The Warburg Effect in Diabetic Kidney Disease

Guanshi Zhang, PhD,[*,†] Manjula Darshi, PhD,[*,†] and Kumar Sharma, MD[*,†]

Summary: Diabetic kidney disease (DKD) is the leading cause of morbidity and mortality in diabetic patients. Defining risk factors for DKD using a reductionist approach has proven challenging. Integrative omics-based systems biology tools have shed new insights in our understanding of DKD and have provided several key breakthroughs for identifying novel predictive and diagnostic biomarkers. In this review, we highlight the role of the Warburg effect in DKD and potential regulating factors such as sphingomyelin, fumarate, and pyruvate kinase muscle isozyme M2 in shifting glucose flux from complete oxidation in mitochondria to the glycolytic pathway and its principal branches. With the development of highly sensitive instruments and more advanced automatic bioinformatics tools, we believe that omics analyses and imaging techniques will focus more on singular-cell-level studies, which will allow in-depth understanding of DKD and pave the path for personalized kidney precision medicine.

Semin Nephrol 38:111-120 Published by Elsevier Inc.

Keywords: Diabetic kidney disease, the Warburg effect, aerobic glycolysis, metabolomics, mitochondrion

Diabetic kidney disease (DKD) develops in approximately 40% of patients with diabetes and is the leading cause of chronic kidney disease worldwide.[1] Metabolic alterations associated with diabetes lead to renal pathologic changes including tubulointerstitial inflammation and fibrosis, glomerular hypertrophy, and glomerulosclerosis.[1] However, because only less than 10% of patients with diabetes ultimately reach end-stage renal disease, there must be something missing in our understanding of the pathophysiology of DKD. Genetic studies have not identified a major genetic contribution,[2,3] although it is likely that there are important genetic determinants.[4,5] As part of the International Society of Nephrology Forefronts Symposium of Systems Biology, the application of systems biology tools to understanding DKD was a major topic.

Detailed roles of mitochondria in DKD has been reviewed previously.[5–7] In the presence of hyperglycemia, the metabolic flux of glucose can be shifted from complete oxidation in mitochondria to the glycolytic pathway, and the deleterious effects of hyperglycemia are considered to be owing mainly to increased activity of five different pathways: pentose phosphate pathway,[8] sorbitol/polyol pathway,[9] advanced glycation end-products pathway,[10,11] protein kinase C pathway,[12] and hexosamine pathway (Fig. 1).[13,14] Activation of the earlier-mentioned pathways was reported to be associated with diabetic complications, either by causing oxidative stress, inflammation, fibrosis, DNA damage, and vascular changes, or by resulting in pathologic gene expression.[5] Overproduction of superoxide in mitochondria might play a unifying role for the activation of the aforementioned metabolic pathways.[15] New evidence indicates that alternative pathways such as enhanced fatty acid oxidation in mitochondria are involved in diabetic complications.[15,16] However, it still is unclear whether mitochondrial dysfunction in DKD results in altered glycolysis flux, or if glycolysis flux/accumulation of glycolytic intermediates in DKD drives the metabolic flux into the five pathways discussed earlier, leading to impaired mitochondrial function, or if a bidirectional causality exists. The current review highlights the diabetes-induced metabolic switch from oxidative phosphorylation to glycolysis and the potential link to downstream effects on kidney function and disease progression.

WARBURG EFFECT/AEROBIC GLYCOLYSIS AND ITS POTENTIAL ROLE IN THE DEVELOPMENT OF DKD

The Warburg effect or aerobic glycolysis, first observed in 1924 by Otto Warburg, has had a profound influence on cancer metabolism.[17] Warburg proposed that, independent of cellular oxygen, tumor cells synthesize adenosine triphosphate (ATP) through

[*]*Center for Renal Precision Medicine, Division of Nephrology, Department of Medicine, University of Texas Health, San Antonio, TX.*

[†]*Audie L. Murphy Memorial VA Hospital, South Texas Veterans Health Care System, San Antonio, TX.*

Financial support: Supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (5R24DK082841-08 and 1UG3DK114920-01) and the Juvenile Diabetes Research Foundation to KS.

Conflict of interest statement: none.

Address reprint requests to Kumar Sharma, MD, Division of Nephrology, Department of Medicine, University of Texas Health San Antonio, 7703 Floyd Curl Dr, MC 7882, San Antonio, TX 78229. E-mail: sharmak3@uthscsa.edu (K. Sharma),

0270-9295/ - see front matter

Published by Elsevier Inc.

