Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

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Type 2 diabetes mellitus causes excessive morbidity and premature cardiovascular (CV) mortality. Although tight glycemic control improves microvascular complications, its effects on macrovascular complications are unclear. The recent publication of the EMPA-REG OUTCOME study documenting impressive benefits with empagliflozin (a sodium–glucose cotransporter 2 [SGLT2] inhibitor) on CV and all-cause mortality and hospitalization for heart failure without any effects on classic atherothrombotic events is puzzling. More puzzling is that the curves for heart failure hospitalization, renal outcomes, and CV mortality begin to separate widely within 3 months and are maintained for >3 years. Modest improvements in glycemic, lipid, or blood pressure control unlikely contributed significantly to the beneficial cardiorenal outcomes within 3 months. Other known effects of SGLT2 inhibitors on visceral adiposity, vascular endothelium, natriuresis, and neurohormonal mechanisms are also unlikely major contributors to the CV/renal benefits. We postulate that the cardiorenal benefits of empagliflozin are due to a shift in myocardial and renal fuel metabolism away from fat and glucose oxidation, which are energy inefficient in the setting of the type 2 diabetic heart and kidney, toward an energy-efficient super fuel like ketone bodies, which improve myocardial/renal work efficiency and function. Even small beneficial changes in energetics minute to minute translate into large differences in efficiency, and improved cardiorenal outcomes over weeks to months continue to be sustained. Well-planned physiologic and imaging studies need to be done to characterize fuel energetics–based mechanisms for the CV/renal benefits.

Type 2 diabetes mellitus (T2DM) is a chronic debilitating disease that leads to excessive morbidity and premature cardiovascular (CV) mortality worldwide. Although studies have documented the benefits of optimal glycemic control on microvascular complications, the effect of tight glycemic control on macrovascular complications is unclear (1). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, tight glycemic control increased CV and all-cause mortality (2). Glitazones and saxagliptin (a dipeptidyl peptidase 4 inhibitor) increase the risk of hospitalization for heart failure (HF) (3,4). In this context, the recent publication of the EMPA-REG OUTCOME study documenting impressive benefits with empagliflozin (a sodium–glucose cotransporter 2 [SGLT2] inhibitor) on CV/all-cause mortality and hospitalization for HF is a game changer, and if replicated, it may lead to a

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paradigm shift in the treatment of T2DM (5). Of note, empagliflozin treatment did not have any effects on classic atherothrombotic events (no change in myocardial infarction [MI] and a trend toward higher rates of stroke). The dramatic change driving the superiority of the primary composite major adverse CV events outcome was a significantly lower CV death rate with empagliflozin (38% relative risk reduction). In addition, there were impressive 35% and 38% relative risk reductions in hospitalization for HF and death from any cause (Table 1). These results are reminiscent of the CV benefits of lipid lowering with statins (6), with the main difference being that statins reduce atherothrombotic event rates; most of the patients in EMPA-REG OUTCOME study were on statins.

The EMPA-REG OUTCOME study also demonstrated impressive beneficial renal outcomes (7). Compared with placebo, empagliflozin treatment was associated with a 46% risk reduction in the composite of doubling of serum creatinine, initiation of renal replacement therapy (dialysis or renal transplant), or death caused by renal disease ($P = 0.0002$) (Table 2).

A puzzling feature of the EMPA-REG OUTCOME results is that the CV and renal benefits of empagliflozin occurred in the absence of any dramatic differences in glycemic, lipid, or blood pressure (BP) control. The study authors postulated several potential vascular, neurohormonal, and cardiorenal mechanisms besides additional effects on hyperglycemia, weight, visceral adiposity, and BP as potentially contributing to the CV benefits. Others have commented on the potential benefit of combination SGLT2 inhibitor and ACE inhibitors/angiotensin receptor blockers on the vascular endothelium (8). However, a paucity of data fully supports many of these mechanisms. Even if they do play a role, one must explain why the HF hospitalization, renal outcome, and CV mortality curves began to separate widely within 3 months and were maintained for >3 years. BP, diuretic effects, or even neurohormonal/vascular effects unlikely could produce such dramatic results in a short time frame.

