Ketone Bodies Are an Alternative Energy Source and Exert Antioxidant Effects

To the Editor:
The EMPA-REG OUTCOME trial tested the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin in patients with type 2 diabetes and high cardiovascular (CV) risk. Results showed a striking risk reduction. Kaku et al also present striking data of their subanalysis of the EMPA-REG OUTCOME study in Asian type 2 diabetic patients with high CV risk.1 Thus, the EMPA-REG OUTCOME trial established the cardioprotective effects of empagliflozin in high-risk diabetic patients, but the underlying mechanisms remain elusive. Ketone body β-hydroxybutyrate (βOHB) levels are elevated in patients treated with SGLT2 inhibitors. Ferrannini et al2 postulated the “thrifty substrate” hypothesis, suggesting that SGLT2 inhibitors may optimize cardiac energy metabolism and improve myocardial energetics and substrate efficiency, thus reducing cardiac failure. They suggested that this increase in circulating ketone levels offers significant cardioprotection to high-risk patients with diabetes. However, Lopaschuk and Verma4 reported that the relationship between myocardial ketone oxidation and the cardioprotective effects of empagliflozin is far from clear and they questioned if empagliflozin actually increases or decreases ketone oxidation in the heart.

Ketone bodies are important vectors of energy transfer. The relative capacity for tissues to utilize ketone bodies for energy is thought to be determined by their levels of a ketolytic enzyme: succinyl-CoA:3-ketoacid CoA transferase (SCOT).4 SCOT is expressed at higher levels in the myocardium than brain, kidney, and skeletal muscle.4 Although fatty acids, glucose, and βOHB may all compete for acetyl-CoA in the TCA cycle, this high level of distribution of myocardial SCOT is consistent with the preference for utilization of βOHB for energy in the diabetic heart under empagliflozin treatment. Interestingly, Nagao et al recently reported that in pressure-overloaded mice, the gene and protein expression levels of SCOT were decreased in failing hearts, causing βOHB accumulation because of the decline in its utilization.5 Consequently, increased myocardial βOHB plays a compensatory role against oxidative stress in failing hearts. This suggests that SCOT expression levels or regulation could determine the roles of βOHB in organs or particular cell types.

βOHB accumulation in skeletal muscle because of decreased utilization caused by downregulation of SCOT may induce antioxidant effects,6 resulting in amelioration of insulin resistance, which is caused by oxidant stress in the setting of type 2 diabetic skeletal muscle. However, it is unlikely that increasing βOHB levels will decrease hypertrophic signaling,6 because SCOT is highly expressed in the human heart.

Accordingly, it is postulated that modestly elevated circulating βOHB during treatment with SGLT2 inhibitors has different beneficial effects on organs or cells, depending on the SCOT level. Thus, it is necessary to elucidate the organ-specific regulation of SCOT and the stress-induced regulation of SCOT in various cell types including vascular endothelial cells.

References

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