Mitochondrial Dysfunction and Signaling in Diabetic Kidney Disease: Oxidative Stress and Beyond

Nicole Bernadette Flemming, BBiomedSc, Hons,[*,†] Linda Alba Gallo, PhD,[*,†] and Josephine Maree Forbes, PhD[*,‡]

Summary: The kidneys are highly metabolic organs that produce vast quantities of adenosine triphosphate via oxidative phosphorylation and, as such, contain many mitochondria. Although mitochondrial reactive oxygen species are involved in many physiological processes in the kidneys, there is a plethora of evidence to suggest that excessive production may be a pathologic mediator of many chronic kidney diseases, including diabetic kidney disease. Despite this, results from clinical testing of antioxidant therapies have been generally underwhelming. However, given the many roles of mitochondria in cellular functioning, pathways other than reactive oxygen species production may prevail as pathologic mediators in diabetic kidney disease. Accordingly, in this review, mitochondrial dysfunction in a broader context is discussed, specifically focusing on mitochondrial respiration and oxygen consumption, intrarenal hypoxia, oxidative stress, mitochondrial uncoupling, and networking.
Semin Nephrol 38:101-110
Keywords: Mitochondrial dysfunction, diabetic kidney disease, oxidative stress, hypoxia, uncoupling

Diabetes mellitus, characterized by hyperglycemia, is a global pandemic. The World Health Organization reported that approximately 8.5% of the world's adult population had clinically diagnosed diabetes in 2014[1] and this incidence is projected to almost double by the year 2035. A large proportion of individuals with diabetes develop chronic vascular complications that are major contributors to their overall morbidity and mortality.

Diabetic kidney disease (DKD) is a microvascular complication that affects 25% to 40% of individuals with diabetes. A range of structural and functional abnormalities within the kidney characterize DKD, including albuminuria, glomerular scarring, tubulointerstitial fibrosis, and a progressive decrease in kidney function. The majority of individuals with DKD will progress to end-stage renal disease (requiring dialysis or transplant) or die prematurely from a cardiovascular event.[2] Strict glycemic control and inhibition of the renin angiotensin system are prescribed for DKD, but these only slow disease progression.

It increasingly is appreciated that mitochondrial dysfunction contributes to the development and progression of DKD (Fig. 1). There are two key theories that describe the pathologic role of mitochondrial dysfunction within the kidney: an increase in mitochondrial oxygen consumption and superoxide production resulting in oxidative damage, and a general impairment of mitochondrial function leading to reduced mitochondrial efficiency (ie, ultimately culminating in decreased adenosine triphosphate [ATP] production).

ENERGY REQUIREMENT AND PRODUCTION IN THE KIDNEY

The kidneys require vast quantities of energy (ATP) to facilitate the active reabsorption of sodium and other metabolites from the urinary filtrate, regulate glomerular filtration rate (GFR), as well as for protein synthesis and degradation (Fig. 1). Proximal tubule cells also consume ATP for the synthesis and conversion of metabolic substrates (ie, gluconeogenesis) using lactate, glutamine, and glycerol as precursors.[3] The kidneys, in particular the proximal tubule, require large amounts of oxygen for metabolism and contain the second highest density of mitochondria in the body (by organ weight).[4] The renal proximal tubule accounts for the greatest proportion of oxygen consumption within the kidney as a result of its extensive ATP-dependent processes.

[*]*Glycation and Diabetes Group, Mater Research Institute, The University of Queensland, Translational Research Institute, Woolloongabba, Queensland, Australia.*
[†]*School of Biomedical Sciences, The University of Queensland, St Lucia, Queensland, Australia.*
[‡]*Department of Medicine, The University of Melbourne, Melbourne, Victoria, Heidelberg, Australia.*

Financial support: Supported by Australian Postgraduate Scholarships (N.B.F.), by an Early Career Fellowship from the National Health and Medical Research Council and Heart Foundation Australia (1089763 and 100519 to L.A.G.), and by a Senior Fellowship from the NH&MRC (1102935 to J.M.F.).

Conflict of interest statement: none.

Address reprint requests to Josephine Maree Forbes, PhD, Mater Research Institute, The University of Queensland, Translational Research Institute, Level 4, 34 Kent St, Woolloongabba, Queensland 4520, Australia. E-mail: josephine.forbes@mater.uq.edu.au (J.M. Forbes),

0270-9295/ - see front matter

https://doi.org/10.1016/j.semnephrol.2018.01.001

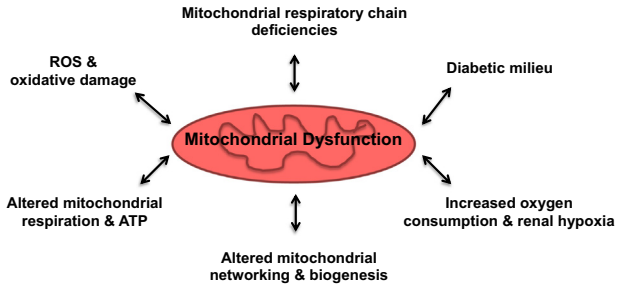

Figure 1. A roadmap to mitochondrial dysfunction beyond oxidative stress. Changes to mitochondrial function are evident in diabetes. Excess production of mitochondrial ROS, including superoxide, has been implicated in the pathogenesis of disease, however, the clinical testing of antioxidant therapies has been mostly disappointing. Given the intimate relationship between mitochondrial and kidney function, it is likely that other mitochondrial pathways will prevail as pathologic mediators in DKD.

