Anti-Oxidative Therapy in Diabetic Nephropathy

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Abstract

Chronic kidney disease is generally progressive and currently has no reliable treatment to reverse a decline in kidney function or to slow the progression of the disease. Diabetic nephropathy is one of the leading causes of end-stage kidney failure. Kidney damage in diabetic nephropathy is largely attributed to the increased oxidative stress, affecting its metabolic activity, metabolic pathways, and hemodynamic pathways. In diabetic patients, hyperglycemia causes an increase in the production of reactive oxygen species that further increase oxidative stress. These reactive oxygen species are created through a variety of pathways, providing the opportunity for treatment using anti-oxidative defense mechanisms to prevent vascular injury. This review will give an overview of oxidative stress, along with the current treatments and limitations of diabetic nephropathy. We will also discuss the potential of antioxidative therapies, with an emphasis on the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway.

Keywords: review; diabetic nephropathy; antioxidative therapies; oxidative stress; diabetes; hyperglycemia; hypertension

1. Introduction

Diabetic nephropathy (DN) is one of the serious complications of diabetes occurring in 20% to 40% of diabetic patients and is one of the most common causes of end-stage renal disease (ESRD) [1]. Currently, there is no curative therapy for DN. Dialysis and kidney transplantation are typically required for advanced chronic kidney disease (CKD) or ESRD.

Evidence suggests that the progression of DN is a result of metabolic and hemodynamic interactions and dysregulation [2]. As such, DN treatment plans typically include glycemic and hypertensive care to help reestablish metabolic and hemodynamic control to delay renal injury. However, there is no single hypertensive therapy that is a “one size fits all” for every patient, and aggressively pursuing a lower blood pressure in patients with pre-existing cardiovascular diseases is often contraindicated [3]. Additionally, tight control of blood pressure may contribute to the slower progression of DN to ESRD but cannot completely halt it.

Given the lack of definitive treatment for DN, there is a need for new therapeutic agents and targets that can either reduce the risk, further slow, or outright prevent the progression of DN to full-blown ESRD. One such approach aims to mitigate the deleterious effects of DN-associated oxidative stress on the kidney by increasing renal cell antioxidant capacity.

Oxidative stress has been shown to play a central role in the pathogenesis of DN [4]. The metabolic and hemodynamic dysregulation that are characteristic of diabetes result in the accumulation of intracellular reactive oxygen species (ROS) leading to impaired cellular function and chronic disease [4–6]. Thus, a therapeutic approach aimed at increasing the antioxidative capacity of renal cells under diabetogenic conditions is a promising approach in the treatment of DN. Nuclear factor erythroid 2–related factor 2 (Nrf2), the central regulator of the cellular response to oxidative stress, is a promising target for therapies aimed at increasing renal cell antioxidant capacity in patients with DN [7].

In this review, we discuss the role of oxidative stress in the pathogenesis of DN, the Nrf2 pathway, and pre-clinical antioxidative therapies that have been shown to slow the progression of diabetic kidney disease [4,8,9].

2. Diabetic Nephropathy and Oxidative Stress

2.1 Renal Impairment

DN is the main cause of ESRD and it is identified based on renal histological and functional alterations [10]. Diabetic insults induce microvascular injuries within the glomeruli and tubulointerstitial compartment [11]. In the glomeruli, thickening of basement membranes, mesangial expansion, hypertrophy, and loss of podocytes, specialized epithelial cells, occurs alongside the expansion of the tubular basement membranes, tubular atrophy, interstitial fibrosis, and arteriosclerosis [11].

Hyperglycemia and hypertension are two major insults that result in the decline of renal function, and both occur through different cellular pathways [12,13]. Hyperglycemia causes renal impairment through inducing renal
Table 1. List of reactive oxygen species accompanied by their formula.

