Cardiorenal protective effect of sodium–glucose cotransporter 2 inhibitors and mitochondrial function

The cardiorenal protective effect of sodium–glucose cotransporter 2 (SGLT2) inhibitors is well established by three large clinical trials, Empagliflozin, Cardiovascular Outcome Events Trial in Type 2 Diabetes Patients (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS) and, most recently, Dapagliflozin Effect on Cardiovascular Events Trial 58 by the Thrombolysis in Myocardial Infarction Study Group (DECLARE–TIMI 58). Three different SGLT2 inhibitors, empagliflozin, canagliflozin and dapagliflozin, were proven effective not only for their glucose-lowering effect, but also in reducing deterioration of renal function and preventing hospitalization as a result of heart failure. However, differences between the drugs were found. Although empagliflozin reduced major cardiovascular events (MACE), cardiovascular (CV) mortality and all-cause mortality, as well as hospitalization as a result of heart failure, canagliflozin reduced MACE, but not CV mortality, and dapagliflozin was not superior in reducing MACE as well as CV mortality than placebo. Renal failure, heart failure and CV diseases are among the most deadly complications of diabetes. It is not surprising, therefore, that diabetologists are excited about having a new kind of drug that could reduce these deadly complications. Then we have to ask what is the mechanism(s) of these drugs, as the answer(s) could lead to further improvement in treatment. A new clinical observation raises questions directed to molecular biologists.

Even clinicians can easily appreciate that the cardiorenal protective effect is not due solely to the glucose-lowering effect, as beneficial effects are unique to this class of agents. As they were made to inhibit glucose reuptake in renal tubules, thus enhancing glycosuria (and sodium diuresis), one could also appreciate these effects are secondary to removal of a significant amount of circulating glucose, independent of insulin action. For renal protection, lowering of intraglomerular pressure is considered as a key mechanism, although improvement in arterial stiffness, a decrease in serum uric acid levels and tubulointerstitial hypoxia are also considered. Reductions in glomerular hypertension are thought to result from increased sodium reaching the macula densa, induced by increased glycosuria, thus restoring tubuloglomerular feedback, and causing afferent arteriole vasomodulation.

For cardioprotection, hemodynamic explanation is proposed among the various physiological explanations, such as a decrease in blood volume (reflected by increases in hematocrit and hemoglobin concentration), decrease in bodyweight and blood pressure, and sodium diuresis, all of which could improve cardiac function. Then there is a caveat. If the cardioprotective effect of a drug is due to hemodynamic effects induced by the drug's glycosuric (and natriuretic) effect, why are MACE and CV mortality rates so different? An observation made in the EMPA-REG OUTCOME trial was also difficult to explain from a hemodynamic perspective; the high-risk patients taking SGLT2 inhibitors had the same event rates for an acute myocardial or cerebral infarction, but a higher proportion of patients survived that event. This observation strongly suggested that this drug protects the heart and brain after the ischemic event is precipitated. To answer these kinds of questions, journals are flooded with reports describing the off-target mechanisms or pleiotropic effects of SGLT2 inhibitors.

Bell and Yellon[1] proposed four hypothetical mechanisms to explain the beneficial effects of SGLT2 inhibitors on the brain and heart, which express negligible SGLT2: (i) inhibition of sodium–hydrogen exchange, which is known to protect the myocardium from ischemia reperfusion injury; (ii) abrogation of excessive reactive oxygen generation induced by ischemia reperfusion injury by SGLT2 inhibitors, particularly canagliflozin, which might be mediated through an interaction between sodium–glucose cotransporter 1/sodium myoinositol cotransporter 1 and gp91[phox] nicotinamide adenine dinucleotide phosphate oxidase; (iii) non-specific inhibition of SGLT2 inhibitors on the sodium–glucose cotransporter 1 receptor, which mediates intracellular sodium and calcium accumulation, which in turn leads to the opening of the mitochondrial membrane permeability transition pore, thus cell death; and (iv) the potential role of the inotropic effect of glucagon on the heart and metabolic substrates switching toward ketones accompanied by mild ketosis, which occurs after SGLT2 inhibitor treatment. There is other mechanism not discussed by Bell and Yellon.

