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Mechanistic and Clinical implications of Niacin in Diabetic Complications

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ABSTRACT

Diabetes mellitus predisposes patients to a spectrum of microvascular and macrovascular complications. Niacin (vitamin B_3), a precursor of nicotinamide adenine dinucleotide and a therapeutic lipid-modifying agent, exhibits anti-inflammatory, antioxidant, and endothelial-protective actions. Biochemical and clinical studies suggest niacin may confer benefits in diabetic nephropathy, neuropathy, and dyslipidemia-related cardiovascular risk. However, clinical use remains constrained by concerns over worsened glycemic control, insulin resistance, and increased risk of developing diabetes. This review synthesizes mechanistic insights, animal and human data, and clinical trials to assess niacin's therapeutic potential and safety in diabetes.

INTRODUCTION

Diabetes mellitus (DM) represents a major public health challenge in Egypt, where its prevalence was 9.9% in 1995 and is projected to increase to 13.3% by 2025, ranking the country among the top ten worldwide in terms of diabetes burden [17]. Insulin plays a critical role in shifting the body from nutrient production to storage following food intake by enhancing glucose and protein uptake in adipose tissue and skeletal muscle. When blood glucose levels rise, pancreatic β-cells release insulin to maintain metabolic balance. However, factors such as physical inactivity and excessive nutrition disrupt this regulation, leading to insulin resistance—a state in which tissues exhibit reduced responsiveness to insulin. This dysfunction is central to the development of metabolic syndrome, obesity, and type 2 diabetes mellitus [15]. Diabetes mellitus complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. Key pathological mechanisms include oxidative stress, inflammation, endothelial dysfunction, and dyslipidemia [12].

Niacin (vitamin B3) is the generic descriptor for two vitamers, nicotinic acid and nicotinamide. It is a pharmacotherapeutic agent used since 1955, making it the oldest pleiotropic hypolipidemic agent [8]. Beyond lipids, niacin gives rise to the biologically active coenzymes, nicotinamide adenine dinucleotide

(NAD) and its phosphate analog, the nicotinamide adenine dinucleotide phosphate (NADP). The two coenzymes take part in redox reactions crucial for energy production [13]. NAD^+ levels fall with aging, obesity and hypertension, and are implicated in cardio-renal-metabolic disease biology [3]. It may modulate oxidative stress and inflammation (Table 1). Exploring the mechanisms and clinical implications of niacin in diabetic complications may hold therapeutic promise.

2. Molecular Mechanisms of Niacin

2.1 Lipid & Lipoprotein Effects

Niacin lowers LDL-C, VLDL-C, lipoprotein(a), and triglycerides, while increasing HDL-C. It acts via G protein-coupled receptors hydroxycarboxylic Acid Receptors 2 ($HCAR_2$), expressed in adipose tissue and immune cells. Activation of this receptor leads to inhibition of adipocyte lipolysis, resulting in reduced release of free fatty acids into the plasma. This, in turn, limits the availability of free fatty acids for hepatic triglyceride synthesis, ultimately reducing the production and secretion of very-low-density lipoprotein (VLDL) particles by the liver [19].

Table 1: Some Antioxidant & Anti-Inflammatory Effects of niacin

Mechanism	Description	Reference(s)
Reduces oxidative stress in vascular endothelium	Lowers Angiotensin II–induced reactive oxygen species (ROS), LDL oxidation, NF-κB activation, VCAM-1 and MCP-1 levels, and monocyte adhesion in human endothelial cells	**[7]**
Induces protective antioxidant enzyme HO-1 via Nrf2 activation	In human coronary artery endothelial cells, niacin upregulates HO-1 expression over time and dose, via Nrf2 and p38-MAPK pathways	**[22]**
Inhibits vascular inflammation in vivo	In guinea pigs on a high-fat diet, niacin reduced arterial macrophages, plasma IL-6 and TNF-α, and NF-κB activation, improved endothelial markers	**[18]**
Suppresses vascular neutrophil infiltration and ROS release	In rabbit carotid injury models, niacin reduced neutrophil infiltration and myeloperoxidase accumulation	**[23]**
Attenuates hepatocyte fat accumulation, ROS, and IL-8 production	In human hepatocytes, niacin reduced palmitic acid–induced lipid accumulation, ROS levels, NADPH oxidase activity, and IL-8 secretion	**[6]**
antioxidant action in diabetic models	In T2DM rats, niacin significantly lowered oxidative stress and inflammatory markers	**[14]**

2.2 Anti-inflammatory signaling via $HCAR_2$ in immune cells

Beyond lipid modulation, niacin exhibits antioxidative, anti-inflammatory, antithrombotic, and endothelial-protective effects. Niacin, via $HCAR_2$, suppresses pro-inflammatory cytokine production (e.g., TNF-α, IL-6, IL-1β) in macrophages. It does so through NF-κB inhibition and other $HCAR_2$-mediated pathways [26].