https://doi.org/10.1016/j.semnephrol.2018.01.002

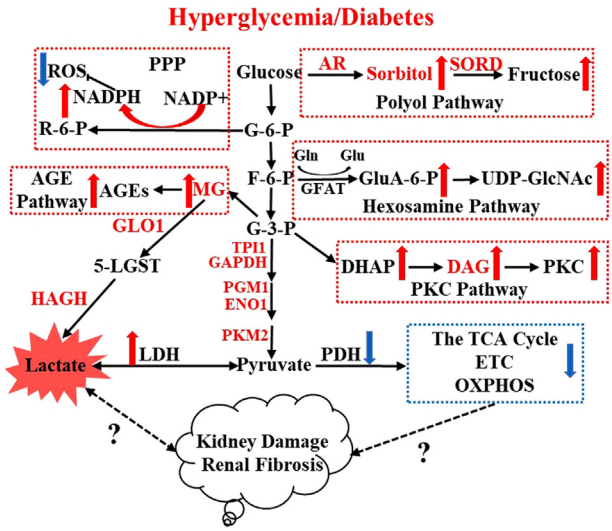

Figure 1. Hyperglycemia enriches metabolic flux to glycolysis and five principal branches including the polyol pathway, pentose phosphate pathway (PPP), hexosamine pathway, protein kinase C (PKC) pathway, and advanced glycation end-products (AGE) pathway. Accumulation of four toxic glucose metabolites such as lactate, sorbitol, diacylglycerol (DAG), and methylglyoxal (MG) might contribute to the development of diabetic kidney disease. Abbreviations: 5-LGST, 5-lactoylglutathione; AR, aldose reductase; DHAP, dihydroxyacetone phosphate; ENO1, alpha-enolase; ETC, electron transport chain; F-6-P, fructose 6-phosphate; G-6-P, glucose 6-phosphate; G-3-P, glyceraldehyde 3-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAT, glutamine:fructose-6-phosphate amidotransferase; Gln, glutamine; Glu, glutamate; GluA-6-P, glucosamine-6-phosphate; GLO1, glyoxalase 1; HAGH, hydroxyacyl glutathione hydrolase; LDH, lactate dehydrogenase; OXPHOS, oxidative phosphorylation; PGM1, phosphoglucomutase-1; R-6-P, ribulose-5-phosphate; SORD, sorbitol dehydrogenase; TPI1, triosephosphate isomerase 1; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine.

glycolysis and a metabolic state involving enhanced glucose uptake leads to local acidification through enhanced lactate production. Although Warburg's[18] studies suggested that mitochondrial dysfunction is the root of aerobic glycolysis, subsequent studies and technical advances have since shown that mitochondria in cancer are indeed functional and that genetic or environmental cues may contribute to this metabolic shift to the glycolysis in tumor cells.[19] Although enhanced glucose entry and glycolysis has been observed in diabetic tissues, the Warburg effect has not been proposed as a major feature in diabetic complications.

Recent omic studies in diabetes and diabetes kidney disease have provided unbiased evidence that both mitochondrial dysfunction and the Warburg effect play pivotal roles in the development of DKD.[16,20,21] Several groups now have found that reduced mitochondrial function plays a key role in DKD both in mouse models and in patients with DKD.[20,22,23] By using transcriptomic, metabolomics, and flux approaches, Sas et al[16] reported significantly increased glycolytic intermediates and enzymes in kidney cortex, along with a significant reduction in mitochondrial function in a type 2 diabetic mouse model. Interestingly, in a very recent study, Qi et al[21] reported that enhanced pyruvate kinase II (PKM2) activity may preserve mitochondrial function by increasing glucose flux through glycolysis in podocytes and alleviate the progression of DKD in patients with diabetes.

To understand how the Warburg effect may play a role in DKD, here we review the major metabolic pathways and associated enzymes and intermediates that are involved in DKD pathometabolism. Compared with mitochondrial respiration, aerobic glycolysis is an inefficient pathway of generating ATP per unit of glucose.[24] Although complete oxidation of one molecule of glucose via pyruvate within the tricarboxylic acid (TCA) cycle in the presence of oxygen generates 38 molecules of ATP, the glycolysis, the first step of glucose oxidation process that occurs in cytosol, generates only two molecules of ATP, leading to pyruvate as a final product. However, the rate of glucose metabolism through aerobic glycolysis is much higher (10-100 times faster) than the complete oxidation of glucose through the TCA cycle and oxidative phosphorylation in the mitochondria. Therefore, in diabetic patients, activation of aerobic glycolysis might help metabolize glucose rapidly from systemic circulation. In addition, with the evidence of mitochondrial dysfunction including low peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) levels, abnormalities in electron transport chain complex assembly/activity, alterations in pyruvate dehydrogenase complex (PDH) phosphorylation, and altered TCA cycle intermediates in DKD,[20,25] it is not surprising that the glucose oxidation through glycolysis is a more favorable process toward ATP synthesis.

METABOLOMICS IDENTIFY MITOCHONDRIAL DYSFUNCTION AND WARBURG MECHANISMS IN DKD

Recent omics studies in diabetes and DKD have provided unbiased evidence that both mitochondrial dysfunction and the Warburg effect play pivotal roles in the development of DKD.[16,20,21] By using targeted metabolomics and systems biology tools we reported that human DKD is associated with mitochondrial dysfunction. Gas chromatography-mass spectrometry–based targeted metabolomics were performed and 94 urinary metabolites were quantified in patients with established DKD and compared with healthy controls.[20] Results indicated a marked reduction in organic anions, the TCA cycle, and amino acid metabolites. We established a 13–urinary metabolite biomarker signature of DKD, all of which were decreased significantly. Correlation analysis between each of 13