

# Benefits of trimetazidine (TMZ) in obese patients

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## Abstract

Obesity is an increasingly prevalent metabolic disorder worldwide, constituting a major risk factor for an array of chronic diseases, including chronic ischemic heart disease (IHD) and stable angina, two leading causes of death and disability. It is commonly known today that obesity is linked to heart damage, as its development results in accelerated fatty acid oxidation (FAO) and uncoupling of glycolysis from glucose oxidation. Subsequent cardiac steatosis favors oxidative stress and apoptosis, followed by mitochondrial damage, further compromising ATP production and contributing to contractile dysfunction and decreased cardiac efficiency. The anti-ischemic agent trimetazidine (TMZ), a selective 3-ketoacyl-coenzyme A thiolase inhibitor, is a commonly known modulator of intracellular metabolism observed in a number of basic and clinical studies to directly provide more energy to ischemic cardiomyocytes by directly inhibiting, in an ischemic myocardium, the energy-consuming FAO in favor of glucose oxidation. In obese subjects likely to experience glucose intolerance and cardiac hypertrophy as a consequence of alterations in cardiac energy metabolism, elevated rates of FAO, and decreased glucose-oxidation rates, TMZ could be particularly beneficial. ■ *Heart Metab.* 2016;69:27-30

**Keywords:** ischemic heart disease; obesity; trimetazidine

## Introduction

Obesity is an increasingly prevalent metabolic disorder affecting both the Western populations and the developing world. According to the World Health Organization's key facts, in 2014, more than 1.9 billion adults (39%) globally were overweight, and among these, over 600 million (13%) were obese.<sup>1</sup> Overweight and obese individuals have an increased prevalence of comorbidities compared with normal weight individuals. Excess weight and obesity are known to be major risk factors for the onset of a variety of chronic diseases—responsible

for 60% of deaths worldwide<sup>1</sup>—among which cardiovascular diseases with ischemic heart disease (IHD) account for the greater part.<sup>2-5</sup>

### Obesity, heart damage, and ischemic heart disease

It is commonly known today that obesity is linked to heart damage.<sup>6,7</sup> Obesity onset and development result in an increased availability of fatty acid (FA), a concomitant over-reliance on FA as an energy source, accelerated FA oxidation (FAO), and an uncoupling of glycolysis from glucose oxidation. Consequently, cardiomyocyte FA uptake often exceeds mi-

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### Abbreviations

**Ca<sub>i</sub><sup>2+</sup>**: intracellular calcium; **FA**: fatty acid; **FAO**: fatty acid oxidation; **IHD**: ischemic heart disease; **PCI**: percutaneous coronary intervention; **SERCA2a**: sarcoplasmic reticulum calcium-transporting ATPase isoform 2a; **TG**: triacylglycerol

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tochondrial oxidative capacity, and cardiac steatosis ensues, leading to a build-up of lipotoxic intermediates, such as ceramide and acylcarnitine. Collectively, these events favor oxidative stress and apoptosis and subsequent mitochondrial damage, further compromising adenosine triphosphate (ATP) production and contributing to contractile dysfunction and to a decrease in cardiac efficiency.<sup>8,9</sup>

Alterations in mitochondrial energy metabolism are common in many forms of heart disease,<sup>10</sup> including IHD and diabetic cardiomyopathies, and precede the development of glucose intolerance and cardiac hypertrophy.<sup>11</sup> In IHD, energy production is impaired due to a limitation in oxygen supply; residual mitochondrial FAO dominates over mitochondrial glucose oxidation. In diabetes, the ratio of cardiac FAO to glucose oxidation also increases, although primarily due to an increase in FAO and an inhibition in glucose oxidation.<sup>8</sup> In many studies, hearts from animals or humans with diabetes mellitus or obesity were characterized by elevated FAO rates and a marked decrease in glucose oxidation rates,<sup>11-16</sup> resulting in mitochondrial FAO dominating as a source of energy in the diabetic or obese heart.

A number of studies have also shown an accumulation of myocardial triacylglycerol (TG) in diabetes and obesity, although TG itself is not believed to contribute to myocardial insulin resistance.<sup>17</sup> The mechanisms involved in the accumulation of lipid intermediates (eg, diacylglycerol, long-chain fatty acyl-CoA esters, and ceramide) are still to be elucidated. Two scenarios are proposed to explain the increased storage of intramyocardial TG and the accompanying cardiac contractile dysfunction accumulation: (i) impaired FAO and (ii) oversupply of FA.<sup>17</sup> As explained by Zhang and Ren,<sup>17</sup> “myocardial TG accumulation may either protect the heart by ‘storing away’ the detrimental lipid intermediates..., or elicit severe lipotoxicity thereby compromising cardiac function; meanwhile, the insulin-resistant heart in obesity and type 2 diabetes is unable to fully use glucose, forcing

the heart to rely on FA for energy demand and thus prompting a vicious cycle of increased cardiomyocyte FA uptake, oxidation, and TG accumulation, all of which are hallmarks of lipotoxic cardiomyopathy.”