2.3 NAD^+ Biology and Sirtuins activation

Nicotinamide and riboside/mononucleotide forms restore NAD^+, augment SIRT1 activity, improve mitochondrial fatty-acid oxidation, and modulate inflammasomes. In diabetic kidney, NAD^+ replenishment restores metabolic programs and attenuates inflammation in animal models [24].

3. Effects of Niacin on Diabetic Complications

3.1 Diabetic Nephropathy

Diabetic nephropathy (DN) is a common complication of diabetes, classified into normoalbuminuria, microalbuminuria, and macroalbuminuria. Early stages are marked by glomerular hyperfiltration, followed by declining glomerular filtration rate with persistent albuminuria. Its progression is influenced by factors such as hypertension, poor glycemic control, obesity, dyslipidemia, and female gender. DN pathogenesis involves metabolic, hemodynamic, inflammatory, and fibrotic mechanisms, with key roles for circulating cytokines and renin–angiotensin system activation [16].

Oxidative stress is central to DN. The transcription factor Nrf2 counteracts oxidative damage by inducing antioxidants such as HO-1 and SODs. Molecular mechanisms of DN onset and progression demonstrated in Figure 1. Nicotinamide enhanced Nrf2 and SOD expression, reduced nitrotyrosine, and suppressed ROS accumulation in diabetic kidneys confirming its antioxidant effect. Renal fibrosis, driven by TGF-β1 signaling, is another hallmark of DKD, involving extracellular matrix deposition, myofibroblast accumulation, and epithelial-to-mesenchymal transition. Nicotinamide attenuated fibrosis in STZ-diabetic mice. Prior studies show Sirt1 inhibits TGF-β1–Smad3/4 signaling, and Nicotinamide supplementation restored Sirt1 levels in diabetic kidneys supporting its renoprotective role [25].

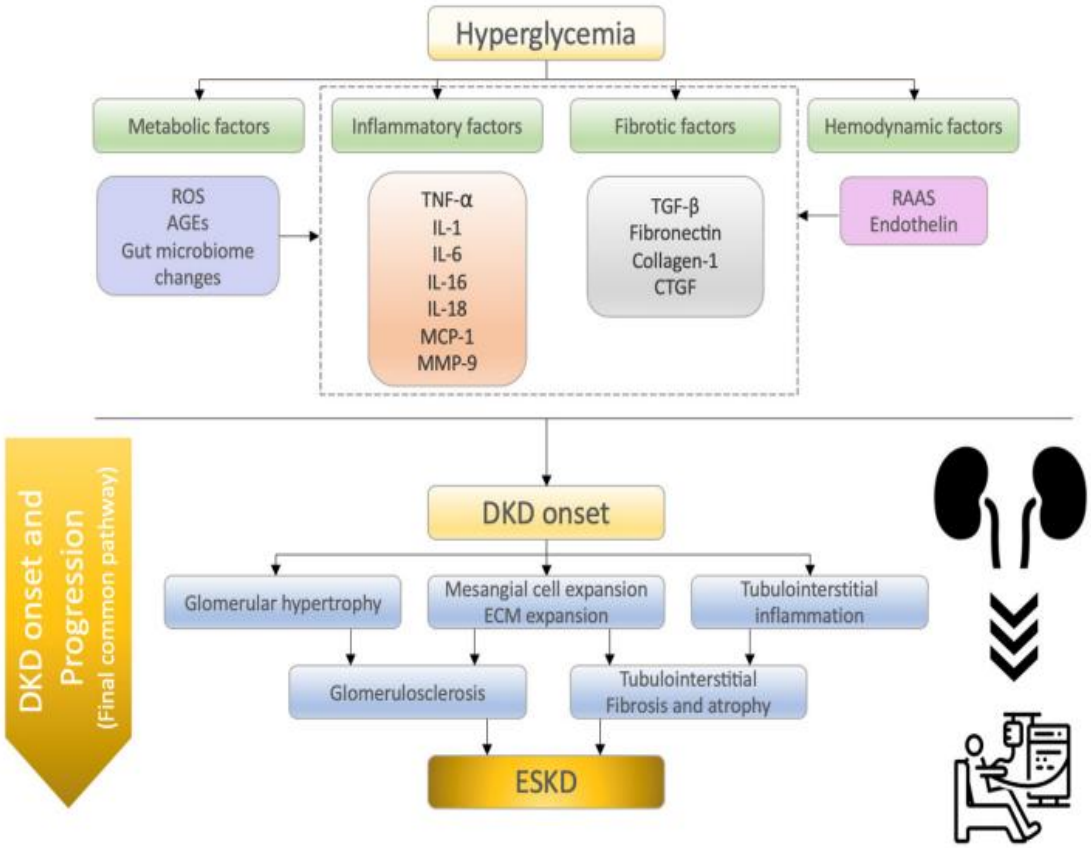

Figure 1: Summary of the molecular mechanisms of diabetic kidney disease (DKD) onset and progression. ROS, reactive oxygen species; AGEs, advanced glycation end products; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; IL-6, interleukin-6; IL-16, interleukin-16; IL-18, interleukin-18; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; RAAS, renin–angiotensin–aldosterone system; DKD, diabetic kidney disease; ESKD, end-stage kidney disease [21]

