Mitochondria-Targeted Drugs for Diabetic Kidney Disease

Vincent King*

Editorial Office, Journal of Kidney, Brussels, Belgium

Corresponding Author*

Vincent King

Editorial Office, Journal of Kidney, Brussels, Belgium

E-mail: info@longdom.org

Received: 05-January-2022, Manuscript No. jok-22-15906 (M); **Editor assigned:** 07-January-2022, PreQC No. jok-21-15906 (P); **Reviewed:** 16-January-2022, QC No. jok-22-15906 (Q); **Revised:** 18- January-2022, Manuscript No. jok-22-15906 (R); **Published:** 26-January-2022, DOI: 10.35248/2472-1220.22.8.1.05-07

Abstract

In the United States, Diabetic Kidney Disease (DKD) is one of the most common causes of Chronic Kidney Disease (CKD). DKD is assumed to be caused mostly by chronic hyperglycemic conditions. Clinically, however, achieving glycemic control in people with diabetes is difficult. Recent breakthroughs in mitochondrial biology have given us a new perspective on mitochondrial malfunction in DKD. A range of diabetes problems, including DKD, have been linked to reduced mitochondrial activity; moreover, aberrant mitochondrial fission may play a role in DKD development. Metformin or Sodium-Glucose coTransporter 2 (SGLT2) inhibitors have been shown to protect the kidneys by enhancing mitochondrial dynamics and lowering oxidative stress. As a result, medicines that target mitochondrial function restoration may become innovative treatment agents for DKD. Imeglimin is the first of a new family of oral anti-diabetic medications that can lower reactive oxygen species and boost mitochondrial DNA synthesis. The possible treatment strategies that impact mitochondrial activity and prevent DKD are discussed in this review.

Keywords: Diabetic Kidney Disease (DKD) • Imeglimin • Metformin • Mitochondrial function • Reactive oxygen species (ROS) • Sodium-glucose co-transporter 2 (SGLT2)

Introduction

Chronic Kidney Disease (CKD) is most commonly caused by diabetes, and chronic hyperglycemia is a significant cause of Diabetic Renal Disease (DKD). Several studies have found a link between blood glucose management and the development of problems in diabetic individuals . Patients who underwent intense blood glucose control had a lower incidence of cardiovascular disease with atherosclerosis, according to long-term follow-up data from the Diabetic Control and Complications Trial (DCCT) [1]. Multiple variables, including as insulin resistance and fatty acid and cholesterol levels, have also been linked to an increased risk of DKD. Despite this data, traditional diabetes treatments that aim to keep blood glucose levels stable do not usually prevent DKD from progressing. As a result, new medications that can assist achieve glycemic control and ameliorate DKD are needed. Long-term hyperglycemia is hypothesized to block the catabolic pathway and increase the formation of Reactive Oxygen Species (ROS) by mitochondria, which may contribute to the development of DKD [2]. Mitochondrial homeostasis is influenced by a number of factors, including mitochondrial dynamics such as fission and fusion. In DKD patients, mitophagy suppression is said to affect mitochondria in the proximal tubules. As a result, DKD treatment may aid in mitochondrial function restoration. Metformin has been shown to diminish the generation of Reactive Oxygen Species (ROS) at mitochondrial respiratory-chain complex 1 and inhibit mitochondrial-mediated apoptosis, suggesting that it may protect renal cells against oxidative stress-induced death. Empagliflozin, a Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor, also modulates mitochondrial biogenesis and the balance of proteins involved in mitochondrial fission and fusion, lowering ROS in cultured proximal tubular cells [3].

Imeglimin is a new oral hypoglycemic drug that is being investigated in clinical trials as a monotherapy or as an add-on treatment to lower fasting blood glucose levels or haemoglobin A1c levels [4]. Imeglimin treatment increased glucose tolerance in people and animals through a number of mechanisms, including reduced hepatic lipids, enhanced insulin signaling in the liver and muscle, and improved -cell function. Imeglimin reduces endothelium mortality by reducing the size of the mitochondrial permeability transition pore, which plays a key role in cell death, without impeding mitochondrial respiration, according to new research. These findings imply that this class of oral anti-diabetic medications has a Reno protective impact in the kidneys through enhancing mitochondrial activity. We go through the possible advantages of imeglimin, as well as other medicines, in treating DKD in this review [5].

Several prior investigations have found that both type 1 and type 2 diabetes produce oxidants. When the rate of oxidant generation surpasses the rate of scavengers, oxidative stress ensues. Changes in the ratio of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) to Nicotinamide Adenine Dinucleotide (NADP) can also cause it [6]. Previously, abnormal glucose and Free Fatty Acid (FFA) metabolism in the mitochondrial pathway, as well as Protein Kinase C (PKC)-mediated activation of NADPH oxidase, were identified as components leading to oxidant generation. In earlier research, we found that under diabetes or insulin-resistant circumstances, Reactive Oxygen Species (ROS) levels were raised in the kidney and retina. Both diabetic rats and patients had considerably higher levels of plasma 8-hydroxydeoxyguanosine, isoprostanes, and lipid peroxides. As a result, improper glucose and FFA metabolism is linked to increased ROS generation in diabetes mellitus. This process might explain why insulin-resistant people without diabetes have higher levels of oxidative stress.

