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Oxidative Stress in Diabetic Nephropathy: Molecular Mechanisms and Biomarkers

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Abstract: ***Diabetic nephropathy is one of the leading causes of chronic kidney disease and end-stage renal failure worldwide. Persistent hyperglycaemia induces multiple metabolic and hemodynamic alterations that culminate in renal injury. Among these, oxidative stress plays a central role in the initiation and progression of diabetic nephropathy. Excess generation of reactive oxygen species (ROS) leads to cellular damage, inflammation, and fibrosis within renal tissues. Several biochemical pathways, including the polyol pathway, advanced glycation end product (AGE) formation, protein kinase C activation, and mitochondrial dysfunction, contribute to oxidative stress in diabetes. The nuclear factor erythroid 2–related factor 2 (NRF2)–Kelch-like ECH-associated protein 1 (KEAP1) pathway is a key endogenous antioxidant defense mechanism that regulates cellular redox balance. Dysregulation of this pathway has been implicated in the progression of diabetic kidney disease. Biomarkers reflecting oxidative stress and renal injury may aid in early detection and monitoring. This review highlights the molecular mechanisms underlying oxidative stress in diabetic nephropathy and discusses potential biomarkers and therapeutic implications.***

Keywords: Diabetic nephropathy; Oxidative stress; Reactive oxygen species; NRF2; KEAP1; Biomarkers

1. Introduction

Type 2 diabetes mellitus (T2DM) marked by persistently high blood sugar levels occurs due to body developing resistance to insulin (the hormone primarily responsible for blood sugar regulation) and insulin producing cells of pancreas start to decrease. If T2DM isn't treated timely, it can lead to macrovascular and microvascular complications, one of which is diabetic nephropathy (DN). A study on the global, regional and national burden of diabetes showed surge in prevalence of T2DM as high as 90% of all diabetes patients. There were 537 million adults living with diabetes as of 2021 and is projected to become 783 million by 2045 which point towards the urgency for screening and early management of T2DM (1).

Recent studies show that T2DM incidence is growing in low to middle socio-demographic regions. As per a 2024 study, worldwide, the rate of death and the number of disability years lived due to T2DM are rising with significant increases in countries with lower socio-demographic pointers. Rising population with an aging demographic, urbanisation, changes in diet and increasing sedentary lifestyle are contributing factors. It reflects how interspersed our health is with the environment we live in and around us (2).

Increasing prevalence in young adults (before 40 years of age) known as early onset T2DM is ever increasing, denoting longer duration and therefore higher risk of complications. 50% of the diabetes burden is traceable to high BMI (3) (4).

People with T2DM face serious health complications such as renal disease, neurological damage and ophthalmic conditions. Besides affecting health, T2DM also exerts a huge financial strain on our healthcare system that is concerning in low to middle income nations due to inconsistent availability and accessibility to treatment. The crisis is evident in areas like sub-Saharan Africa and parts of South Asia due to limitations in the healthcare resources needed for proper management of T2DM and a large proportion of patients go undiagnosed until it is too late to prevent the complications. This consequently increases the rates of disability, affecting the quality of life highlighting the need for early detection and timely intervention (5).

The increase in the prevalence of diabetes is so substantial that from 1990, it has doubled in most countries. In India, the rise has been more steep with the numbers being consistently higher in urban than rural. Current predictions expect India's adult diabetic population to exceed 130-140 million by 2045 and over 780 million worldwide (6).

A significant proportion of people with T2DM go undiagnosed, commonly in rural India where ICMR-INDIAB study showed less awareness and therefore poor control over blood glucose levels even among known diabetics (7). Numerous patients are diagnosed late due to delayed presentations owing to lack of screening, low awareness, limited access to healthcare in addition to delayed diagnosis of comorbidities like hypertension, dyslipidaemia accentuating the disease progress. Other challenges include treatment accessibility, financial constraints at the levels of diagnosis, treatment, monitoring and follow up, adherence to the treatment advised, and lifestyle modification.

DN: Epidemiology and Clinical Impact

One of the most serious complications of T2DM is diabetic nephropathy (DN), also called diabetic kidney disease (DKD). Due to a global rise in T2DM cases, DN's prevalence, illness, and death rates are also increasing. Worldwide, a large percentage of diabetics are affected by DN. A widely cited review estimates that 20–40% of diabetic patients develop DKD (defined as elevated urine albumin excretion, reduced glomerular filtration rate (eGFR), or both) during the course of disease (8).