NAD^+ depletion in renal tubular cells is a critical driver of diabetic nephropathy. Niacin replenishes NAD^+ stores and activates sirtuins (particularly SIRT1 and SIRT3), which enhance mitochondrial fatty acid oxidation and suppress profibrotic signaling. Studies in chronic kidney disease models show that niacin reduces albuminuria, attenuates tubulointerstitial fibrosis, and preserves glomerular function. Nicotinamide has also been shown to inhibit advanced glycation end-product (AGE) formation and reduce poly (ADP-ribose) polymerase (PARP) overactivation, both of which contribute to diabetic renal injury [5].

Additionally, in patients with chronic kidney disease CKD, higher dietary niacin intake correlated with reduced all-cause and cardiovascular mortality, indicating potential systemic benefit in nephropathy settings [28].

3.2 Diabetic Neuropathy & Diagnostic Biomarkers

Diabetic microvascular complications such as retinopathy (DR) and nephropathy (DN) significantly contribute to the development of diabetic foot disease and related amputations. Peripheral neuropathy affects an estimated 6–51% of adults with diabetes, with prevalence influenced by glycemic control, disease duration, and patient age. Clinical presentation varies from asymptomatic cases to painful neuropathy. Despite advances in managing hyperglycemia, dyslipidemia, and hypertension, the incidence of microvascular complications continues to rise [1].

Peripheral neuropathy involves microvascular injury to nerve capillaries. A novel study found that the niacin-induced skin flushing response (NSFR), triggered by topical methyl nicotinate, is significantly diminished in diabetic patients—especially those with peripheral neuropathy—suggesting NSFR's potential as a diagnostic adjunct for diabetic neuropathy [10].

NAD^+ precursors (Nicotinamide Riboside / Nicotinamide Mononucleotide) reverse experimental DPN phenotypes in mice: improving neurite growth via SIRT1, reducing inflammation, and protecting small nerve fibers independent of full glycemic normalization [4].

3.3 Cognitive impairment

Chronic poor glycemic control in diabetes is linked to cognitive decline. Evidence from several studies indicates that diabetes adversely affects the hippocampus, increasing the risk of memory deficits and cognitive impairment, particularly among older individuals with the disease [2].

Systematic preclinical reviews report consistent improvements in behavior, memory tasks, and histologic markers in rodents treated with niacin or NAD^+ precursors across models of cognitive impairment and ischemic stroke. Studies show reduced neuronal loss, lower neuroinflammation (microglial activation, pro-inflammatory cytokines), and improved mitochondrial morphology. In diabetic rodent models there is evidence that NAD^+ precursors rescue cognitive deficits linked to metabolic dysfunction, suggesting particular relevance for diabetes-associated cognitive decline [9].

3.4 Diabetic Retinopathy

Diabetic retinopathy is a major complication of diabetes, with approximately 20% of patients at the time of diabetes diagnosis and approximately 40–45% during the disease. This condition is marked by the dysfunction of two key cell types present in the retina: endothelial cells, responsible for forming blood vessels in the retinal microvasculature, and pericytes, which offer support and regulate the activities of the endothelial cells [20]. Hyperglycemia, the presence of harmful substances like AGEs, and oxidative stress collectively contribute to the disruption of tight junctions between endothelial cells in the retina's blood

vessels. Consequently, pericytes, which support and regulate these endothelial cells, become detached and undergo cell death (apoptosis). This early loss of pericytes is a significant factor in diabetic retinopathy, a condition that affects the eyes in people with diabetes. The detachment and apoptosis of pericytes result in increased permeability of the blood-retina barrier, allowing harmful substances to leak into the retina and contributing to the progression of the disease [27].

In diabetic rodent models, nicotinamide has been shown to protect the retina at multiple levels, especially the inner retina. (1) Reduced oxidative DNA damage, a significant decrease in superoxide levels 8-hydroxy-2'-deoxyguanosine (a marker of DNA damage) was observed following nicotinamide treatment. (2) Attenuated gliosis and apoptosis: Reactive gliosis (indicated by GFAP) and ganglion cell apoptosis were both reduced in treated retinas. (3) Preserved retinal structure: Electron microscopy demonstrated better retinal ganglion cell integrity and reduced myelin degeneration [11].

4. Conclusion

Niacin exhibits multifaceted actions such as antioxidant, anti-inflammatory, endothelial- protective, and lipid modifying that may offer therapeutic benefits for diabetic complications, particularly nephropathy and dyslipidemia-driven cardiovascular disease. Yet, its clinical use is tempered by concerns over insulin resistance, glycemic worsening, and new-onset diabetes risk. Further targeted research is essential to delineate the role of niacin in managing diabetic complications.

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