In the September issue of this journal, Takagi et al.[2] reported a new SGLT2 inhibitor, ipragliflozin, protects mitochondrial function. They fed mice a high-fat diet to induce insulin resistance and treated them with ipragliflozin, which restored mitochondrial damage induced by a high-fat diet. A high-fat diet increased 8-hydroxydeoxyguanosine concentration in the urine (evidence of oxidative stress) of mice and damaged the proximal kidney tubule, as well as showing morphological evidence of mitochondrial damage. Ipragliflozin reversed that damage to a normal state. In in vitro studies using a tubular epithelial cell

line HK-2 and MitoTracker Green uptake to cells, and expression of optic atrophy factor-1 and mitofusin-2 (two small guanosine triphosphatases important for mitochondrial fusion) as markers measuring mitochondria function status, it was found that ipragliflozin normalizes high glucose- or high palmitate-induced suppression of mitochondrial function. This suppression is interpreted secondary to SGLT2 inhibition, as small interfering ribonucleic acid of SGLT2, as well as ipragliflozin, restored that mitochondrial dysfunction. Although this study observed very few markers measuring mitochondrial function and is the only study reporting the beneficial effect of an SGLT2 inhibitor, ipragliflozin, the evidence is enough to conclude that this drug exerts a mitochondrial protective effect.

This observation is consistent with a report by Hawley et al.[3], who showed that canagliflozin activates adenosine monophosphate-activated protein kinase by inhibiting complex I of the mitochondrial electron transfer chain. Only canagliflozin showed this effect, whereas dapagliflozin, empagliflozin and phlorizin did not activate adenosine monophosphate-activated protein kinase to any significant extent. These observations were made at a whole cell (HEK-293) level. In primary mouse hepatocytes, which were made permeable with digitonin, both canagliflozin and dapagliflozin inhibited complex I-supported mitochondrial respiration in a concentration-dependent manner. The effect of dapagliflozin was less than that of canagliflozin (estimated half-maximal effects were 40 ± 3 μmol/L for dapagliflozin and 18 ± 1 μmol/L for canagliflozin). Digitonin treatment removes the cell membrane barrier, thus exposing mitochondria directly to drugs. These results clearly show that dapagliflozin and canagliflozin could directly affect mitochondrial function.

Another report confirmed the inhibitory effect of SGLT2 inhibitors to mitochondrial complex I and extended further; canagliflozin inhibited not only complex I, but also mitochondrial glutamate dehydrogenase[4]. Dapagliflozin and empagliflozin were without significant glutamate dehydrogenase inhibition or complex I inhibition activities. Interestingly, they observed a non-significant increase in maximal respiration and spare respiratory capacity of cells by dapagliflozin (50 μmol/L) and empagliflozin (50 μmol/L), and a lower level (10 μmol/L) of canagliflozin than dimethylsulfoxide, which was used as a control. Canagliflozin inhibited both maximal and spare respiratory capacity of cells at a low level (10 μmol/L) as well as at 50 μmol/L.
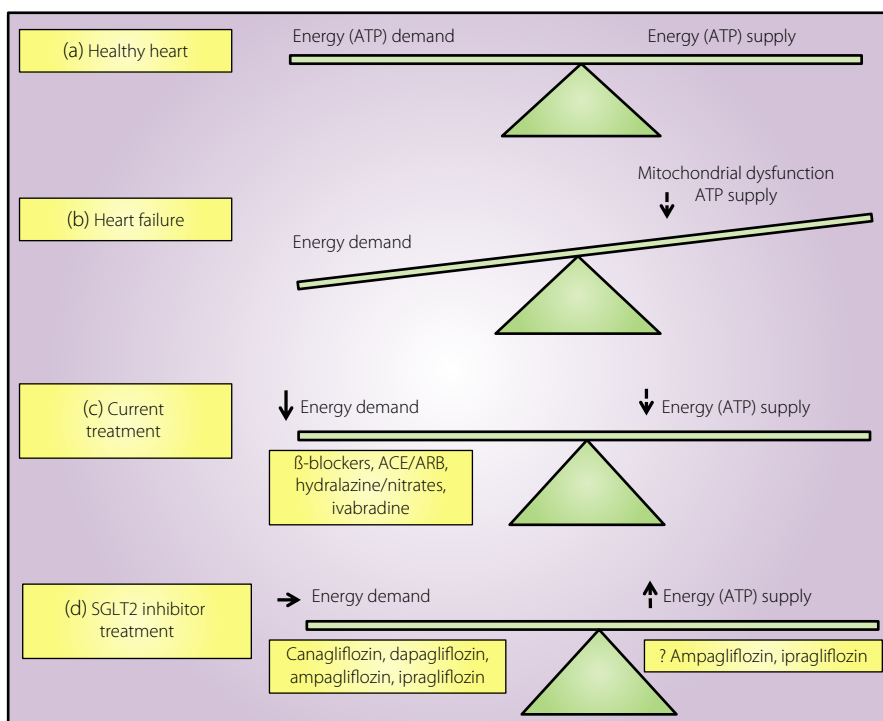