It is relevant to briefly describe the adaptive physiologic mechanisms that likely occur after SGLT2 blockade in the S1 segment of the proximal convoluted tubule. Several compensatory mechanisms come into play to oppose this acute loss of sodium and glucose. Although there is initial natriuresis, this is compensated for by an increase in renin/aldosterone and increased distal sodium reabsorption (9). With regard to the acute blockade of glucose reabsorption by SGLT2 inhibition in the proximal convoluted tubule and consequent urinary glucose loss, we believe that the following adaptive mechanisms come into play. Continuous urinary glucose (and calorie) drainage in the setting of SGLT2 inhibition is akin to the accelerated starvation situation seen in pregnancy where there is a continuous drain of glucose/nutrients by the fetus in the setting of intermittent feeding and fasting by the mother and increased free fatty acid (FFA) and ketone levels during fasting in the setting of low glucose and insulin levels (10). SGLT2 blockade similarly induces a continuous glucose loss through the kidney in the setting of intermittent feeding and fasting by a patient with T2DM on SGLT2 inhibitor therapy. This elicits the following physiologic adaptive responses to counter the continuous glucose drain: *1*) increased glucose reabsorption by SGLT1 downstream to limit urinary glucose loss; *2*) increased endogenous glucose production partly through an increase in glucagon and decrease in insulin levels (11,12); *3*) increased FFA and ketone levels with a shift in whole-body fuel metabolism toward increased dependence on fat oxidation at the expense of glucose oxidation (11); and *4*) increased carbohydrate consumption in the setting of lower glycemia, lower insulin doses, and lower body weight (9). Despite these compensatory mechanisms that increase blood glucose levels to counter the continuous urinary glucose excretion, studies have documented improved glycemia with SGLT2 inhibitor therapy. Furthermore, we believe that the shift in fuel metabolism that occurs with SGLT2 blockade plays a major role in the cardiorenal benefits of empagliflozin.

Accordingly, we postulate that the CV and renal benefits of empagliflozin are due to a shift in myocardial and renal fuel metabolism. This shift in organ fuel metabolism is rapid in onset, is sustained in duration, and leads to improved cardiac and renal outcomes.

Table 1—Cardiovascular outcomes in the EMPA-REG OUTCOME study

CV outcome	Placebo group (n = 2,333)	Pooled empagliflozin group (n = 4,687)	Relative risk reduction
CV death, nonfatal MI/stroke	12.1	10.5	−14*
Death from any cause	8.3	5.7	−32*
CV death	5.9	3.7	−38*
Hospitalization for HF	14.5	9.4	−35*
Fatal/nonfatal MI (excludes silent MI)	5.4	4.8	−13**
Nonfatal stroke	3.0	3.5	+24**

Data are %. *Significant. **Nonsignificant.

FUEL METABOLISM AND EMPAGLIFLOZIN EFFECTS ON HEART FAILURE AND CV OUTCOMES

HF is a frequent, forgotten, and often fatal complication of diabetes (13). Epidemiological analyses reveal a twofold higher risk for HF in men and a threefold higher risk in women with T2DM, after adjustment for age and CV risk factors (14). In the UK Prospective Diabetes Study (UKPDS), HF hospitalization incidence was similar to that of nonfatal MI and stroke (15). The prognosis of patients with HF is poor, with a mortality rate of 20% within 1 year of initial diagnosis and an 8-year mortality rate of 80%, a frequency exceeding that of many cancers (16). Most deaths are sudden and unexpected. In the EMPA-REG OUTCOME study, the 35% relative risk reduction in hospitalization for HF with empagliflozin was associated with a 38% reduction in CV death, 31% reduction in sudden death, and 75% reduction in death caused by worsening HF. Because HF is associated with high mortality rates (especially in patients with diabetes), it is reasonable to expect that a medication that improves myocardial function would lead to less HF and lower CV death. Our hypothesis is that empagliflozin improves myocardial fuel metabolism, myocardial contractility, and cardiac efficiency by shifting fuel

Table 2—Renal outcomes in the EMPA-REG OUTCOME study

Renal outcome	Pooled empagliflozin group (n = 4,687) vs. placebo (n = 2,333)		
	Hazard ratio	Relative risk reduction (%)	P value
New-onset or worsening nephropathy	0.61	39	0.0001
Composite of: Doubling of serum creatinine Initiation of renal replacement therapy (includes dialysis/transplantation) Death due to renal disease	0.54	46	0.0002

utilization away from lipids and glucose (which are less energy efficient) toward ketone bodies that produce ATP energy more efficiently than glucose or FFA and that act as a super fuel (17).

MYOCARDIAL DYSFUNCTION IN DIABETES

Myocardial dysfunction in diabetes results from a complex interaction of the cardiotoxic triad: myocardial ischemia, hypertension, and a specific diabetic cardiomyopathy (13). Factors playing a role in the pathogenesis of diabetic cardiomyopathy are persistent hyperglycemia with glycation of interstitial proteins and effects on myocardial stiffness/contractility; autonomic dysfunction; metabolic, ion channel, and calcium abnormalities; interstitial fibrosis; renin-angiotensin system upregulation; increased oxidative stress; mitochondrial dysfunction; and altered substrate metabolism (18). Myocardial energy abnormalities in diabetes involve defects in substrate uptake and use, mitochondrial dysfunction, and impaired energy transfer from mitochondria to myofibrils. Herein, we focus on the role of substrate metabolism as a major cause of impaired myocardial contractility and progressive HF in T2DM.