<table>
<thead>
<tr>
<th>ROS</th>
<th>Formula</th>
</tr>
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<tbody>
<tr>
<td>superoxide anion</td>
<td>O2−</td>
</tr>
<tr>
<td>hydrogen peroxide</td>
<td>H2O2</td>
</tr>
<tr>
<td>hydroxyl radical</td>
<td>•OH</td>
</tr>
<tr>
<td>singlet oxygen</td>
<td>O=O</td>
</tr>
<tr>
<td>peroxyl radical</td>
<td>ROO•</td>
</tr>
<tr>
<td>alkoxyl radical</td>
<td>R–O•</td>
</tr>
<tr>
<td>lipid hydroperoxide</td>
<td>LOOHs</td>
</tr>
<tr>
<td>peroxynitrite</td>
<td>ONOO−</td>
</tr>
<tr>
<td>hypochlorous acid</td>
<td>HOCl</td>
</tr>
<tr>
<td>nitric oxide</td>
<td>NO</td>
</tr>
</tbody>
</table>

R indicates any carbon groups, L indicates any lipids, and NO is grouped as a reactive nitrogen species that is relevant to diabetic nephropathy.

In hyperglycemic conditions, the overproduction of ROS can be induced through different mechanisms based on cytosolic and mitochondrial sources [11]. Mitochondrial sources of ROS are oxidative phosphorylation, uncoupling of the respiratory chain, and dysregulation of complex I, coenzyme Q, and complex III [11,27–30]. The metabolism of glucose produces energy for the mitochondrial respiratory chain via oxidative phosphorylation by converting it to pyruvate in order to be reduced into NADH and FADH2. NADH is responsible for donating electrons to the respiratory chain and in hyperglycemic conditions, the NADH/NAD+ ratio is increased in stressed porcine endothelial cells [31]. It is important to note that free fatty acids can produce NADH and FADH2 via the tricarboxylic acid cycle, thus excess free fatty acids can mimic hyperglycemic damage to the mitochondria [11]. In vivo studies have shown that ROS production has been prevented by inhibiting the electron transport chain complex II via uncoupling oxidative phosphorylation, protein-1, and manganese superoxide dismutase [32]. It was shown that controlling mitochondrial ROS production the formation of advanced glycation end-products (AGE) was also inhibited [32]. AGEs are capable of inducing apoptosis and over-expressing vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein-1 (MCP-1) [33]. VEGF and MCP-1 are linked to early phases of DN [33]. AGEs have been shown to increase ROS production and inhibit anti-oxidative protection mechanisms but there is also evidence that ROS can cause the production of some AGEs [34].

Cytosolic sources can be attributed to non-enzymatic pathways such as advanced glycation and glucose auto-oxidation or through enzymatic pathways such as xanthine oxidase, NADPH oxidase, sorbitol flux, uncoupled nitric oxide synthase (NOS), and glycolysis [11]. The NADPH oxidase pathway, which is found in mesangial cells, proximal tubular epithelia, vascular smooth muscle cells, endothelial and interstitial fibroblasts, is a major contributor to the progression of DN [27,35–40]. Subunits of NADPH oxidase were shown to be elevated in models of diabetic kidney disease and renal injury due to ROS in experimental models [41–44]. Another cytosolic origin for ROS is the uncoupling of NOS. Through different isoforms and cofactors of NOS, this uncoupling produces nitric oxide (NO) radicals [11]. It is speculated that NO plays a role in the early stages of DN through inducing hemodynamic changes [44–47]. Excess production of ROS due to hyperglycemic conditions and activated anti-nuclear factor-κB (NF-κB) is linked to increased inflammatory cytokine concentrations in the kidneys of diabetic rats [30,48].
2.4 Hypertension and Oxidative Stress

