement in cellular energy reserve, as evidenced by the significant increase in PCr/ATP compared with placebo. As a reference comparison, after trimetazidine, PCr/ATP level is similar to that observed in a control population (b).*
Abbreviation: *PCr/ATP, ratio of phosphocreatine to adenosine triphosphate; TMZ, trimetazidine.*
Data for placebo and trimetazidine (a) from reference 15: *Fragasso et al.* Eur Heart J. *2006;27:942-948. © 2006, European Society of Cardiology.*
Data for healthy subjects (b) from reference 16: *Perseghin et al.* J Am Coll Cardiol. *2005;46:1085-1092. © 2005, American College of Cardiology Foundation.*

have demonstrated the beneficial effects of trimetazidine in patients with CAD,[17] and it is currently indicated by the European Society of Cardiology for the treatment of angina pectoris.[18] Trimetazidine appears particularly effective in the presence of hyperglycemia and hyperinsulinemia,[19] 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.[20] 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.[21] 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.[22]

Finally, since glucose metabolism derangement is the greatest risk factor for restenosis after percutaneous myocardial revascularization,[23] 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.[24] 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[25] and improved peripheral glucose extraction and utilization. In fact, trimetazidine has also been shown to reduce ET-1 release (*Figure 2*),[26,27] which is associated

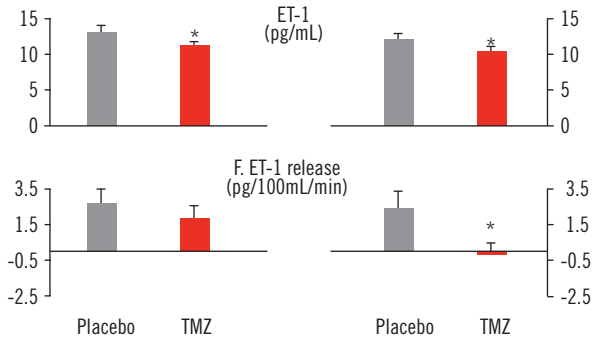

Fig. 2 *Endothelin-1 in the basal state (left) and at the end of the euglycemic clamp studies (right) in 15 type 2 diabetic patients with cardiomyopathy after 15 days of trimetazidine (red bars) and after 15 days of placebo (gray bars). When on trimetazidine, endothelin-1 and forearm release of endothelin-1 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.*
Adapted from reference 26: *Monti et al.* Am J Physiol Endocrinol Metab. *2006;290:E54-E59. © 2006, American Physiological Society.*

with the severity of myocardial ischemia and dysfunction; its levels correlate with prognosis. Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium[28] could influence not only myocardial function but also endothelial function. By decreasing endothelial damage, trimetazidine may inhibit ET-1 release, which would, in turn, decrease myocardial damage and improve glucose metabolism. A second possibility is that trimetazidine may inhibit 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.[29] 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.[30] 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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