FUEL METABOLISM IN THE HEALTHY HEART

The human heart contracts continuously, with a daily turnover rate of ATP of ~6–35 kg (19), high coronary blood flow (~200 mL/min), and the highest oxygen consumption per tissue mass (4.3 mmol/kg/min) (20,21). Nearly 95% of myocardial energy is derived from mitochondrial oxidative metabolism and ~5% from glycolysis and guanosine-5'-triphosphate formation (22). The normal fuel for mitochondrial oxidative metabolism is a balance among FFAs (~60–70%), glucose (~30%), lactate, and, to a lesser degree, ketones and amino acids (22). The healthy heart is able to rapidly switch among energy sources based on workload, hormonal milieu, level of tissue perfusion, and substrate availability.

In the fasting state, FFAs are the preferred myocardial fuel for oxidative metabolism (22). In the fed state, glucose and insulin levels are high, FFA levels are low, and glucose oxidation is promoted, whereas fat oxidation is suppressed. During intense exercise, lactate levels increase and become a predominant fuel. Ketone bodies contribute significantly to myocardial energy metabolism only when serum levels are increased (e.g., during starvation because their cellular uptake is concentration dependent). Under hypoxic conditions (ischemia and increased workload), myocardial substrate oxidation switches from fat to carbohydrate oxidation, and glucose becomes the preferred substrate because glycolytic ATP production through conversion of glucose to lactate is independent of oxygen supply. Additionally, glucose is a more oxygen-efficient fuel compared with FFAs because it has a better ATP yield per oxygen atom consumed (P/O ratio) of oxidative phosphorylation (Table 3). This ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain (22). The complete oxidation of one palmitate molecule generates 105 molecules of ATP and consumes 46 atoms of oxygen (P/O ratio 2.33), whereas the complete oxidation of one molecule of glucose generates 31 molecules of ATP and consumes 12 atoms of oxygen (P/O ratio 2.58). FFA as a substrate generates more ATP, but this is at the expense of a greater oxygen requirement than glucose. Thus, at any level of left ventricular (LV) function, an increased reliance on FFAs relative to glucose as a metabolic fuel, as in the setting of insulin resistance and diabetes, results in a decrease in cardiac efficiency and an increased propensity for HF (23).

METABOLIC INFLEXIBILITY IN THE DIABETIC HEART

Metabolic flexibility denotes the ability of muscle (skeletal and cardiac) to switch between FFAs and glucose as the predominant fuel source based on substrate availability (24). In patients with diabetes, this ability is impaired, leading to metabolic inflexibility and the myocardium becoming more dependent on FFA oxidation for fuel. Factors responsible for this inflexibility include increased delivery of FFAs to the heart due to peripheral insulin resistance and the inability of insulin to suppress lipolysis. This leads to increased myocardial FFA oxidation and reduced glucose oxidation initially through the Randle phenomenon and later through activation of peroxisome proliferator–activated receptor α, a nuclear receptor that regulates cellular FFA metabolism (24,25). FFAs also impair insulin action by inhibiting insulin signaling pathways, leading to decreased cellular glucose transport and further reductions in glucose oxidation. In this setting, myocardial glucose uptake may be normalized by the presence of hyperglycemia. However, the increased use of FFAs as fuel at the expense of glucose leads to an increased energy cost, a decrease in cardiac efficiency and an increased propensity for impaired LV function. Increased FFA oxidation and hyperglycemia also cause lipotoxicity and glucotoxicity, which are associated with reactive oxygen species overproduction and a deleterious effect on mitochondrial function and other cellular processes (18,25).

Thus, the diabetic heart paradoxically exhibits starvation in the midst of plenty and relatively inefficient contractility in the setting of abundant substrate (glucose and FFAs). This scenario was demonstrated in a recent study that evaluated myocardial fuel selection and metabolic flexibility in 8 patients with T2DM (HbA_{1c} 8.3%) compared with 10 lean control subjects without diabetes (26) by using positron emission tomography to measure rates of myocardial FFA

Table 3—Fuel energetics of various substrates

Substrate	P/O ratio***	Energy liberated, kcal/mol of 2-carbon units
Glucose	2.58	223.6
Pyruvate	2.50*	185.7*
Palmitate	2.33**	298**
BHOB	2.50*	243.6*

*Although the difference in energy produced by BHOB (per oxygen atom consumed) is comparable to pyruvate, more energy is derived from BHOB vs. pyruvate due to BHOB being more reduced. If pyruvate were burned in a bomb calorimeter, it would liberate 185.7 kcal/mol of 2-carbon units, whereas the combustion of BHOB would liberate 31% more calories (243.6 calories/2-carbon unit). **Combustion of palmitate generates 298 kcal/mol of 2-carbon units, but there is loss of ATP due to uncoupling proteins generating heat instead of ATP. ***P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.

oxidation (16-^{18}F-fluoro-4-thia-palmitate), and myocardial perfusion and total oxidation (^{11}C-acetate) under fasting and hyperinsulinemic-euglycemic clamp conditions. The results showed increased FFA oxidation under baseline and insulin-treated conditions in T2DM along with impaired insulin-induced suppression of FFA oxidation. This was accompanied by reduced myocardial work efficiency possibly due to greater oxygen consumption with FFA metabolism.