Diabetes and insulin resistance have been linked to oxidative stress in several studies. The NADPH/$NADP^+$ ratio is reduced when free glucose triggers aldose reductase activity and the polyol pathway. PKC is activated by increased intracellular glucose via de novo Diacylglucose production. DKD has been linked to the DAG-PKC signal transduction pathway, with increased PKC activity known to cause ECM deposition in the glomeruli. Increased oxidative stress might play a role in the progression of DKD. Aldose reductase inhibitors may lessen the effect of hyperglycemia on DKD by inhibiting the polyol pathway. Furthermore, supplementing with vitamins C and E may help to improve DKD symptoms. Vitamin E at high dosages can reduce ROS and improve vascular anomalies induced by the DAG-PKC pathway activation in the kidneys.

Increased ROS and hyperglycemia change mitochondrial energy in diabetic nephropathy. Insulin resistance is linked to the formation of Reactive Oxygen Species (ROS). The mechanism by which a mitochondrion creates more ROS in diabetic patients, however, remains unknown. Hyperglycemia and dyslipidemia increase the synthesis of Nicotinamide Adenine Dinucleotide (NADH) and Dihydroflavine-Adenine Dinucleotide (FADH2), both of which are needed to create ATP in the mitochondrial Electron Transport Chain (ETC). In the progression of DKD, decreases in podocyte number are seen, which contribute to the collapse of the glomerular filtration barrier and are linked to ROS. Diabetes-related alterations in the ETC have been linked to an increase in apoptosis. Inhibition of Insulin Receptor Substrate-1 (IRS1) signalling causes DKD, according to research. Mitochondria are one of the many sources of Reactive Oxygen Species (ROS) that can trigger serine phosphorylation of IRS, resulting in IRS1 signalling impairment. Increased fission, fusion, mitophagy, and lower levels of peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1) are all seen in the early stages of diabetes, which is consistent with our findings. PGC-1 expression was shown to be lower in diabetic rat kidneys, according to research. Furthermore, overexpression of PGC-1 in cultured mesangial cells inhibited hyperglycemia-induced pathophysiological alterations. When cultivated podocytes were exposed with high glucose media, both mRNA and protein levels of PGC-1 were lowered, indicating impaired mitochondrial biogene. Hyperglycemia promotes Advanced Glycation End products (AGEs), which can activate the TGF-/Smad1 pathway, resulting in an increase in the extracellular matrix in mesangial cells. PKC and hexosamine pathways are also activated by AGEs, leading to mitochondrial dysfunction [7].

MELAS stands for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like events, which are all clinical disorders caused by mitochondrial dysfunction. In the transfer RNA (tRNA) leucine (UUR) gene of mitochondrial DNA, most MELAS patients have a heteroplasmic A to G transition at nucleotide 3243 (3243A> G). MELAS syndrome is linked to chronic kidney disease, and renal involvement has been identified in clinical symptoms and molecular genetic research. As a result, mitochondrial dysfunction is assumed to be a cause of CKD, and aberrant mitochondria are seen in podocytes in MELAS patients with renal impairment.

Conclusion

The best way to avoid DKD is to maintain good glycemic control. However, even if diabetes is treated, DKD can still occur. Diabetes-induced mitochondrial dysfunction is widely recognized to involve aberrant mitophagy, fission, fusion, and biosynthesis. Furthermore, if mitochondrial dysfunction is not corrected, renal function may continue to deteriorate, accelerating the progression of DKD. The ability of the mitochondria to produce ATP is critical for the recovery of renal cells and renal function. As a result, a DKD therapy that focuses on oxidative stress suppression or improving mitochondrial homeostasis appears promising.

References

1. Makris, K., & Spanou, L. "Acute kidney injury: Definition, pathophysiology and clinical phenotypes." *Clin Biochem Rev* 37.2 (2016): 85-98.
2. Khwaja, A. "KDIGO clinical practice guidelines for acute kidney injury." *Nephron Clin Pract* 120.4 (2012): 179-184.
3. Bagshaw, S.M., et al. "A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients." *Nephrol Dial Transplant* 23.5 (2008): 1569-1574.
4. Edelstein, C.L. "Biomarkers in acute kidney injury." *Adv Chronic Kidney Dis* 15 (2008): 241-315.
5. Ronco, C., et al. "Acute kidney injury." *Lancet* 394 (2019): 1949-1964.
6. Benfey, P.N. "Molecular biology: microRNA is here to stay." *Nature* 425 (2003): 244-245.
7. Chung A.C. & Lan H.Y. "MicroRNAs in renal fibrosis." *Front Physiol* 6 (2015): 50.

Cite this article: King V. Mitochondria-Targeted Drugs for Diabetic Kidney Disease. J Kidney. 2022, 8 (1), 001-002.