Oxidative stress in the kidney and hypertension has a complex relationship (Fig. 1). Evidence has suggested that the development of hypertension can be caused by oxidative stress. This is supported by studies that show that inducing oxidative stress leads to hypertension and the depletion of extracellular superoxide dismutase (EC-SOD), an antioxidative enzyme, increases basal blood pressure [49–53]. Furthermore, ROS produced under hyperglycemic conditions increases vascular NO and transforming growth factor (TGF)-β1, which is associated with vasodilation of the afferent and efferent arterioles [54–58]. Hyperglycemia has also been linked to renin-angiotensin-aldosterone system (RAAS) activation [22]. Hyperglycemia-induced RAAS activation can be inhibited via attenuation of ROS generation, suggesting that ROS generation mediates RAAS activation [59]. Dysregulated RAAS activation, in turn, can aggravate hypertension which in turn could cause renal impairment by increasing glomerular capillary pressure. Given the link between inflammation via ROS, neurohormonal change, and the role of the kidney in modulating blood pressure, interventions to attenuate hyperglycemia-induced oxidative stress present an opportunity to slow the progression of CKD in diabetic kidney disease.

2.5 Downstream Effects of Oxidative Stress and DN

When the overproduction of ROS occurs and there is a disproportionate amount of antioxidants, tissue damage can occur through the oxidation of protein, nucleic acids, carbohydrates, and lipids [11,12,20,60,61]. Not only does the reactivity of these species directly cause damage but ROS can act as signaling molecules, during hyperglycemia, for membrane receptor signaling to induce stress-related pathways that cause damage to cells [62]. ROS can also disrupt DNA by causing breaks in the single or double-stranded helices as well as interfering with histones [63,64]. As such, more targeted therapies specific to anti-oxidation are a potential novel treatment for DN.

3. Current Treatments of Diabetic Nephropathy and Limitations

3.1 Statin

A systematic review and meta-analysis of clinical trials evaluating five types of statins (atorvastatin, cerivastatin, lovastatin, simvastatin, pitavastatin) showed that statins significantly increased estimated glomerular filtration rate (eGFR) and reduced serum creatinine, thus improving renal function. Statin also reduces C-reactive protein (CRP) level, thus protecting the kidney from a high level of inflammation. Blood lipids are also reduced by statin, thus addressing one of the root causes of DN [65].

Previous studies have also shown statins’ ability to reduce lipid deposition on the vascular wall. This is conducive to the treatment of early DN, reducing proteinuria, and delaying the progression of kidney disease [66]. Statin also improves NO activity in the vascular endothelium, improving its function and relieving contraction found in DN [67]. With respect to diabetes, statins reduce the inflammatory response and stabilize platelet function [68].

3.2 Vitamin D

Vitamin D supplementation was found to decrease albuminuria and urinary TGF-β1 in patients with type 2 diabetes, as such, it was expected that vitamin D can protect kidneys from DN [69,70]. Follow-up studies reveal that this anti-nephropathic effect is mixed, with one study showing reduced proteinuria, prevention of kidney injury, both independent of blood pressure and blood glucose level [71]. However, this was contradicted by a study that shows no vitamin D effect on urine albumin to creatinine ratio [72]. A systematic review and meta-analysis of clinical trials examining the effects of vitamin D in DN revealed that vitamin D does improve 24-hour urine protein and inflammation indices. However, vitamin D has no effect on serum creatinine, eGFR, or glycemic control [72].

3.3 Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA) have been used to treat resistant hypertension due to high aldosterone levels [73]. Aldosterone affects sodium and potassium balance by binding to the mineralocorticoid receptor...
(MR) at distal nephrons in the kidney [74]. Overactivation of MR has been found to be common in DN, driving inflammation and fibrosis in the kidney [75]. Initial MRA has been steroid-based, such as spironolactone, eplerenone, and was found to carry a risk of hyperkalemia, with contraindication for patients with serum creatinine >2 mg/dL [76,77]. More recent non-steroid MRA has a lower risk of hyperkalemia, such as finerenone, and was shown to have high selectivity toward MR, with strong anti-inflammatory and anti-fibrotic effects in the kidney, however, it is still not recommended for patients with severe CKD [78,79].