In another study, cardiac phosphorus-magnetic resonance spectroscopy was performed at rest and during leg exercise. Phosphocreatine to ATP (PCr/ATP), an indicator of myocardial energy status, was measured. At baseline, PCr/ATP was reduced by 17% in patients with T2DM versus control subjects without diabetes. During exercise, there was a further 12% reduction in PCr/ATP, but no change in control subjects. Myocardial oxygenation (measured by blood oxygen level–dependent [BOLD] signal intensity change) was also decreased in patients with T2DM versus control subjects (27).

KETONES AS AN ALTERNATIVE MYOCARDIAL FUEL SOURCE

In the setting of the failing diabetic heart unable to optimally use traditional fuels, we propose that empagliflozin treatment, through an increase in ketone body formation, shifts fuel metabolism to ketone bodies. Unfortunately, the words ketone bodies are associated with diabetic ketoacidosis and are regarded unfavorably in the clinical setting. In reality, ketone bodies (3-βhydroxybutyrate) (BHOB) (28) have served as an alternative fuel for >2 billion years and have played a critical role in human survival during periods of starvation, providing fat-derived calories to the brain, heart, kidneys, and other vital tissues (29).

Three ketone bodies exist, with acetoacetate being the central one (17,30). BHOB (although properly not a ketone) is interchangeable with acetoacetate through BHOB-dehydrogenase, and its equilibrium is a function of the cellular NADH/NAD$^+$ ratio (17,30). Acetoacetate is also slowly and irreversibly decarboxylated to acetone, which is excreted through the skin, lungs, and urine (17). Ketones are almost exclusively synthesized in the liver when circulating FFA concentrations are high and the production of acetyl-CoA exceeds hepatic cellular energy requirements (30). These ketone bodies diffuse into the circulation for use in extrahepatic tissues, especially the heart and the kidney, which have the greatest capacity for ketone body utilization, and into the brain as a major energy source during prolonged fasting. In the healthy state, BHOB and acetoacetate are <0.1 mmol/L. After an overnight fast of up to 12 h, serum BHOB levels do not exceed 0.4 mmol/L. During prolonged starving, BHOB levels rise to ~5–8 mmol/L and acetoacetate to ~1–2 mmol/L (17). In diabetic ketoacidosis, BHOB may rise to 10–20 mmol/L and acetoacetate to ~2–5 mmol/L.

Elevated Ketone Bodies With SGLT2 Inhibitors and in HF

It is well documented that ketone bodies are elevated in patients treated with SGLT2 inhibitors (31). In a post hoc analysis from an open-label Japanese study in ~1,300 subjects, fasting ketones were >1 mmol/L in 12–20% of patients treated with 100–200 mg canagliflozin daily for 52 weeks (32). Unfortunately, there was no control group in this study. In another study, 4 weeks of empagliflozin 25 mg daily doubled fasting BHOB levels in patients with T2DM (from 0.25 to 0.56 mmol/L) (33). Serum ketones are also elevated in patients with HF, and in a study in 45 patients with chronic HF, blood ketones were almost double (median 0.27 vs. 0.15 mmol/L in patients with and without HF, respectively, $P < 0.05$) (34).

Myocardial Ketone Body Utilization

The myocardium is the highest consumer of ketone bodies per unit mass and oxidizes ketone bodies in proportion to their delivery. Animal studies have shown that ketone body oxidation takes place at the expense of fatty acid oxidation and glucose oxidation (35). However, in the setting of the EMPA-REG OUTCOME study, it is important to know whether the failing myocardium is able to use ketones. This was demonstrated in a study where ketone body concentrations in arterial, coronary sinus, and central venous beds were measured to derive myocardial and skeletal muscle ketone body utilization in 11 patients with advanced HF (LV ejection fraction 0.22 ± 0.02) compared with 10 healthy control subjects (LV ejection fraction 0.57 ± 0.05) undergoing electrophysiology procedures (36). As expected, the mean myocardial arteriovenous oxygen difference was significantly increased in patients with HF versus control subjects (8.3 ± 0.4 vs. 7.0 ± 0.5 mL/dL, respectively; $P = 0.05$). In addition, skeletal muscle ketone body extraction was markedly lower in the patients with HF (0.18 ± 0.06 vs. 0.40 ± 0.04 in control subjects, $P = 0.01$). On the other hand, mean myocardial ketone body extraction ratios were relatively unchanged (0.49 ± 0.05 in patients with HF vs. 0.54 ± 0.06 in control subjects, $P = 0.53$), Thus, despite impairments in skeletal muscle ketone body utilization, myocardial ketone body utilization was preserved in HF (36).

