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# Nicotinamide Role among Kidney Disease: Review Article

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) also called chronic renal failure is a syndrome defined as structural and /or functional abnormality of the kidney. Nicotinamide (NAM) is the amide form of vitamin B3, which is a water soluble vitamin. It can be synthesized in the body through metabolism of tryptophan or obtained from diet from either plant or animal sources.

**Objective:** Review of the literature on nicotinamide role among kidney disease.

**Methods:** We looked for data on Nicotinamide and kidney disease in medical journals and databases like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between September 2005 and September 2022. References from related works were also evaluated by the writers. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study.

**Conclusion:** NAM and its precursor NAD+ are cosubstrates for multiple regulatory proteins that improve various metabolic dysfunctions including kidney disease and extend cellular life span. Because the kidney is such a metabolically active organ, NAD and its metabolites play a crucial role in the pathogenesis, progression, and treatment of kidney disease. Sirtuins (SIRT1 and SIRT3), which are NAD+ dependent deacetylases proteins activation and PARP inhibition mediated by NAM administration may prevent and decrease progression of CKD

**Keywords:** Nicotinamide, Kidney disease.

## INTRODUCTION

Structural and/or functional abnormalities of the kidney constitute the syndrome known as chronic kidney disease (CKD), also known as chronic renal failure. Symptoms of these conditions include a lowered glomerular filtration rate (GFR), albuminuria, and unusual imaging, histology, and urine sediment. If any of these abnormalities persist for more than three months, a diagnosis of CKD can be made [(1)].

### Prevalence:

CKD is a rapidly growing global health problem. Its prevalence has increased greatly in the last few years, it became about 5-15% worldwide [(2)]. So, it became the 12th cause of death globally [(3)]. This prevalence is worse in developing countries than developed countries. About 1.2 million lives are lost annually and 28 million life years are shortened because of it. By 2040, it is expected that chronic kidney disease will overtake lung disease as the fifth greatest cause of mortality worldwide, and that the number of years of life lost due to renal failure would increase by a factor of two [(2)]. Renal fibrosis is the terminal common clinical manifestation of many chronic kidney illnesses. It destroys all kidney compartments, including the glomeruli, the vasculature, and the tubulointerstitial tissue, unlike acute kidney damage (AKI), which heals fully [(4)].

Endothelial damage, smooth-muscle cell proliferation, mesangial cell proliferation, and podocyte death all contribute to glomerulosclerosis. Hypertension-induced endothelial cell activation is the first step in the development of glomerular microinflammation. Mesangial cells are triggered to multiply by inflammatory cells. Mesangial cells become mesangioblasts in response to growth stimuli. Mesangioblasts then produce an abundance of extracellular matrix, leading to mesangial enlargement, which is an early indicator of glomerulosclerosis [(5)].

Abnormally filtered urine proteins cause tubulointerstitial fibrosis by stimulating tubular epithelial cells to generate inflammatory products and reactive oxygen species. These inflammatory mediators and cells interact with and stimulate interstitial fibroblasts leading to fibrosis. Once fibrosis occurs injured tubular epithelium fails to regenerate and apoptosis occurs creating non-functioning glomeruli and tubular atrophy [(5)].

### CKD and inflammation:

**Definition:** Inflammation is the vascular and/or tissue reaction to a harmful stimuli. It represents an important part of CKD, as it has a role in its pathophysiology and it is also a contributing factor for its multiple complications and mortality. Both acute and chronic inflammatory mediators are present in CKD, which lead to its progression and increase its mortality and morbidity. These mediators induce production of cytokines and adhesion molecules that induce T cells adhesion and migration to interstitium and attraction of profibrotic factors [(6)].

There are many factors that lead to this inflammatory state such as increased production and decreased clearance of inflammatory cytokines, hypoalbuminemia, acidosis, advanced oxidation protein products, atherosclerosis, malnutrition, recurrent infections and disturbed metabolism [(7)].



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Nicotinamide (NAM) is the amide form of vitamin B3, which is a water soluble vitamin. It can be synthesized in the body through metabolism of tryptophan or obtained from diet from either plant or animal sources. It is stored in small amounts in the liver while its major part is catabolised to provide important products by which it produces its action or being excreted [8]. The effectiveness of NAM was first reported by **Elvehjem *et al.*** [9] in treatment of pellagra in dogs, then NAM has shown effectiveness in treatment of many diseases in both animal and clinical studies during the last years [10, 11].