3.4 α-lipoic Acid + Valsartan

Valsartan is an angiotensin 2 receptor blocker (ARB), used to treat hypertension. Low-dose valsartan with no clinical effect on blood pressure was shown to decrease urinary albumin excretion in patients with DN. It’s theorized that valsartan dilates the efferent more than afferent arterioles resulting in decreased intraglomerular pressure, protein filtration, and proteinuria [80]. In combination with angiotensin-converting enzyme (ACE) inhibitor, valsartan delays glomerular sclerosis and improves renal function in patients with type 1 DN; although, combined ARB and ACE inhibitor increases the risk for adverse drug event and are not generally used in clinical practice.

α-lipoic acid (ALA) is an antioxidant that was shown to up-regulate the expression of Nrf2-mediated antioxidant genes, peroxisome proliferator-activated receptors-regulated genes, and was used to treat diabetes [81]. In this case, ALA improved insulin sensitivity, protecting remaining β-cells by reducing their oxidative stress, reducing lipid peroxidation, and inhibiting protein glycation [81,82]. Meta-analysis of the combination of ALA and valsartan in DN showed that this combination significantly reduces urinary albumin, level of oxidative stress markers, increases antioxidant capacity, and alleviates renal function damage [83].

3.5 SGLT2 Inhibitor

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, commonly known as gliflozins, are used to lower blood glucose levels by inhibiting glucose absorption at proximal tubules [84]. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) trial, empagliflozin reduced progression to macroalbuminuria, decreased serum creatinine, and resulted in a 39% reduction in the death rate by kidney failure [85]. The SGLT2 inhibitor also has a blood glucose-lowering effect, reducing HbA1c with its maximum effect at 6 months post-treatment, and maintaining the effect from then on up to 1 year in the clinical trial [86]. Its hypoglycemic risk is low, similar to metformin [87].

SGLT2 inhibitor improves kidney health in DN by the following actions:

1. Restoring tubuloglomerular feedback: Increased adenosine expression, which causes vasoconstriction of the afferent arteriole, thus reducing glomerular pressure and hyperfiltration [88].

2. Reducing tubular workload and hypoxia: Diabetic patients have enhanced proximal tubular glucose reabsorption because of their hyperglycemia, leading to increased glomerular hyperfiltration [88]. This increased reabsorption increases oxygen demand by the cells, leading to tubular hypoxia, and is a strong indication of the progression of diabetic kidney disease [88]. By decreasing glucose reabsorption, SGLT2 inhibitors lower the workload and reduce tubular hypoxia.

3. Diuretic and natriuretic effect: SGLT2 inhibitors function as a diuretic, but with preferential fluid mobilization from the interstitial compartment rather than the intravascular compartment [89]. This helps to reduce the amount of interstitial fluid in the kidney, which may reduce cortical and medullary hypoxia.

4. Anti-inflammatory and antifibrotic effect: SGLT2 inhibitors reduce the markers of DN: Nuclear factor-B (NFB), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), and the serum uric acid level, thus reducing the risk of kidney inflammation [90,91].

3.6 Curcumin

Curcumin, found in turmeric, has strong anti-inflammatory properties that were expected to reduce inflammation-mediated kidney damage in DN. In clinical trials, it was found to have a positive impact on proteinuria, however, it has no impact on blood urea nitrogen, creatinine, eGFR, and serum albumin [92].

3.7 ACE Inhibitor/ARB (General)

Angiotensin-converting enzyme (ACE) inhibitor, or Angiotensin receptor blocker (ARB), are common hypertension medications that have also been used for the treatment of DN [93]. This is especially recommended for non-pregnant patients with both diabetes and hypertension comorbidity, as per American Diabetes Association (ADA) guideline in 2018. However, neither ACE inhibitor nor ARB is recommended for primary prevention of diabetic nephropathy, in diabetic patients with normal blood pressure, normal urinary albumin to creatinine ratio, and normal eGFR [93]. The mechanism of ACE inhibitors in diabetic nephropathy is suggested to be the lowering of glomerular intracapillary pressure, while still maintaining the flow of renal plasma. Additionally, ACE inhibitors may also prevent cellular and glomerular hypertrophy, and reduce mesangial matrix accumulation [94]. Meanwhile, ARB has been shown to prevent or delay DN independent of its action on hypertension, in patients with type 2 diabetes and microalbuminuria [95]. This data was supported by further clinical trials, except for analysis on obese or overweight patients [96].
3.8 Glycemic Control