Ketone Bodies and Cardiac Work Efficiency

In T2DM with HF, there is dysregulated fatty acid oxidation and impaired glucose uptake/oxidation, which lead to myocardial dysfunction. In this setting of restricted fuel selection and low energetic reserve, ketone bodies are a super fuel (29), producing ATP more efficiently than glucose or FFAs with a P/O ratio of 2.50 (compared with 2.33 for palmitate and

2.58 for glucose) (28) (Table 3). Although the difference in energy produced (per oxygen atom consumed by BHOB) is comparable to pyruvate (end product of glycolysis), more energy is derived from BHOB versus pyruvate due to BHOB being more reduced. If pyruvate were burned in a bomb calorimeter, it would liberate 185.7 kcal/mol of 2-carbon units, whereas the combustion of BHOB would liberate 31% more calories (243.6 calories per 2-carbon unit) (28) (Table 3). Of note, combustion of palmitate generates 298 kcal/mol of 2-carbon units, but there is loss of ATP due to uncoupling proteins, generating heat instead of ATP. In a perfused working rat heart model, the addition of a physiological ratio of ketone bodies to buffer with 10 mmol/L glucose increased cardiac work efficiency (hydraulic work/energy from oxygen consumed) by 25% (37).

From these data, one can see that in the failing diabetic heart an apparent inherent metabolic advantage exists in using ketone bodies as a fuel (Fig. 1). Furthermore, ketone body levels are elevated in patients with HF and in those on SGLT2 inhibitor treatment. More importantly, the failing myocardium is able to effectively use ketone bodies as an alternative fuel. The relevant question is whether the increase in ketone bodies with empagliflozin treatment is able to favorably influence myocardial fuel metabolism and cardiac work efficiency, leading to the impressive CV outcomes seen in the EMPA-REG OUTCOME study in patients with HF and in those without HF. It should be noted that insulin levels play a major role in fuel flux after SGLT2 blockade. Insulin levels decrease in both the fasting and the fed state after SGLT2 inhibitor treatment (33). Lower insulin levels in both the fasting and the fed states with SGLT2 blockade lead to higher lipolysis, higher FFA levels, higher fat oxidation, and higher BHOB levels. According to our hypothesis, the increased FFA oxidation would take place mainly in skeletal muscle, whereas BHOB oxidation would increase in the heart and kidneys (Fig. 2). To accurately evaluate this possibility, measurements of glucose, insulin, FFA, BHOB, and lactate/pyruvate will need to be evaluated simultaneously with SGLT2 inhibitor treatment to allow for modeling of the collective effect of these changes on the heart or kidneys in a more systematic manner. In addition, changes in myocardial fuel energetics and oxygen consumption will need to be evaluated with SGLT2 inhibitors by using positron emission tomography and magnetic resonance imaging (MRI) isotope tracer studies with ^{11}C-acetate and ^{18}F-fluorodeoxyglucose.

RENAL OUTCOMES IN THE EMPA-REG OUTCOME STUDY

The EMPA-REG OUTCOME study included patients with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2, and most patients had impaired kidney function (52% eGFR 60–90 and 26% eGFR 30–60 mL/min/1.73 m^2). Furthermore, 29% had microalbuminuria, and 11% had macroalbuminuria (5). Compared with placebo, empagliflozin reduced new-onset/worsening nephropathy by 39% (P = 0.0001). More importantly, empagliflozin reduced by 46% the composite outcome of doubling of serum creatinine (accompanied by an eGFR ≤45 mL/min/1.73 m^2), initiation of renal replacement therapy, or death due to renal disease (P = 0.0002) (Table 2). The Kaplan-Meier curves for renal outcomes, like the CV outcomes, began to separate by 3 months and occurred in the setting of 80% of study subjects treated with ACE inhibitors/angiotensin receptor blockers.

It is difficult to fully attribute empagliflozin's renal benefits to its modest diuretic, BP lowering (systolic BP ~3 mmHg), HbA_{1c} reduction (~0.3%), weight reduction (~1 kg), or uric acid reduction effects or even to its small functional GFR reduction and neurohormonal changes, especially because the renal benefits occur within 3 months. Although the sum of these effects may make a difference, it seems likely that we are missing a key mechanism. Renal hypoxia, stemming from a mismatch between renal oxygen delivery and demand, is increasingly being recognized as a unifying pathway in the development of chronic kidney disease (CKD) independent of hyperglycemia and oxidative stress (38). Therefore, we hypothesize that empagliflozin also improves renal fuel energetics and efficiency. More specifically, its renal benefits may be partly due to a shift in fuel metabolism, including increased ketone body utilization. This would provide more energy-efficient oxygen consumption and, thereby, potentially less hypoxic stress on the diabetic kidney.