**Metabolism of NAM:**

There are two pathways for NAM metabolism; salvage pathway and denovo pathway. Once NAM is taken into the cells it is converted into nicotinamide mononucleotide (NMN) in reaction catalysed by NAM phosphoribosyltransferase (NAMPT), then NMN is converted to nicotinamide adenine dinucleotide ($NAD^+$) the enzyme NMN adenylyltransferase (NMNAT) through salvage pathway, which represents the major pathway for NAD production. While, through denovo pathway smaller amounts of $NAD^+$ can be synthesized from tryptophan through its metabolism in the liver into nicotinic acid mononucleotide (NAMN) and then by the enzyme nicotinic acid mononucleotide adenylyltransferase (NaMNAT) it is converted to $NAD^+$ [8]. $NAD^+$ production from Nam represent the major pathway by which NAM can produce its therapeutic effects [10]. This was proved by **Hasmann *et al.*** [12] by supplementation of NAMPT inhibitor that inhibited the salvage pathway and abolished NAM effects in many cases.

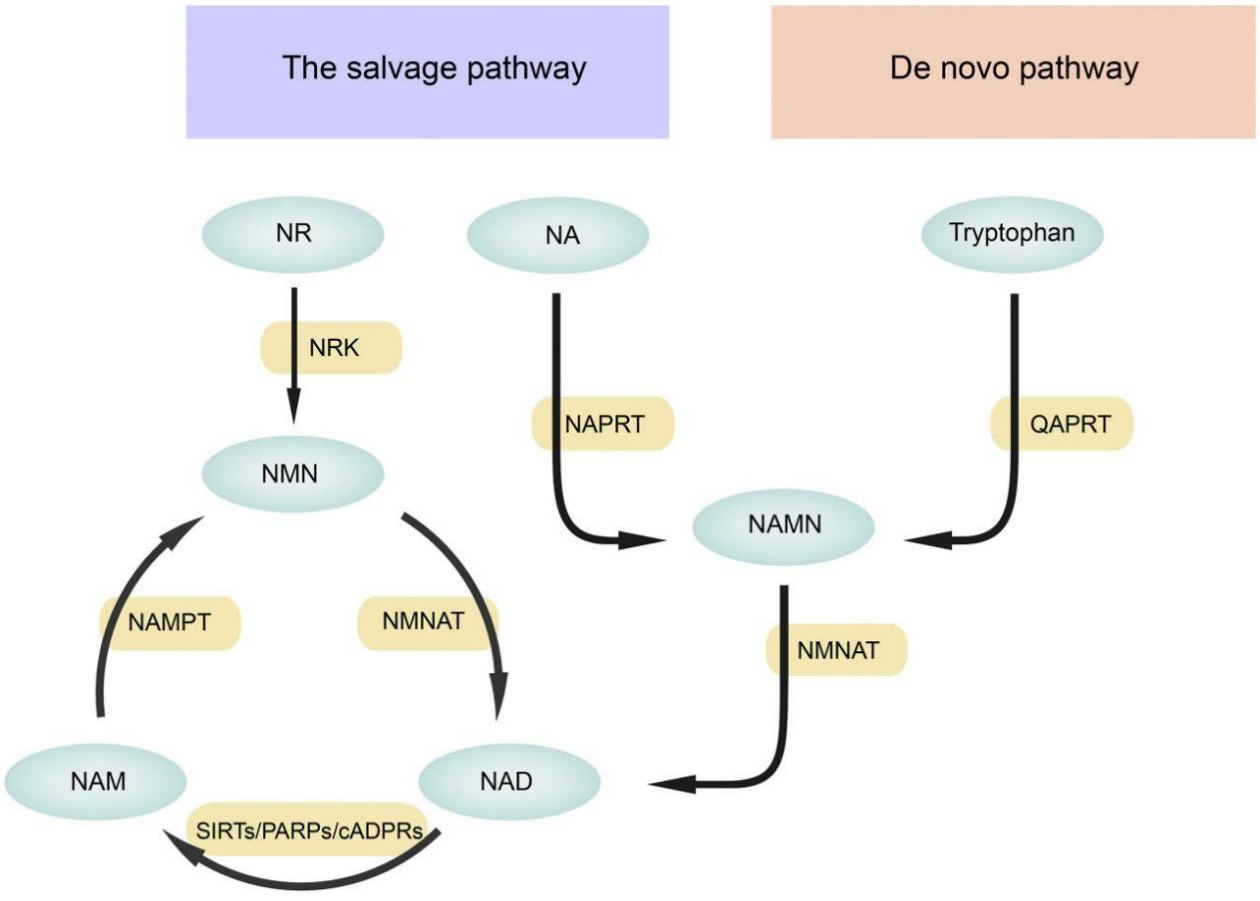


**Figure (1):** Salvage and De novo pathway of nicotinamide synthesis phosphoribosyltransferase, SIRTs: sirtuin [13].

**Mechanism of action of NAM:** NAM acts mainly by increasing cellular NAD level. This increase in NAD level reduces mitochondrial reactive oxygen species production, improves mitochondrial quality and protects the cells through different mechanisms [11]**.** that include elevation of NAD/NADH ratio that leads to decrease membrane potential and superoxide production [14, 15]**,** and activation of certain proteins that maintain mitochondrial quality, cell homeostasis and survival and normal metabolism and resist stress such as sirtuins **(**SIRT1 and SIRT3), which are $NAD^+$ dependent deacetylases proteins having different functions and cellular site of action and are the main two proteins by which NAM exerts its therapeutic effects [10].

