Sweet Debate: Fructose versus Glucose in Diabetic Kidney Disease

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The prevalence of diabetes continues to increase worldwide.1 Renal disease shows the strongest correlation with excess mortality in diabetes, yet the mechanisms of diabetic kidney disease (DKD) remain poorly understood. It has been repeatedly demonstrated that hyperglycemia plays a crucial role in DKD initiation, both in patients and in animal models. Cells that are unable to downregulate their glucose transporters in response to hyperglycemia will experience increased intracellular glucose flux.2 Intracellular glucose is eventually metabolized to pyruvate by a series of enzymatic reactions called glycolysis. Intracellular glucose is first rapidly converted via an energy-dependent mechanism into fructose 6-phosphate and then by the phosphofructokinase to fructose 1,6-phosphate. Phosphofructokinase is a rate-limiting enzyme in glycolysis. Fructose 6-phosphate can also be diverted into the hexosamine pathway to become glucosamine, an important mediator of diabetic complications.

Increased fructose consumption has been suggested to play a role in obesity, hypertension, and metabolic syndrome development. There is a correlation between the use of high fructose corn syrup and the increase in obesity rates in the United States.3 Dietary fructose mostly enters the cells via glucose transporter-5 and is metabolized, primarily in the liver, by phosphorylation on the 1-position by the hexokinase also known as fructokinase or ketohexokinase (Khh) enzyme, a process that bypasses the rate-limiting phosphofructokinase step in glycolysis. There are slight differences in glucose versus fructose metabolism because fructose results in trioses that lack phosphate thus need to be phosphorylated for mitochondrial oxidation. Hepatic metabolism of fructose favors lipogenesis because fructose metabolites contribute to triglyceride backbone structure. Furthermore, the ADP formed from ATP after phosphorylation of fructose on the 1-position can be further metabolized to uric acid,4 which utilizes nitric oxide, a key modulator of vascular function. Indeed, an association between fructose intake, uric acid, and triglyceride levels has been observed.3 In addition to dietary fructose, intracellular glucose can be converted into fructose by the aldose reductase enzyme in the polyol pathway.5 Aldose reductase and the polyol pathways play an important role in the development of diabetic complications.

Increased accumulation of intracellular reactive oxygen species is considered the final common mechanism that mediates hyperglycemia-induced intracellular biochemical changes and development of diabetic complications. Increased reactive oxygen species generation can cause increased cell stress and apoptosis and is also shown to turn on the pleiotropic transcription factor NF-κB.6,7 NF-κB is an important regulator of the immune system and its activation has been reported in patient samples and animal models with DKD.8 Increased NF-κB activation is associated with increased expression of proinflammatory cytokines, including monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 and TNF-α.9 TNF-α levels positively correlate with and can predict DKD development in patients with type 1 or type 2 diabetes. In addition, genetic ablation or inhibition of monocyte chemoattractant protein-1 significantly ameliorates DKD development in animal models.10 Although DKD was traditionally grouped under nonimmune-mediated kidney diseases, recent reports suggest that inflammation and cytokines play an important role in DKD development.11

In this issue of JASN, Lanaspa et al.12 add yet another piece to the complex picture of the metabolic basis of DKD. Lanaspa et al. examined the role of endogenous fructose in the pathogenesis of DKD in vivo, by using a fructokinase-deficient mouse model (Khh−/−). The authors demonstrate that endogenous fructose, produced from glucose in diabetes through the activation of the polyol pathway in the proximal tubule, is involved in development of tubulointerstitial inflammation and renal injury. Wild-type diabetic (streptozotocin-induced) mice developed metatarsal diabetes, although Khk−/− knockout mice developed a similar inflammatory response, including a lower expression of inflammatory cytokines and reduced abundance of macrophages in the renal cortex, is responsible for the protective phenotype. The diminished inflammatory response, including decreased NF-κB activation, was also demonstrated in vitro in HK-2 proximal tubule cells, in which KHH expression was silenced.

The pathogenic activation of the proinflammatory system in diabetic proximal tubules was induced through the excessive
activation of the polyol pathway and resulting oxidative stress. The authors found higher expression of aldose reductase, as well as increased levels of fructose and sorbitol in diabetic mice consistent with the activation of the polyol pathway. In addition, uric acid and superoxide levels were increased, whereas ATP levels were lower in diabetic mice. Some of these features were blunted in the Khk$^{-/-}$ knockout animals. Interestingly, although most of these changes took place in proximal tubule cells, glomerular injury was also reduced in diabetic Khk$^{-/-}$ knockout mice.

The importance of these findings and the polyol-fructose pathway in human diabetic nephropathy is still to be determined, because data in humans supporting a causal link between fructose metabolism and DKD are lacking. Whether the kidney indeed uses glucose as its primary energy source is another important issue that is yet to be resolved. Different lines of evidence suggest that fatty acids are a major source of ATP in renal cells. Increased reliance of glucose oxidation is an important characteristic of clear cell renal cancer. Therefore, the significance of polyol pathway induction and fructose metabolism in DKD in humans, especially as a potential therapeutic target, is still elusive. Further studies are needed to examine renal epithelial cell metabolism at baseline and in the diabetic condition.

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REFERENCES