FUEL METABOLISM IN THE NONDIABETIC KIDNEY

The kidney is highly active metabolically, with ~80% of energy consumption fueling sodium reabsorption through the Na^+/K^+ ATPase pump. To meet energy requirements and sustain the GFR, the kidney has a high blood flow (~25% of the cardiac output). Consequently, renal

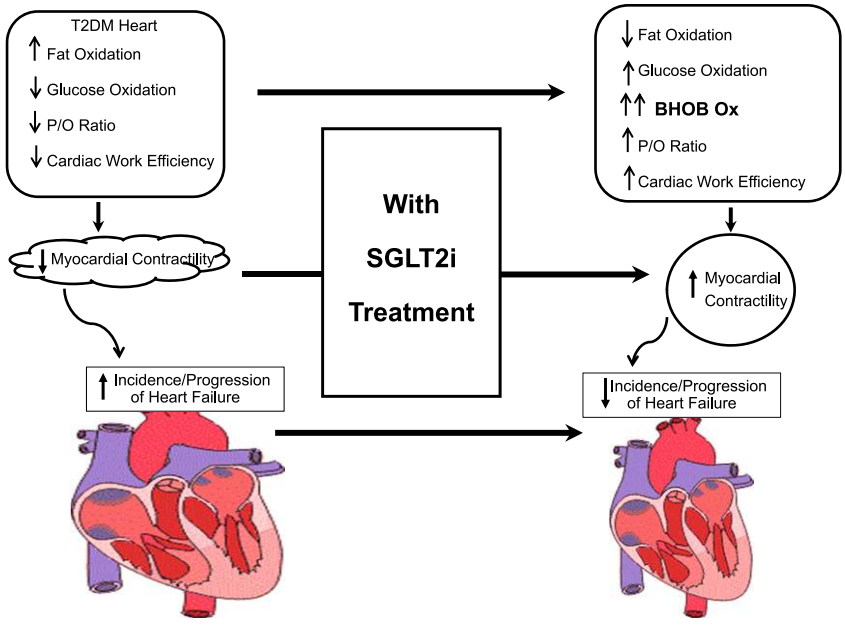

Figure 1—Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.

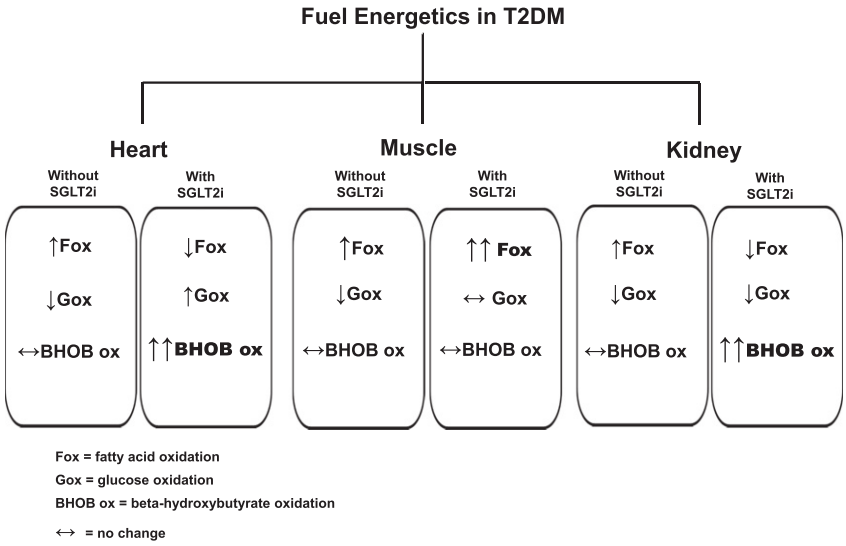

Figure 2—Postulated changes in whole-body and organ fuel energetics in T2DM before and after SGLT2 inhibitor (SGLT2i) therapy.

oxygen consumption (QO2) per gram of tissue is second only to the heart (2.7 vs. 4.3 mmol/kg/min, respectively) (21). Oxidative metabolism is the principal source of energy in the kidney. The renal cortex (including S1/S2 segments) uses many metabolic substrates, including lactate, FFAs, glutamine, citrate, ketone bodies, and, to a very small extent, glucose (Fig. 3). The outer renal medulla containing portions of the proximal straight tubule (S3 segment), the thick ascending limbs, and collecting tubules also has a high rate of QO2 and uses substrates like lactate, glucose, FFAs, and the ketone body BHOB. Substrate utilization and QO2 in this region are sensitive to the tubular sodium load, and metabolism increases with increasing ambient sodium concentrations (39). Of note, BHOB is effectively used in all nephron segments except the S1/S2 segments of the proximal tubule, where the capacity of BHOB to support ATP production is far less than that provided by glutamine or lactate (21).