SIRT1 regulates metabolism by increasing lipolysis and fatty acid oxidation, increase cellular life span and promotes its proliferation, reduces age related disorders, maintains hormone homeostasis and stress resistance. Also, it has anti-inflammatory effects by decreasing the activity of nuclear factor kappa B (NF-KB) which is a key transcription factor for pro-inflammatory genes [10].

Additionally, SIRT1 has anti-oxidant effect by increasing antioxidant gene expression. It also maintains mitochondrial quality through maintaining mitochondrial turn over by providing factors involved in their biogenesis that include peroxisome activation SIRT1 mediates autophagy gene activation, which in turn activates the DNA repair machinery and the peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-11α), a key mitochondrial protein genes transcription factor [10].

SIRT3 is a mitochondrial sirtuin which enhances mitochondrial fatty acid oxidation and ATP production through deacteylation and activation of mitochondrial proteins to do with fatty acid oxidation. SIRT3 also lowers reactive oxygen species production and maintains mitochondrial membrane integrity by blocking off the mitochondrial pore that allows protons and other tiny molecules to escape. In addition, SIRT3 also promotes cell survival and hinders the initiation of apoptosis [10].

Interestingly, NAM has anti-inflammatory and anti-oxidant effects against poly (ADP-ribose) polymerases (PARPs) induced inflammation by feedback inhibition of activated PARPs. Additionally, it protects cells against apoptotic and necrotic death caused by marked depletion of adenine tri phosphate (ATP) and $NAD^+$ induced by PARPs [11]**.**