Mitochondria are the organelles that efficiently produce a majority of cellular ATP. Glucose, free fatty acids, and amino acids such as glutamate are transported to mitochondria and fed into the tricarboxylic acid cycle and converted to reduced electron carriers, Nicotinamide adenine dinucleotide (reduced; NADH) and Flavin adenine dinucleotide, through a series of orchestrated biochemical reactions. These electron carriers/acceptors enter the mitochondrial respiratory chain (complexes I-V) and electrons are delivered to the terminal electron acceptor, oxygen; a process collectively termed *oxidative phosphorylation*. Electrons from the respiratory chain provide the energy to pump protons from the mitochondrial matrix to the intermembrane space (via the inner mitochondrial membrane). This generates an electrochemical gradient that subsequently drives the generation of ATP at complex V (ATP synthase) of the respiratory chain. Given the fuel and oxygen requirements of the kidneys, it is not surprising that an imbalance between supply and demand, such as that seen in diabetes, could culminate in DKD.

Glycolysis metabolizes glucose to pyruvate, of which approximately 90% is transported into the mitochondria.[5] Hyperglycemia-induced flux through glycolytic pathways has been postulated to contribute to mitochondrial dysfunction in diabetes,[6] likely via increased ATP and reactive oxygen species (ROS) generation. However, with a long duration of diabetes, increased expression and activity of pyruvate kinase has been identified in individuals without kidney disease as compared to those with kidney disease,[7] suggesting that increased metabolic flux through the glycolytic pathway may in fact protect against heightened intracellular glucose accumulation.[7] After exposure to high glucose levels, mouse and human podocytes showed decreased pyruvate kinase activity, whereas mesangial and endothelial cells remained unaffected.[7] Finally, Pkm2 activation protected against mitochondrial dysfunction in cultured podocytes (via increased glycolytic flux and peroxisome proliferator-activated receptor γ coactivator 1-α [PGC-1α]), as well as mitochondrial and renal impairment in diabetic mice.[7]

HYPOXIA IN DIABETIC KIDNEY DISEASE

Intrarenal hypoxia has been identified as a key pathway to kidney damage (proteinuria) in diabetes.[8] Cortical hypoxia in particular is considered a common pathway to end-stage renal disease, regardless of etiology.[9] The renal proximal tubules, which constitute approximately 90% of the renal cortex, preferentially use free fatty acids, glutamine, and lactate as primary energy sources used to generate ATP within mitochondria. Hyperglycemia, hyperlipidemia, and changes to circulating amino acids, as seen in diabetes, therefore are thought to alter mitochondrial respiration in this highly metabolic segment of the nephron tubule.[10] Although it is postulated that glomerular injury in diabetes reduces renal blood flow and renal oxygen delivery exacerbating tubulointerstitial fibrosis,[11] metabolic changes (ie, changes in renal oxygen consumption) are thought to precede structural fibrotic changes in experimental diabetes[12] and therefore may mediate renal impairment. A number of studies have proposed that the diabetic kidney[12–14] and cultured renal cells exposed to diabetic-like environments[15–17] undergo an early phase of enhanced oxygen consumption. This phenomenon, which contributes to intrarenal hypoxia, has been attributed to oxidative stress, mitochondrial uncoupling, and solute transport inefficiency, each of which are discussed in detail later.

Hypoxia-inducible factor-1α (HIF-1α) regulates the cellular response to hypoxia. Significant renal impairment and mitochondrial dysfunction is evidenced in a subtotal nephrectomy model of chronic kidney disease.[18] Activation of HIF-1α improved mitochondrial function (correcting increased oxygen consumption and superoxide production, and increasing mitochondrial volume density), renal blood flow, GFR, and sodium reabsorption.[18] In diabetic rats, renal hypoxia, hyperfiltration, increased renal oxygen consumption, and reduced sodium transport efficiency was ameliorated via activation of HIF-1α[19] (Fig. 2).

Oxidative Stress

In addition to directly damaging renal cells via oxidation pathways (discussed later), increased oxygen consumption and superoxide production are thought to drive renal hypoxia (Fig. 3). Superoxide reacts directly with nitric oxide (NO) to form peroxynitrite radicals, limiting NO bioavailability, and may modify the function of mitochondrial proteins such as the