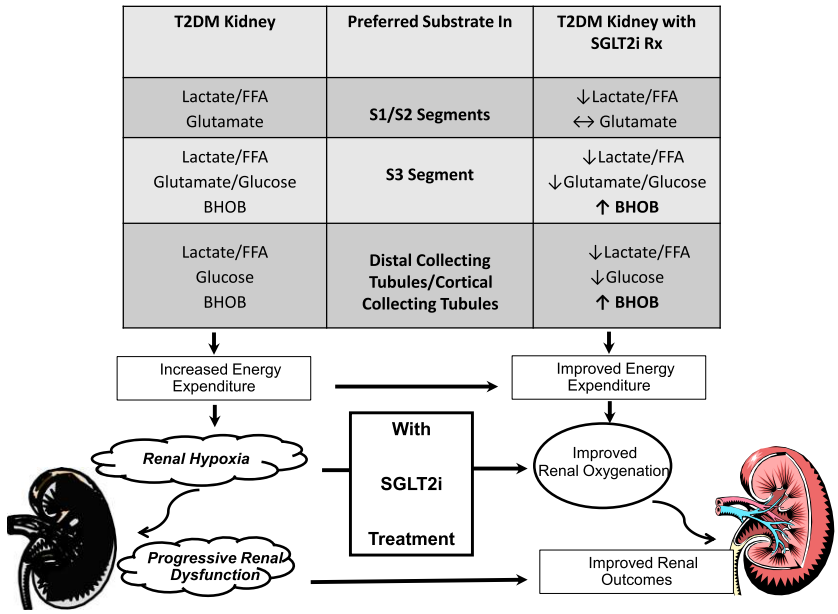

Figure 3—Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. Rx, treatment.

INCREASED OXYGEN CONSUMPTION IN THE DIABETIC KIDNEY

In diabetes, the proximal tubules are exposed to high glucose concentrations. Glucose is mainly reabsorbed through SGLT2 located in the brush border membrane of early proximal tubular cells and to a lesser extent through SGLT1 in the later parts of the proximal tubule, including the S3 segment in the outer medulla (21,40). High luminal glucose concentrations enhance tubular sodium/glucose reabsorption (primarily through SGLT2), leading to increased intracellular Na^+ concentration, increased activation of the Na^+/K^+ ATPase pump (basolateral side), and increased QO2. In a study in rats, induction of experimental diabetes significantly increased renal tubular Na^+/K^+ ATPase activity coupled with significantly higher renal blood flow (RBF), GFR, and Na^+ reabsorption (41). Total renal QO2 as well as QO2 in cortical tissue (mainly proximal tubular cells) were significantly (approximately twofold) higher in diabetic than in control rats. This increase in tissue QO2 was entirely caused by increased Na^+/K^+ ATPase–dependent QO2. Treatment with phlorizin (a nonselective SGLT inhibitor) increased urinary glucose excretion, improved glycemia, and abolished the increase in Na^+/K^+ ATPase activity, Na^+ reabsorption, QO2, RBF, and GFR in diabetic rats. The authors concluded that diabetes is associated with increased renal QO2 secondary to increased Na^+ reabsorption through the proximal tubule SGLT transporters and Na^+/K^+ ATPase activity. They speculated that the diabetic kidney requires higher RBF to meet the increased oxygen demand.

Mathematical modeling indicates that the largest contributor to the increase in renal Na^+ reabsorption and QO2 in diabetes is the augmented GFR, which increases tubular sodium and glucose loads (42). According to the tubular hypothesis, GFR increase in the diabetic kidney is due to primary proximal tubular hyperreabsorption caused by increased SGLT activity and tubular growth (43). Consequently, SGLT2 inhibition can lower QO2 in the diabetic kidney by lowering GFR (and the tubular Na^+ load) and by direct inhibition of SGLT2-mediated Na reabsorption in the early proximal tubule (44). Thus, it is possible that in humans QO2 is significantly increased in patients with diabetes and that treatment with SGLT2 inhibitors decreases renal QO2

and leads to less hypoxic stress on the diabetic kidney. Assuming that CKD is associated with deleterious glomerular hyperfiltration in the remaining intact nephrons and high-glucose delivery to the individual early proximal tubule, SGLT2 inhibition is expected to modestly lower GFR and tubular Na^+ load in patients with diabetes and CKD in accordance with the tubular hypothesis (43) and clinical data (40).