Controlling blood sugar levels is a key requirement for living with diabetes which includes insulin treatments and healthy lifestyle habits such as diet and exercise. A strict and intense diabetic treatment plan aimed at glycemic control showed a delayed onset of diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes mellitus [97]. Controlling glycemic levels in adolescent patients is especially challenging as they now take responsibility for their diabetic management and still require more education, support systems, and guidance [98]. In adolescent patients, HbA1c levels were 1–2% higher in both the intensive and conventional treatments compared to adults according to the DCCT research group [97].

4. Anti-Oxidative Therapy and the NrF2 Pathway

Identifying anti-oxidative therapies aimed at slowing and reversing the progression of CKD has become a central focus of treating DN. Largely, two approaches have been taken to restore redox balance in kidneys under diabeticogenic conditions:

1. Upregulating anti-oxidative enzymes through activation of NrF2 pathways;
2. Reducing the production of ROS through attenuation of mitochondrial dysfunction.

The NrF2 is a transcription factor that is centrally involved in the management of oxidative stressors throughout the body. NrF2 is expressed in all cells at low levels under normal physiologic conditions [99]. Common sources of oxidative stress include superoxide anions, hydroxyl radicals, and hydrogen peroxide produced by mitochondria, endoplasmic reticuli (ER), and peroxisomes as a part of normal metabolic function [2,100]. The role of NrF2 in limiting cellular damage to such ROS means that it is integral in maintaining overall cell health. As such, a dysregulation of the NrF2 pathway results in an inability of cells to cope with oxidative stress leading to overall cellular dysfunction and disease. Studies utilizing NrF2 deficient mice have associated NrF2 dysregulation with a host of diseases including cancer, Alzheimer’s disease, cardiovascular disease, and DN [100–102].

When oxidative stress is low, NrF2 is bound to the E3 ubiquitin ligase subunit: Kelch-like ECH-associated protein 1 (Keap1) [102]. When complexed with Keap1, NrF2 is targeted for ubiquitination and subsequent protosomal degradation (Fig. 2) [103]. In this way, nuclear translocation of free NrF2 is suppressed when ROS levels are low. When oxidative stress is high, ROS react with Keap1 releasing NrF2 to translocate to the nucleus and bind with the antioxidant response element (ARE) promoter region (Fig. 2) [99]. NrF2-ARE binding activates transcription of a multitude of different antioxidant, metabolic, and anti-inflammatory proteins in addition to an upregulation of NrF2 transcription [99]. Overexpression of NrF2 and/or loss of Keap1 function is also associated with increased rates of autophagy [104].

NrF2, Diabetic Nephropathy, and Anti-Oxidative Therapies

Hemodynamic and metabolic changes in individuals with diabetes result in an increase in the production of ROS which leads to alterations in renal cell structure and a decrease in kidney function [105]. In DN, the accumulation of ROS leads to an overall increase in free cytosolic NrF2, however, NrF2 nuclear translocation is impaired [106]. This suggests that an increase in NrF2 production alone is not sufficient to combat the increased oxidative stress present in DN. In light of this information, NrF2 nuclear translocation should also be a target of therapies seeking to mitigate the effects of kidney disease in individuals with DN. Mohan et al. [107] demonstrated the efficacy of epigallocatechin-3-gallate (ECGC) in increasing NrF2 translocation in diabetic mice as measured by increased expression of functional HO1, γ-GCS, and NQO1. Pharmacologic ARE inducers like sulforaphane, Oltipraz, CDDO-Im, BHT increase free NrF2 through binding of cysteine thiol groups in the Keap1 repressor [100]. Either ECGC, ARE inducers, or a combination thereof could hold promise as potential therapies for DN. Evidence also shows that NrF2 activators have been shown to slow the progression of DN [105,108–114]. For example, dimethyl fumarate (DMF) is an NrF2 activator with anti-oxidative, anti-inflammatory, and immunomodulating effects that are currently used as a treatment for psoriasis and relapsing-remitting multiple sclerosis [115]. In a study of 30 diabetic mice, different doses of DMF, low, medium, and high were given for three months to assess DN, lipid profile, renal hypertrophy, oxidative stress in the kidney, and renal histopathological changes [116]. It was found that high dose DMF (80 mg/kg) was able to attenuate DN significantly [117].