The systemic inflammation, generalized enlargement of fat deposits, and uncontrolled release of FA into the circulation associated with type 2 diabetes and obesity support the occurrence of cardiac adiposity, characterized by an increase in intramyocardial TG content and in the volume of fat surrounding the heart and vessels.<sup>18</sup> Whereas initially these events may be defense mechanisms, helping to distribute energy, when excessive they can lead to myocardial damage and heart disease.<sup>18</sup>

FAO inhibition has emerged as a novel approach for the treatment of IHD, subsequent to accumulating evidence that modulating cardiac energy metabolism by increasing glucose oxidation directly, or indirectly by FAO inhibition, can improve cardiac function of the ischemic heart.<sup>8</sup> The potential for FAO inhibition to treat cardiac disease has been called upon in many basic and clinical studies, some of them using FAO inhibitors such as TMZ to achieve this metabolic effect.<sup>19-21</sup> TMZ directly provides energy to the ischemic cardiomyocytes by directly inhibiting, in an ischemic myocardium, the energy-consuming free-FA oxidation in favor of glucose oxidation.

### Preclinical data

A recent study of Yao et al<sup>22</sup> studied TMZ's influence on sarcoplasmic reticulum calcium-transporting ATPase isoform 2a (SERCA2a) in diet-induced obese rats and palmitic acid-treated cardiomyocytes. SERCA2a has an important role in maintaining the calcium (Ca<sup>2+</sup>) balance and contractile function of cardiomyocytes. In obese and type 2 diabetic models, reduced activity and expression of SERCA2a were observed to play a significant role in cardiac dysfunction.<sup>22</sup> Yao's study found that TMZ partially restored SERCA2a protein in diet-induced obese rats and palmitic acid-treated cardiomyocytes.<sup>22</sup>

The same TMZ mechanism of action is involved in the cardiomyocyte protection from hypoxia-induced ischemia. A study by Wei et al<sup>23</sup> was designed to test the hypothesis that treatment with TMZ would improve intracellular Ca<sup>2+</sup> (Ca<sub>i</sub><sup>2+</sup>) handling in hypoxic myocardial injury. The investigators found that in TMZ-treated cardiomyocytes, the amplitude of Ca<sub>i</sub><sup>2+</sup>

oscillations and sarcoplasmic reticulum  $\text{Ca}^{2+}$  load were recovered; the diastolic  $\text{Ca}_i^{2+}$  concentration was decreased; and the activities of ryanodine receptor 2 (RyR2),  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX), and SERCA2a were increased. Hypertrophy was reduced in TMZ-treated hypoxic cardiomyocytes, and TMZ treatment enhanced the “metabolic shift” from lipid oxidation to glucose oxidation in the cardiomyocytes. These results suggest that TMZ ameliorates  $\text{Ca}_i^{2+}$  homeostasis through a switch from lipid to glucose metabolism, thereby producing the cardioprotective effect and the reduction in hypoxic cardiomyocyte damage.<sup>23</sup>

In a murine model, a recent study aimed to determine whether pharmacologic inhibition of 3-ketoacyl-coenzyme A thiolase (3-KAT), which catalyzes the final step of FAO, could improve obesity-induced cardiomyopathy. The investigators observed that a 3-week treatment with TMZ prevented obesity-induced reduction in both systolic and diastolic function, concluding that targeting cardiac FAO may be a novel therapeutic approach to alleviate the growing burden of obesity-related cardiomyopathy.<sup>24</sup>

### Clinical data and clinical implications

Bucci et al<sup>25</sup> conducted a study to dissect the contributions of plasma and intracellularly bound FA to myocardial FAO in obese individuals, and to investigate whether the hypothesized action of TMZ to shift myocardial metabolism from the utilization of FA to that of glucose occurs in humans. In these obese subjects, one important finding of the study was that myocardial TG represented a major source of FAs that underwent oxidation, and it was demonstrated that myocardial intracellular TG oxidation significantly provides FA-derived energy for mechanical work. In this study, data showed an important effect of TMZ in reducing the oxidation of TG-derived myocardial FAs from endogenous sources, improving myocardial efficiency.<sup>25</sup>

In a previous study, the same authors studied regional FA metabolism in skeletal muscle and adipose tissue in humans and investigated the long-term effects of TMZ on glucose and FA metabolism.<sup>26</sup> TMZ was observed to significantly increase skeletal muscle FA esterification and mildly upregulate glucose phosphorylation. The authors suggest that human obesity is characterized by a defect in tissue-FA storage capability, which is accompanied by an (potentially

compensatory) elevation in skeletal muscle FAO; TMZ diverted FA from oxidative to nonoxidative pathways and provoked an initial activation of glucose metabolism in skeletal muscle.

More recently, a study by Shehata<sup>27</sup> evaluated the effect of periprocedural administration of TMZ on the incidence of percutaneous coronary intervention (PCI)-induced myocardial injury and contrast-induced nephropathy in overweight (body mass index, 27-28  $\text{kg}/\text{m}^2$ ) diabetic patients with mild-to-moderate renal dysfunction. TMZ intake before elective PCI in these patients was associated with decreased incidence of contrast-induced nephropathy and myocardial injury.<sup>27</sup>

### Conclusions

In obese subjects likely to experience glucose intolerance and cardiac hypertrophy as a consequence of alterations in cardiac energy metabolism, elevated rates of FAO, and decreased glucose oxidation rates, the use of agents such as TMZ could be particularly beneficial. The specific properties of this modulator to reduce the oxidation of TG-derived myocardial FAs and to increase the glucose oxidation, therefore improving myocardial efficiency, possibly represents the additional value of this agent in preventing or minimizing the consequences of obesity, particularly in patients with IHD. ■

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