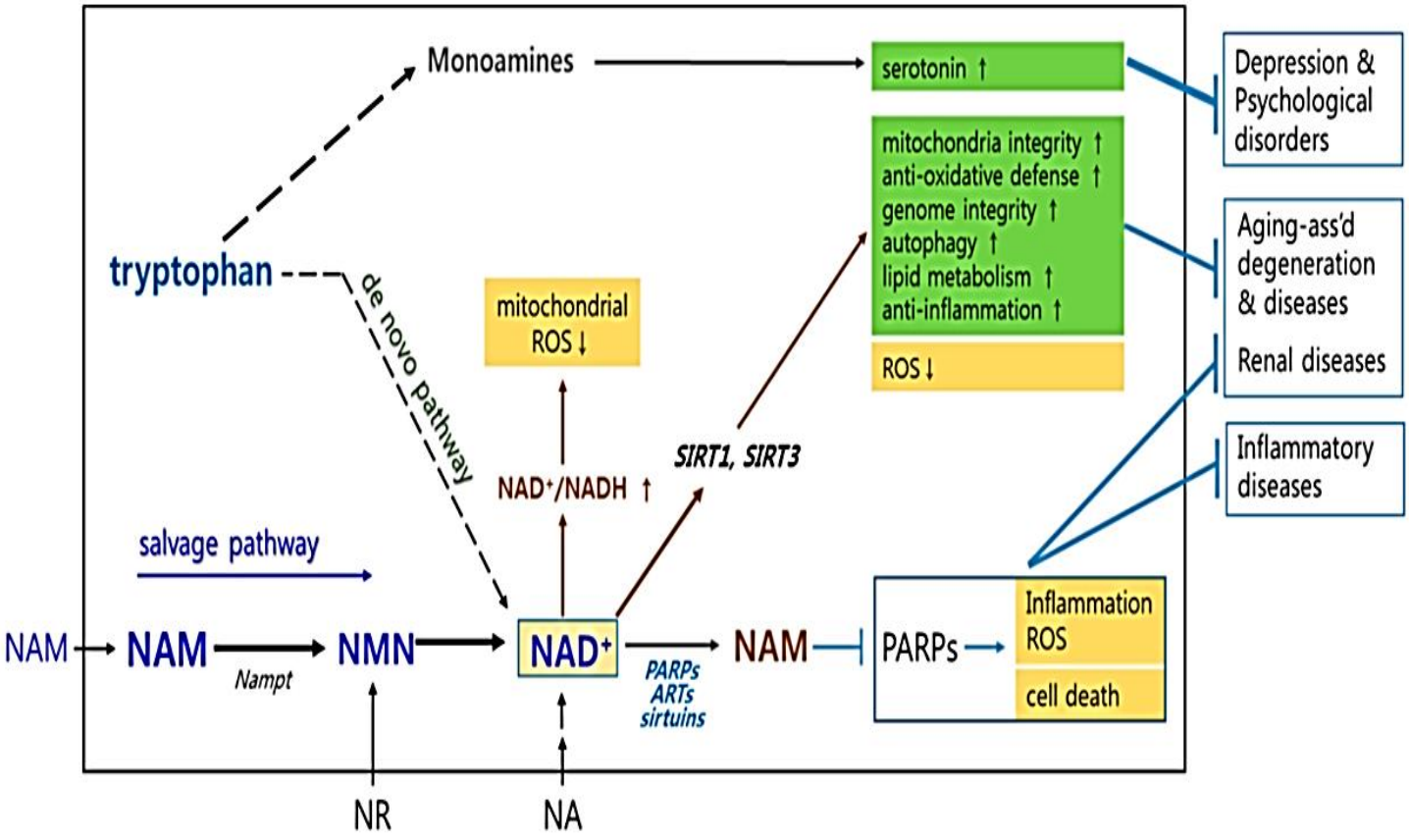


**Figure (2):** Metabolism and beneficial effects of nicotinamide [11]**.**

**Nicotinamide and kidney disease:** NAM and its precursor $NAD^+$ are cosubstrates for multiple regulatory proteins that improve various metabolic dysfunctions including kidney disease and extend cellular life span. Because the kidney is such a metabolically active organ, NAD and its metabolites play a crucial role in the pathogenesis, progression, and treatment of kidney disease [16].

NAM is taken by brush border of renal proximal tubular cells by an unidentified transporter for NAD synthesis. Kidneys can also synthetize NAD from tryptophan. There is decrease in NAD levels during kidney injury, which leads to decrease energy production and impaired kidney functions of solutes transport. Additionally, a reduced NAD level during kidney injury is associated with reduced PGC-1α, leading to impaired mitochondrial biogenesis and its deficiency also increases local inflammation in kidney injury [17].

CKD is characterized by inflammation, oxidative stress and fibrosis which are highly linked to PARP and NF-KB activation. Also, SIRT1 dysfunction and low levels has been reported in diabetic nephropathy and supplementation of SIRT1 agonist improved renal function, decreased inflammation and preserved kidneys**.** Additionally, SIRT1 activation decreased renal fibrosis. So, SIRT1 activation and PARP inhibition mediated by NAM administration may prevent and decrease progression of CKD [10]. CKD is also characterized by hyperphosphatemia, NAM prevented its development by decreasing phosphate uptake in renal tubules and intestine [18]**.**

Interestingly, **Liu *et al.*** [19] and **Faivre *et al.*** [20] concluded that impairment of NAD synthesis is present in CKD. Additionally**, Zheng *et al.*** [21] lowered renal fibrosis by decreasing tubular shrinkage, degeneration, and apoptosis, as NAM supplementation was hypothesised to do. During unilateral ureteral obstruction, NAM significantly reduced the expression of proinflammatory cytokines including TNF- and IL-1 in renal tissues, demonstrating its anti-inflammatory properties. Recently**, Kumakura *et al.*** [22] found that Even though NAM slowed the development of chronic kidney injury in adenine-treated mice, it plays no part in the later stages of the illness.

