Comment on Ferrannini et al. Diabetes Care 2016;39:1108–1114. Comment on Mudaliar et al. Diabetes Care 2016;39:1115–1122

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In their recent articles, Ferrannini et al. (1) and Mudaliar et al. (2) suggest that increased ketonemia, improving heart function, might explain the positive results of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study. This suggestion perfectly fits with our recently published hypothesis that glucagon could be the key player of the observed results of EMPA-REG OUTCOME (3). Empagliflozin increases glucagon levels (3), and we suggest that the reduced risk of hospitalization for heart failure with empagliflozin might be partly explained by a direct enhancement of myocardial function, determined by the increased levels of glucagon, and by its natriuretic effect (3). In the nonfailing heart, glucagon determines a rise in heart rate, almost without changes in cardiac output and auricular pressure; in the failing heart, it increases heart rate and cardiac output, together with a dose-dependent increase in coronary blood flow and oxygen consumption (4). As an inotropic agent, glucagon increases the work of the heart and, consequently, it increases oxygen consumption, lipolysis, and β-oxidation of lipids (4). It is noteworthy that both insulin and glucagon increase fuel availability in the heart, but it is well known that glucagon is the most potent ketogenic hormone (5). In this view, the theories of Ferrannini et al. (1) and Mudaliar et al. (2) could be considered, biochemically, the next step of our hypothesis: the increase of glucagon, induced by empagliflozin, has a direct effect on the heart and some effects mediated by increased ketogenesis. It is noteworthy, however, that their theories do not fully explain the main outcome of EMPA-REG OUTCOME, which is the cardiac death, and that the direct beneficial effect of glucagon on disturbances of cardiac rhythm could be responsible for the reduction of cardiovascular mortality with empagliflozin (3).

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