Diabetes is a cardiovascular risk equivalent. Results from the East and West Study showed that non-diabetic patients who had a previous myocardial infarction (MI) have a similar risk of developing a future MI when compared with diabetic patients without previous MI. Furthermore, diabetic patients who develop MI have a markedly higher mortality compared with patients without diabetes. Diabetic patients also have a decreased awareness of myocardial ischaemic pain and hence many suffer from silent ischaemia which is associated with a reduced survival. Because of the frequent presence of multi-vessel disease involving both the proximal and peripheral branches, diabetic coronary patients often develop heart failure. The severity of this diabetic ischaemic cardiomyopathy is strongly related to changes in energy metabolism of the myocytes. It has been demonstrated that ischaemic damage may be exacerbated by the excessive use of fatty acids by the diabetic heart. This observation have led to the consideration of pharmacological manipulation of cardiac metabolism and optimising myocardial energy production as a promising approach to counteracting the deleterious consequences of myocardial ischaemia, particularly in coronary artery disease (CAD) patients with diabetes.

Metabolic dysfunction in the diabetic myocardium during ischaemia

Diabetes mellitus impairs glucose uptake and glycolysis of myocardial cells. In the case of myocardial ischaemia, glucose oxidation is reduced, and this reduction is more pronounced in diabetic hearts along with a more accelerated rate of free fatty acid (FFA) oxidation which is less efficient than glycolysis in energy production. In the diabetic heart, the preferential increased uptake and utilisation of FFA during ischaemia causes not only a diminished energy production, but also an increase of intermediate metabolic products which are toxic to the myocardium and cause disturbances in calcium homeostasis which may lead to systolic and diastolic dysfunction. Because of the altered metabolism in these patients, even a small reduction of myocardial oxygen supply may cause significant reduction of contractility. This may accelerate the development of overt heart failure in the presence of reduced coronary blood flow such as during acute myocardial ischemia or chronic CAD, or during increased myocardial energy requirement as occurs with hypertension.

Trimetazidine: metabolic benefits beyond anti-ischaemia

Traditional anti-anginal drugs such as beta-blockers, nitrates and calcium channel blockers act either by reducing oxygen consumption or by increasing oxygen supply via increases in coronary blood flow. However, these agents do not address the myocardial metabolic abnormalities that are characteristically found in patients with diabetes. A new approach to treat myocardial ischaemia is to improve the efficiency of oxygen utilisation by cardiac tissues. Metabolic agents like trimetazidine that modify the use of energy substrates in the heart improve cardiac performance during ischaemia. This additional metabolic effect is particularly beneficial for diabetic patients. Trimetazidine is the first of a new class of metabolic anti-ischaemic agents know as 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors. Under ischaemic conditions, trimetazidine optimises cardiac metabolism by shifting from FFA to glucose oxidation, secondary to selective inhibition of the mitochondrial long-chain 3-KAT. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because energy production is greater when glucose, rather than FFA, is the preferred energy substrate. The beneficial effect of trimetazidine in patients with angina and diabetes has been attributed to the preservation of the intracellular levels of adenosine triphosphate, the reduction of cell acidosis and calcium overload, the reduction of free radicals, and the inhibition of oxidative phosphorylation. Due to its purely metabolic mode of action, trimetazidine provides benefits in angina patients without changes in hemodynamic parameters, such as heart rate, blood pressure, or rate-pressure product at rest or during exercise. Unlike beta-blockers, trimetazidine therapy has a favourable effect on lipid and glucose levels. It is generally better tolerated than calcium antagonist and beta-blockers. There is also no evidence that long term therapy can lead to tolerance as observed with nitrate therapy. Mild gastrointestinal disorders such as heartburn are the most frequently reported adverse reactions, but their overall incidence is low.
Evidence-based efficacy in patients with diabetes and CAD

Trimetazidine is an effective anti-ischaemic agent in patients with angina.\(^{10}\) It significantly improves symptoms and exercise tolerance in patients with stable angina when used either as monotherapy or when combined with beta-blockers or calcium antagonists. In a study of stable angina patients with diabetes whose angina remained uncontrolled with conventional treatment, four weeks of treatment with trimetazidine resulted in improved exercise capacity and exercise duration, and a significant reduction in the number of angina episodes.\(^{11}\) It was well tolerated during the entire period of the study and no drug interaction was recorded. In another study of patients with ischaemic cardiomyopathy and depressed left ventricular function, trimetazidine produced significant improvements in left ventricular ejection fraction.\(^{12}\) It has also been shown that trimetazidine improves left ventricular function and functional capacity in diabetic patients with ischaemic cardiomyopathy receiving background anti-ischaemic therapy.\(^{13,14}\) Given that diabetic patients are at risk of silent ischaemia, anti-ischaemic drugs with a long duration of action would be desirable to prevent cardiovascular events. It has been shown that the modified release formulation of trimetazidine (trimetazidine MR 35mg taken twice a day) offers a sustained anti-ischaemic and anti-anginal efficacy even at trough plasma concentration, twelve hours after the intake of the drug.\(^{15}\) Randomised controlled trials with hard endpoints will be required to show its benefit over conventional therapy.

Patients with diabetes mellitus frequently have erectile dysfunction (ED) as a consequence of atherosclerosis, endothelial dysfunction and autonomic neuropathy. It is effective and safe for coronary patients to receive phosphodiesterase type 5 (PDE5) inhibitors. However, PDE5 inhibitors are contraindicated in patients taking nitrate therapy and beta-blockers may further worsen ED. Trimetazidine, because of its mode of action and an absence of negative effect upon ED, is the drug of choice for the treatment of patients with CAD and ED who require treatment with PDE5 inhibitors. It has also been shown that trimetazidine plus sildenafil are more effective than nitrates in the control of myocardial ischaemia during sexual activity in patients with CAD.\(^{16}\) Putting the evidence together, trimetazidine may be a better therapeutic option over conventional anti-anginal therapies for CAD patients with diabetes complicated by ED.

Conclusions:

Modulation of cardiac energy metabolism has proved to be an attractive option for the treatment CAD, particularly in patients with diabetes, as reflected by the significant improvements obtained in exercise capacity, symptom relief, and left ventricular function. Due to its purely metabolic mode of action, trimetazidine does not affect hemodynamic parameters and is well tolerated. It is also a safe and effective treatment for diabetic coronary patients and those who have erectile dysfunction requiring treatment with PDE5 inhibitors.

References