The rate of DN in India's T2DM patients differs greatly due to the diagnostic method, location, and illness length. A 2021 Clinical Epidemiology and Global Health review found ~34.4% DKD prevalence in India's T2DM patients. The article also mentioned that some studies estimate a higher

combined prevalence of diabetic-CKD (chronic kidney disease), reaching around 62% in some groups, but these figures are affected by age, other health problems, and hospital data. Indian studies often find that diabetes duration, high HbA1c, hypertension, obesity, dyslipidaemia, older age, smoking, and delayed treatment raise risk. Regional differences are significant. Higher prevalence reported in southern states (Tamil Nadu, Kerala) than in northern/rural regions, potentially due to urbanization, better detection, aging population, lifestyle. Lifestyle changes are now affecting rural areas. Also, socio-economic status, medical access, awareness play a role (9).

In addition to monetary costs, the social impact is substantial: lowered living standards, decreased earning ability, dependency. Mortality rates vary: men compared to women, urban areas versus rural, young people versus old. Men experience higher DN-related mortality in many locations. The risk increases with an earlier T2DM start. DN develops in a significant portion (20-40% globally, ~30-40% in many Indian T2DM cohorts) of T2DM patients (as defined by albuminuria/eGFR). Albuminuria-independent presentations of disease are frequent, and focusing on albuminuria alone can miss early disease (10).

Oxidative Stress-Driven Pathogenesis of DN

Prolonged high blood sugar is the root of almost all diabetes complications, including DN. Renal cells such as glomerular endothelial cells, podocytes, and mesangial cells are particularly vulnerable to glucose overload. Several interconnected biochemical pathways are initiated. Persistent high glucose causes proteins and lipids to undergo non-enzymatic glycation, creating advanced glycation end-products (AGEs). They build up in the glomerular basement membrane (GBM) and extracellular matrix, changing how it's structured. The interaction of AGEs with its receptors triggers intracellular signalling pathways, resulting in reactive oxygen species (ROS) production, NF-κB (nuclear factor kappa beta) activation, and the release of pro-inflammatory cytokines (11). The GBM becomes stiffer because of AGE crosslinking, raising its permeability to albumin. Excess glucose in the cell enters the polyol pathway, where it is converted to sorbitol by aldose reductase, which uses nicotinamide adenine dinucleotide phosphate (NADPH). Sorbitol dehydrogenase later converts sorbitol to fructose. This flux lowers NADPH, which prevents the renewal of reduced glutathione (GSH), an important cellular antioxidant. The result is heightened susceptibility to oxidative injury. Protein kinase C (PKC) activation results from hyperglycaemia raising intracellular diacylglycerol (DAG), thus activating PKC isoforms (mainly β and δ). Endothelial dysfunction, increased vascular permeability, elevated vascular endothelial growth factor (VEGF), and stimulated transforming growth factor beta (TGF-β) are all promoted by PKC signalling. Additionally, it leads to mesangial expansion and basement membrane thickening (12). The hexosamine pathway is another glucose-sensing method; it converts fructose-6-phosphate into glucosamine-6-phosphate and uridine diphosphate (UDP) -N-acetylglucosamine. This causes transcription factors to glycosylate abnormally, changing gene expression and causing fibrosis and cytokine imbalance (13).

These findings clarify why DN therapy relies on Renin–angiotensin–aldosterone system (RAAS) blockade with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Oxidative stress is a central mediator of DN pathogenesis. Mitochondrial electron transport chain leakage, NADPH oxidases, uncoupled nitric oxide synthase (NOS), AGEs reacting with receptors of AGE, PKC signalling, and the polyol pathway generate ROS (14). Excessive superoxide anions are produced by mitochondria in chronic hyperglycaemia. Changes in structure involve a decrease in mitochondrial biogenesis, changes in membrane potential, and cytochrome c release, leading to apoptosis of podocytes and tubular epithelial cells. Antioxidant systems are compromised in DN. Enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase) and non enzymatic antioxidants (glutathione, vitamins C and E) are reduced in renal tissue and in peripheral blood mononuclear cells of DN patients (15).

Hyperglycaemia and ROS activate NF-κB in podocytes, mesangial, and tubular cells. Inflammatory genes, adhesion molecules, and fibrotic mediators are upregulated by NF-κB. TGF-β signalling: TGF-β is a master regulator of renal fibrosis. It boosts ECM creation (collagen IV, fibronectin) but inhibits matrix metalloproteinases, causing mesangial growth and GBM increase. Tubulointerstitial fibrosis is caused by the toxic effect of proteinuria on tubular cells. Protein filtration activates inflammatory and apoptotic responses, resulting in interstitial fibrosis, which is linked to eGFR reduction (16).

The NRF2–KEAP1 signalling axis is a crucial antioxidant defense mechanism.