While increasing anti-oxidative enzyme expression is an important aspect of treating DN, reducing the production of ROS and inflammation is also important in the long-term management of DN. Diabeticogenic conditions result in abnormal metabolism of glucose and fatty acids by the mitochondria, resulting in dysfunction and activation of NADPH oxidase, one of the major contributors of ROS production [118].

Several other macromolecules and pathways have been implicated in ROS production including advanced glycation end products (AGE), defects in polyol pathway, and uncoupled nitric oxide synthase (NOS). In this review, we focus on mitochondrial dysfunction and therapeutic agents targeted at restoring mitochondrial homeostasis as an important point of intervention to suppress ROS production [25]. Early diabetic kidney disease has been associated with mitochondrial fragmentation, fission, impaired mitophagy, decreased mitochondrial membrane potential, and ROS production [119]. Several agents such as Tilapia Skin Peptides, berberine, Sirte 6, and progranulin have been
shown to impede the progression of DN by restoring mitochondrial morphology and function [120–125]. In particular, pyruvate kinase M2, a glucose metabolic enzyme, was found to be elevated in kidneys of diabetic patients who did not develop DN but remained low in patients with progressed to DN [120]. Pyruvate kinase muscle isozyme 2 (PKM2) activation by TEPP-46 reversed diabetes-induced defects in mitochondrial function and prevented the development of glomerular pathology evidenced by a mouse model of DN [120]. Unfortunately, these agents are yet to be studied in humans and thus the safety and efficacy are unknown. Nrf2 activators, in addition to elevating the expression of antioxidants, have also shown to exhibit their therapeutic effects by restoring mitochondrial homeostasis. Human proximal tubular cells, human kidney-2 (HK-2) cells, cultured under hypoxic ambiance to emulate the hypoxic state under diabetic conditions resulted in increased mitochondrial fragmentation, ROS production, mitochondrial membrane potential loss, and apoptosis; these results were reversed with cotreatment with an HO-1 agonist [125]. Furthermore, MitoQ and CoQ10, mitochondrial antioxidants restored mitophagy and mitochondrial quality control in vivo in streptozotocin-induced DN [107,117]. Thus, further advancements and identification of Nrf2 activators that also restores mitochondrial homeostasis is a promising approach in the treatment and prevention of DN.

5. Conclusions

DN and oxidative stress are intertwined in CKD progression. The overproduction of ROS causes vascular damage and over time impairs the kidney. Hyperglycemia further aggravates oxidative stress by inducing more production of ROS. Current treatments have long been known to delay the progression of diabetic kidney disease; however, the majority of patients with DN progress to ESRD. Therefore, targeted therapies on the antioxidation via the Nrf2 pathway can be a promising option. Ultimately, a multimodal therapeutic approach involving traditional and newer anti-oxidative therapies applicable in clinical practice should be further explored to mitigate CKD progression in patients with DN.

Author Contributions

HI (Author F) conceived the idea of writing a review on DN and anti-oxidative stress. LFH (Author A) developed the idea into a draft outline and wrote the abstract, introduction, DN and Oxidative stress section, conclusion, and made the tables and figures. NE (Author B) wrote about current anti-oxidative treatments, assisted in the organization of the paper, and provided help and advice in the development of the paper. DW (Author C) wrote about the Nrf2 pathway, offered advice, and assisted in the development of the paper. MA (Author D) wrote the current treatment and limitations section and assisted in the development of the paper. LFH, NE, DW, MA and ET (Author A, B, C, D, and E) wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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