So, **Fontecha-Barriuso *et al.*** [17] suggested that administration of Vit B3 and other $NAD^+$ precursors might have a role in kidney protection, so they recommended more studies to fully understand the dose, time and route of administration, the optimal molecules and the underlying mechanisms that protect the kidney (Figure 3).

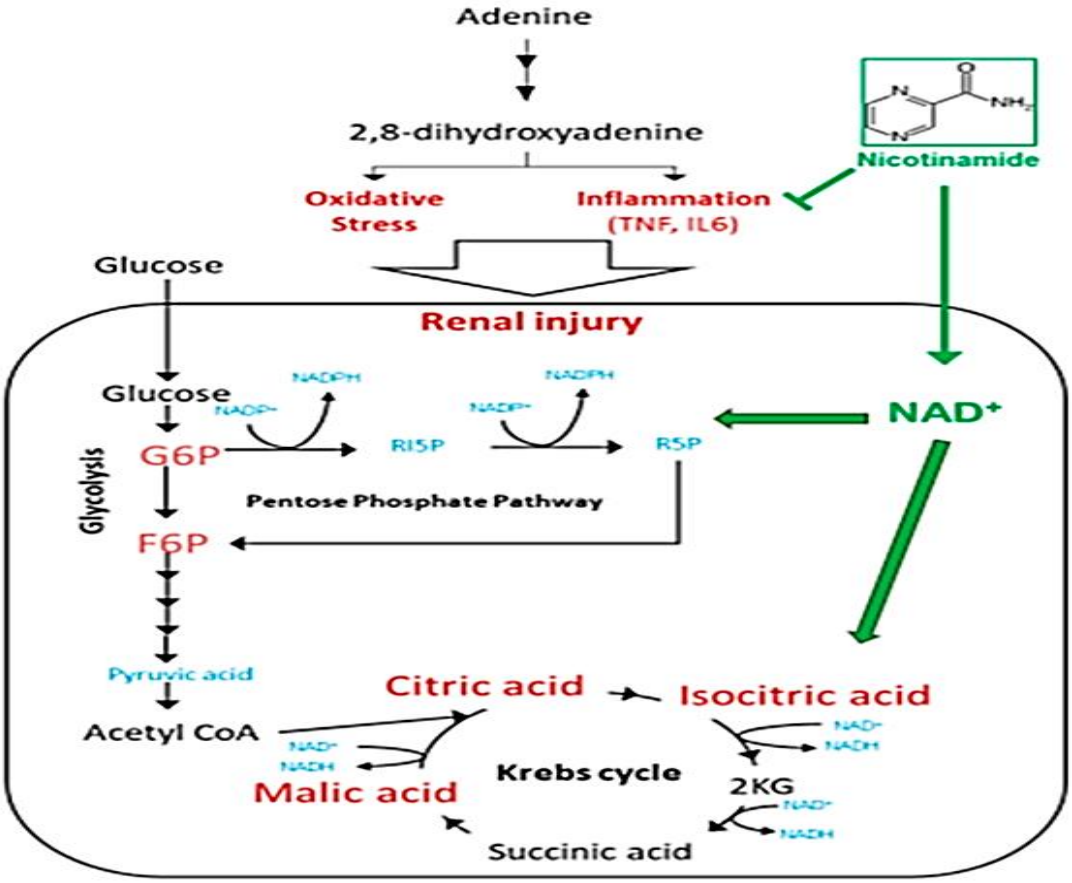


**Figure (3):** Mechanism of NAM-induced renoprotection

Several studies have demonstrated that NAD+ or its metabolites slow the development of acute renal illness when given as a supplement. A decrease in inflammation and production of reactive oxygen species have both been linked to increased NAD+ levels, which have been shown to activate sirtuin, a family of NAD+-consuming enzymes [23]. We showed that in an acute kidney injury model, increasing NAD+ production had a renoprotective impact [24], including the animal model of diabetic kidney dysfunction [25]. Few research, however, have looked at NAM's effects in CKD models. In a recent investigation on rats with unilateral ureteral obstruction (UU'O), it was found that administering NAM before to UU'O surgery reduced inflammation induced by IL-1 beta, therefore preventing renal fibrosis [21]. Confirming our findings that renal inflammation and fibrosis can be avoided with continuous NAM treatment. Supplementing with NAM in a rat model of advanced adenine-induced chronic kidney disease showed decreased phosphate buildup and decreased rise of serum creatinine and blood urea nitrogen [18].

Supplementation with NAM decreases phosphate buildup and increases creatinine clearance, as shown in an adenine-induced CKD rat model [18]. It was shown that prophylactic elevation of plasma creatine and urea nitrogen was avoided because inflammation and fibrosis in the kidneys were slowed by treatment with NAM. Further, the renoprotective benefits of NAM varied with dosage. NAM's plasma concentration was raised after low dose injection but returned to normal after greater dose administration, which was a surprising finding. These findings revealed a heightened need for NAD+ and hence, a higher incidence of NAM consumption in patients with early-stage kidney illness. However, the demand for elevated NAD+ production might not be met by low-dose NAM administration. As a result of the latter, unutilized NAM builds up in plasma and the supply of NAD+ is insufficient to prevent the deterioration of renal function. NAM is included in the list of uremic toxins [26]. Since its byproducts have been linked to decreased renal function [27]. The therapeutic benefits of NAM require that the appropriate dosages be carefully evaluated.

