Comment on Sodium-Glucose Co-Transporter 2 Inhibitors and Heart Failure

Dear sir,

We read with great interest the review article by Ghosh et al "Sodium-Glucose Co-transporter 2 Inhibitors (SGLT-2i) and Heart Failure (HF)."[1] SGLT-2i has started to be used in HF treatment as it causes salt and fluid excretion, and reduces blood glucose. In addition to the mechanisms mentioned in the article,1 we think that SGLT-2i reduces mortality and morbidity in HF by lowering the lactate level. We would like to draw attention to several points in this regard.

The heart is one of the most energy-consuming organs in the body; therefore, the heart needs significant energy sources. Under normal aerobic conditions, myocardium provides most of the energy source from free fatty acids (FFAs); however, it uses glycogen as the energy source in the case of hypoxia or mild ischemia. The citrate cycle may decrease due to hypoxic conditions in HF. Since sufficient adenosine triphosphate (ATP) cannot be provided for the myocardium, the anaerobic glycolysis pathway is activated and ATP is tried to be obtained.[2] As a result of the anaerobic glycolysis pathway activation, lactate formation from pyruvate increases.[3] In addition, when liver dysfunction occurs in a hypoxic environment, lactate clearance decreases.[4] Lactate is known to increase pro-inflammatory cytokine release. Inflammation worsens the hypoxic state. Beta oxidation of FFAs decreases as a result of reducing long-chain carnitine acyltransferase enzyme activity due to hypoxia and increased lactate level.[5] In the aerobic environment, acetyl-CoA is formed by pyruvate dehydrogenase enzyme from pyruvate. Due to the increase of lactate formation from pyruvate in anaerobic conditions, the formation of acetyl-CoA from pyruvate decreases. Intracellular acetyl-CoA level decreases due to reduced beta-oxidation and raised lactate formation from pyruvate.[5] Since the heart cannot use FFAs as an energy source, its contraction strength decreases.

In addition to the known effects of Dapagliflozin, an SGLT-2i, it can have a protective effect on HF by several different mechanisms. First, epicardial adipose tissue is known to release lactate and adipocytokines. In a recent study, dapagliflozin has been reported to inhibit lactate release from epicardial adipose tissue tissue.[6] The inhibitory effect of lactate on beta-oxidation ends due to decreased lactate levels with dapagliflozin use. Energy production continues again through the activation of acetyl-CoA and Krebs cycle. Second, SGLT-2i has been shown to reduce the oxygen consumption of tissues.[7] SGLT-2i causes glucose to enter the aerobic pathway instead of the anaerobic pathway by reduced oxygen consumption in patients with HF. Thus, lactate formation decreases, beta-oxidation, and acetyl-CoA formation continue. Third, it is known that lactate level increases due to hyperglycemia. It has been reported that lactate levels remain stable at 80 to 120 mg/dl of glucose levels.[8] The glycosuric effect of SGLT-2i stops when the blood glucose level drops below 80 mg/dl, thus hypoglycemia is not expected. SGLT-2i causes up to 70 mg of glucose excretion daily from the kidney. SGLT-2i reduces lactate formation by keeping glucose at optimum levels in heart failure regardless of diabetes. In conclusion, dapagliflozin lowers the lactate level in HF and may prevent myocardial damage. It may reduce mortality and morbidity in HF.

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13 February 2020

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https://doi.org/10.1016/j.amjcard.2020.03.001