Figure 1 | The cardiorenal protective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors are explained from the perspective of "heart failure as a disease of bioenergetic failure" advanced by Brown et al.[5] (a) In a healthy state, energy (adenosine triphosphate [ATP]) supply meets energy demand to maintain energy balance. (b) In heart failure, energy supply from heart muscle could not meet its demand due to mitochondrial dysfunction. (c) Most of the currently used drugs decrease energy demand and often do not fully address the underlying causes of progressive ventricular dysfunction. (d) SGLT2 inhibitors prevented development of heart failure in clinical trials and showed a mitochondrial protective effect in vitro and in vivo, suggesting that they might improve energy supply. ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

I am focusing on the effects of SGLT2 inhibitors on mitochondrial function, because mitochondrial function or bioenergetics is emerging as a key to the understanding of heart failure and its therapeutic target. Heart failure has been a serious clinical problem among cardiologists. Over the past two decades, the treatment of ischemic and valvular heart disease has enormously improved, but patients are left to live with residual cardiac dysfunction and other comorbidities, which frequently lead to heart failure. The vast majority of clinical trials on heart failure carried out in the past decade were labeled as neutral. In 2015, leaders in cardiovascular medicine held a consensus development roundtable discussion meeting and published their opinion in an expert consensus document entitled "Mitochondrial function as a therapeutic target in heart failure"[5]. I could not reintroduce key arguments of this document here, but emphasize the fact that these experts recognized heart failure as a bioenergetics disease. They focused on the insufficient energy production in heart failure, the role it has in progressive left ventricular dysfunction, and recommended exploring drugs that might preserve and improve energy supply. They presented detailed mechanisms of impaired cellular energy production, and explained the effects of drugs used to treat heart failure from the various aspects of mitochondrial dysfunction or bioenergetics. From the insights into the mechanisms of mitochondrial dysfunction in heart failure, methods to improve the mechanisms were presented, along with an overview of emerging treatments by targeting mitochondria. This concept is illustrated in Figure 1. This document did not consider SGLT2 inhibitors, as it was drafted before publications of clinical trials of SGLT2 inhibitors. I overlaid the results of clinical trials of SGLT2 inhibitors to the scheme presented in the consensus document developed by the leaders of cardiovascular medicine.

The knowledge gap between the science of heart failure and the science of SGLT2 inhibitors is huge, in that just four SGLT2 inhibitors were studied in some detail for their effects on mitochondria, and the mitochondrial function of two cell lines and one tissue (liver) was studied. Further studies are required. Then, we have to realize that heart failure is a bioenergetics failure of the heart, and SGLT2 inhibitors improved it. Therefore, studying the effects of SGLT2 inhibitors from bioenergetics perspectives will be very helpful in understanding heart failure, but will also help us to understand their renal protective effect.

DISCLOSURE

The author declares no conflict of interest.

Hong Kyu Lee* ID
Department of Internal Medicine, Eulji University and Eulji General Hospital, Seoul, Korea
*E-mail: hkleemd@eulji.ac.kr

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