**NAM Administration Did Not Exert Beneficial Effects in Mice with Advanced Kidney Disease:**

The majority of the prior research into the effects of NAM or NAD+ derivatives in animal models of renal illness treated the animals at either an early stage of disease or prophylactically to prevent the start of disease. It was also discovered that studies of NAM's effects were conducted in more severe disease models. It was found that a high dose of NAM given via drinking water was intolerable in patients with a kidney illness that was progressing. For those with advanced kidney illness, it's important to note that excessive doses of NAM may cause a slew of unwanted side effects. By the time we began giving the NAM to the RF + NAM mice, their water consumption had already increased. As a result, post-intervention, a subset of mice took on a NAM-heavy diet. Particularly, on day one after treatment, mice with severe kidney disease given 0.6% NAM assumed over 2500 mg/kg/day nicotinamide (data not shown), while mice given 1.2% NAM assumed over 4000 mg/kg/day nicotinamide [28]. It appears that the NAM consumption in the 1.2% treatment group was higher above the safe limit. Renal tubule cells participate in the ubiquitous process of NAD+ synthesis, hence it is these cells that supply the kidneys with the NAD+ they require. Consequently, the renal tubule cells' damage prevented them from producing enough NAD+ to meet the body's needs. When comparing RF + NAM animals given the same 1.2% NAM at the onset of CKD, it appears that NAD+ production may be impaired in the former group. Perhaps this is why giving NAM at a later stage of a disease's progression did not help. However, imply that indoxyl sulphate buildup was mitigated by the administration of NAM at a concentration of 0.3%. To thoroughly confirm the efficacy of this chemical in advanced disease, it is necessary to additionally examine the effects of lower NAM dosages [28].

## CONCLUSION

NAM and its precursor NAD+ are cosubstrates for multiple regulatory proteins that improve various metabolic dysfunctions including kidney disease and extend cellular life span. The kidney is a metabolically active organ dependent on tissue NAD+ levels, thus NAD and its metabolites have important role in kidney disease. Sirtuins (SIRT1 and SIRT3), which are NAD+ -dependent deacetylases proteins activation and PARP inhibition mediated by NAM administration may prevent and decrease progression of CKD. Notably, there was a reduction in the buildup of glycolysis and Krebs cycle metabolites, which develop in renal failure, after supplementation with NAM. In this case, the increased availability of NAD+ sped up the metabolic pathways that used NAD+ as a fuel source, producing the observed results. It has been proposed that taking NAM could be an innovative therapeutic strategy for preventing CKD.

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