KETONES AS AN ALTERNATIVE ENERGY-EFFICIENT FUEL

The cost of renal sodium transport can be estimated from sodium pump stoichiometry and the amount of oxygen required to produce ATP. The hydrolysis of one ATP molecule is coupled to the transport of three Na^+ ions out of the cell and two K^+ ions into the cell (21). Mole for mole, BHOB is a more efficient fuel than glucose and FFAs, producing more ATP and more Na^+ ion transport per molecule of oxygen consumed. However, the ability of the kidney to use BHOB as a fuel is based on substrate availability. Under normal circulating concentrations, fasting and postmeal BHOB levels and extraction/utilization rates are low (39). In experimental studies in dogs, BHOB infusion significantly increased ketone utilization and could potentially account for >50% of QO2 (45). Serum ketones are known to be elevated during SGLT2 inhibitor treatment (31). In one study in patients with T2DM, 4 weeks of treatment with empagliflozin resulted in a doubling of fasting BHOB levels from 0.25 to 0.56 mmol/L, with a minimal increase in fasting FFAs and a decrease in fasting lactate (33). In animal and in vitro studies, ketone bodies inhibit the oxidation of pyruvate and the uptake and oxidation of oleate, suggesting that ketone bodies are the preferred renal fuel when available in sufficient quantities (46).

However, if Na^+ reabsorption is blocked in the early proximal tubule, compensatory mechanisms come into play to facilitate Na^+ reabsorption in the more distal nephron to avoid Na^+ loss, which is essential to maintain volume status (21). This distal reabsorption involves QO2 and may nullify the potential savings achieved by blocking early proximal reabsorption and perhaps even increase the cost of oxygen consumption per ATP generated, depending on the fuel used. This is also due to Na^+ transport becoming less energy efficient in the more distal nephron segments (39). In one study in patients with T2DM with preserved GFR and clinical evidence of nephropathy, hypoxia of the renal medulla but not the renal cortex was demonstrated with BOLD MRI. In contrast, in those with more advanced renal disease, hypoxia of the renal medulla diminished while progressive cortical hypoxia developed (38). Other studies have shown inconsistent results, perhaps due to heterogeneity in disease duration and glycemic control. However, diabetic kidney disease clearly influences renal oxygenation.

In a rat single nephron modeling study (44), chronic SGLT2 inhibition lowered renal cortical QO2 by ~30% in diabetic conditions primarily due to GFR reduction, which lowered proximal tubule active Na^+ reabsorption. In the medulla, chronic SGLT2 inhibition was predicted to increase QO2 by 26% in the S3 segment (in part by increasing SGLT1-mediated glucose uptake), by 2% in medullary thick ascending limb, and by 9% and 21% in outer and inner medullary collecting ducts, respectively. However, this model did not take into account the potential greater use of BHOB as an efficient fuel source in the S3 segment/outer medulla.

Thus, in the diabetic kidney, SGLT2 inhibitor treatment could well improve fuel efficiency, thereby lowering QO2, relieving hypoxic stress, improving renal function, and preventing progression to CKD (Fig. 3). However, dedicated studies are needed to establish this in animals and humans by using BOLD MRI to measure tissue oxygenation. It is also possible that other effects of SGLT2 inhibition, including reduction of single nephron GFR and glomerular capillary pressure, and beneficial effects on mesangial expansion, tubular growth, and inflammation play a role in the renal benefits of SGLT2 inhibitors (40,47), but the rapid occurrence of renal benefits points to additional changes that may include critical effects on fuel metabolism occurring early and playing a decisive role.

CONCLUSIONS

It has been nearly 100 years since insulin was introduced as the first pharmacologic agent for diabetes treatment and 20 years since the publication of the UKPDS documenting the benefits of intensive glycemic control on microvascular complications in patients with T2DM. We now have more than a dozen classes of agents to treat T2DM, but until now, we have not had any diabetes medication with proven benefits on CV and all-cause mortality. The enigma in the EMPA-REG OUTCOME study is that the CV/renal benefits occur as early as 3 months and that there is no reduction in traditional atherothrombotic CV events. A partial explanation for this enigma may lie in fuel energetics, with empagliflozin shifting myocardial and renal fuel metabolism away from fat/glucose oxidation to a more energy-efficient fuel like ketone bodies, thereby improving myocardial/renal work efficiency and function. Even small beneficial changes in energetics minute to minute can translate into large differences in efficiency over weeks to months. Furthermore, myocardial changes would benefit the kidney and vice versa. In addition to improved fuel metabolism, BP and natriuretic, diuretic, and neurohormonal/vascular effects could play a role but are unlikely to produce beneficial results within 3 months. Detailed physiologic and imaging studies need to be done to delineate mechanisms for CV/renal benefits.

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