1) Basal state: KEAP1 binds NRF2, targeting it for proteasomal degradation.
2) Oxidative stress: Modification of KEAP1 cysteine residues releases NRF2, allowing it to translocate to the nucleus, bind antioxidant response elements (AREs), and activate transcription of antioxidant genes.
3) Pathological context: In DN, hyperglycaemia and chronic ROS impair NRF2 activation. Studies show that NRF2 expression is suppressed while KEAP1 is upregulated, weakening antioxidant defenses.
4) Protective evidence: Pharmacological NRF2 activators (sulforaphane, bardoxolone, quercetin) attenuate oxidative damage, reduce albuminuria, and ameliorate histopathological lesions in preclinical models (17).

Not all diabetic patients develop DN, and progression rates vary. Factors modifying susceptibility include genetic polymorphisms (variants in RAGE, TGF-β, NRF2, KEAP1, and antioxidant enzyme genes influence risk), epigenetics (DNA methylation of NRF2 promoters and histone modifications reduce antioxidant gene expression), clinical risk factors (duration of diabetes, poor glycaemic control, hypertension, obesity, dyslipidaemia, and smoking increase progression risk), environmental exposures (air pollution and heavy metals intensify oxidative stress) and comorbidities (vascular disease, cardiovascular comorbidities, prior acute kidney injury, and low birth weight further exacerbate renal decline) (18).

Understanding DN pathogenesis leads to biomarker chances and treatment goals. Earlier detection might be possible with

biomarkers for oxidative stress, inflammation, and fibrosis (e.g. TGF-β, NRF2/KEAP1) versus just albuminuria. Therapies addressing upstream drivers (glycaemic control, RAAS blockade) and downstream pathways (antioxidants, anti-inflammatory agents, NRF2 activators) can slow progression. Changes in lifestyle, such as diet and exercise, influence epigenetic regulation and oxidative stress (19).

Linking Gene Expression (NRF2–KEAP1) with Biochemical Markers

Oxidative stress, inflammation, and fibrosis cause diabetic nephropathy (DN). Even though markers like serum creatinine reflect kidney function, they don't show much about the molecular pathways of disease. In contrast, genetic and molecular readouts, such as NRF2 and KEAP1 expression, measure the upstream cellular events that regulate oxidative stress. By linking these molecular markers to biochemical indices, we can get a more comprehensive understanding of DN. NRF2–KEAP1 signalling is a primary controller of antioxidant defense. If NRF2 isn't activated properly or KEAP1 is upregulated, there won't be enough transcription of protective genes like HO-1, NQO1, catalase, and superoxide dismutase (SOD) (20). Renal oxidative damage, podocyte apoptosis, and tubulointerstitial fibrosis are all made worse by a weaker antioxidant defense.

Hence, a combination of molecular and biochemical biomarkers might be able to detect subclinical disease before overt clinical manifestation, find patients at high risk (e.g: DN without albumin) and give a mechanistic explanation that connects oxidative stress pathways to kidney decline.

Few Indian studies' data link NRF2–KEAP1 expression to biochemical markers. Sireesh and colleagues (2018) found the first proof of diminished NRF2 expression and lowered antioxidant gene activity in South Indian T2DM patients (21). However, the study did not evaluate cystatin C or urine markers. Mahashabde et al. (2020) found that cystatin C rose before creatinine in early DN (22). Even though NRF2 expression wasn't measured, this implies that the integration of molecular and biochemical markers may lead to earlier detection.

2. Clinical Implications

Understanding the role of oxidative stress in diabetic nephropathy has important clinical implications. Targeting oxidative stress through pharmacological and lifestyle interventions may help delay disease progression. Antioxidant therapies, glycaemic control, and agents targeting specific molecular pathways such as NRF2 activation are being explored. Early identification of high-risk patients using molecular biomarkers can facilitate timely intervention and improve outcomes. Therapeutic effects are mainly achieved by NRF2 activators by changing KEAP1 cysteine or indirect pathways such as MAPK, PI3K/Akt, and AMPK signalling (23). Once it's activated, NRF2 separates from KEAP1, moves to the nucleus, and triggers the transcription of antioxidant response element (ARE)-driven genes such as HO-1, NQO1, GST, and enzymes in glutathione synthesis (24). By reducing ROS, this activation protects kidney cells, suppresses inflammation, and reduces scarring, and supports mitochondrial function.

3. Conclusion

Oxidative stress plays a central role in the pathogenesis of diabetic nephropathy through multiple interconnected pathways. The NRF2–KEAP1 system is a key regulator of antioxidant defense and represents a promising therapeutic target. Identification of reliable biomarkers of oxidative stress may aid in early diagnosis and monitoring. Further research is needed to translate these insights into effective clinical interventions.

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