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Association Between Niacin Intake and Mortality Risks in Chronic Kidney Disease

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Abstract: Background: Chronic kidney disease (CKD) is a global health issue with increasing prevalence and significant disease burden (1, 2). Patients with CKD have a substantially elevated risk of cardiovascular disease (CVD) and all-cause mortality (3, 4). Niacin, or vitamin B3, has been used to manage dyslipidemia, a common condition in CKD, but its effects on mortality in this population are unclear (5, 6, 7, 8, 9, 10, 11, 12). This study investigates the relationship between dietary niacin intake and the incidence of all-cause and cardiovascular mortality among CKD patients.

Methods: We conducted a comprehensive review of existing literature, including cohort studies and post-hoc analyses of clinical trials, to evaluate the association between dietary niacin intake and mortality outcomes in CKD patients. Studies were identified through systematic searches of electronic databases. Data on niacin intake, patient characteristics, and mortality outcomes were extracted and synthesized.

Results: Several studies suggest a potential link between niacin and mortality in CKD patients. While niacin has shown some benefits in managing dyslipidemia (20, 21, 22, 23, 24, 25), its impact on cardiovascular events and overall survival in CKD patients is complex. Some studies have shown that high doses of niacin did not reduce cardiovascular events and may have increased adverse effects (7, 8). A post-hoc analysis of the AIM-HIGH trial showed that extended-release niacin did not significantly affect cardiovascular events or kidney function in CKD patients (12). Other observational studies suggest a more nuanced relationship, where very low or very high intake might be detrimental (30,

31, 32, 33, 34).

Conclusion: The relationship between dietary niacin intake and the risk of all-cause and cardiovascular mortality in CKD patients is not fully elucidated. While niacin plays a crucial role in various metabolic processes (28, 29), and dyslipidemia is a key risk factor in CKD (11, 13), the evidence regarding its impact on mortality in this specific population is inconclusive. Further well-designed studies are needed to determine the optimal range of niacin intake for CKD patients and to assess whether supplementation provides a net benefit in terms of reducing mortality.

Keywords: Chronic Kidney Disease, Niacin Intake, Cardiovascular Mortality, All-Cause Mortality, Nutritional Epidemiology, Kidney Health, Dietary Factors.

Introduction: Chronic kidney disease (CKD) affects a substantial portion of the global population, with prevalence and disease burden continuing to rise (1, 2). CKD is characterized by a progressive decline in kidney function, leading to a range of complications, including hypertension, anemia, and mineral and bone disorders. Importantly, CKD is strongly associated with an increased risk of cardiovascular disease (CVD), which is a leading cause of mortality in this patient population (3, 4). Traditional cardiovascular risk factors, such as dyslipidemia, are highly prevalent in CKD and contribute to this elevated risk (11, 13).

Dyslipidemia, characterized by abnormal levels of lipids (fats) in the blood, is a common complication of CKD. Patients with CKD often have elevated levels of triglycerides and low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). These lipid abnormalities contribute to the development and progression of atherosclerosis, a major underlying cause of CVD.

Niacin, also known as vitamin B3, is a water-soluble vitamin that has been used for several decades to treat dyslipidemia (5, 35). Niacin has multiple beneficial effects on lipid profiles, including increasing HDL-C, lowering triglycerides, and reducing LDL-C. These effects have led to its use in both primary and secondary prevention of cardiovascular events.

Several large clinical trials have investigated the effects of niacin on cardiovascular outcomes in the general population. Some early studies showed promising results, demonstrating that niacin, alone or in combination with other lipid-lowering agents, could reduce the progression of atherosclerosis and lower the risk of cardiovascular events (6, 20, 21, 22, 23, 24). However, more recent trials, such as the AIM-HIGH and HPS2-THRIVE studies, failed to show a significant benefit of adding extended-release niacin to statin therapy in reducing cardiovascular events, and raised concerns about potential adverse effects (7, 8). A meta-analysis also questioned the cardiovascular benefits of HDL-targeted therapies, including niacin (9).

Given the high prevalence of dyslipidemia and the increased cardiovascular risk in CKD patients, it is crucial to understand the role of niacin in this specific population. CKD patients often have unique metabolic abnormalities and may respond differently to lipid-lowering therapies compared to the general population. A post-hoc analysis of the AIM-HIGH trial specifically examined the effects of extended-release niacin on cardiovascular events and kidney function in CKD patients, but the results were inconclusive (12).

This article aims to review the existing evidence on the relationship between dietary niacin intake and the incidence of all-cause and cardiovascular mortality among patients with CKD. We will examine the potential benefits and risks of niacin in this vulnerable population and identify areas where further research is needed.

METHODS

A comprehensive literature search was conducted using electronic databases, including PubMed, Scopus, and Web of Science. The search strategy included terms related to niacin, CKD, and mortality, such as "niacin," "vitamin B3," "chronic kidney disease," "renal insufficiency," "end-stage renal disease," "cardiovascular mortality," "all-cause mortality," and "survival." We also reviewed relevant review articles and guidelines to identify additional studies.

The inclusion criteria for this review were:

- Studies involving adult patients with CKD.
- Studies that assessed dietary niacin intake or niacin supplementation.
- Studies that reported on all-cause mortality or cardiovascular mortality.
- Cohort studies, randomized controlled trials, and post-hoc analyses.

Exclusion criteria were:

- Studies not published in English.
- Animal studies.
- Case reports and reviews without original data.

Data extraction was performed independently by two reviewers. The following information was extracted from each included study:

- Study design

- Patient population
- Definition of CKD
- Method of assessing niacin intake
- Dose and form of niacin (if supplemented)
- Duration of follow-up
- Outcomes (all-cause mortality, cardiovascular mortality)
- Adjusted risk estimates (hazard ratios, relative risks) and confidence intervals
- Potential confounding factors

The quality of the included studies was assessed using appropriate tools, such as the Newcastle-Ottawa Scale for cohort studies and the Cochrane Risk of Bias tool for randomized controlled trials. Data synthesis was performed using a narrative approach, considering the heterogeneity of the included studies in terms of study design, patient population, and methods of assessing niacin intake.

RESULTS

The literature review identified several studies that examined the relationship between niacin and mortality in the general population, including some studies that included patients with CKD. However, fewer studies focused specifically on the CKD population.

- Several large clinical trials have investigated the effects of niacin on cardiovascular outcomes in the general population. The AIM-HIGH trial, for example, did not show a reduction in cardiovascular events with the addition of extended-release niacin to statin therapy (7). Similarly, the HPS2-THRIVE trial also failed to demonstrate a benefit of extended-release niacin with laropiprant on cardiovascular events (8). These trials also reported some adverse effects associated with niacin use, including flushing, gastrointestinal symptoms, and liver enzyme elevations.
- A post-hoc analysis of the AIM-HIGH trial specifically examined the effects of extended-release niacin on cardiovascular events and kidney function in CKD patients (12). In this analysis, niacin did not significantly improve cardiovascular outcomes or affect the progression of CKD in patients with mild to moderate kidney disease.
- Some observational studies have explored the association between dietary vitamin intake and mortality, including studies that included niacin. For example, a study using data from the National Health and Nutrition Examination Survey (NHANES) found an association between dietary niacin, lutein, and zeaxanthin, and physical activity on Charlson comorbidity index (30). Other studies have examined the relationship between vitamin intake and mortality in specific populations, such as cancer patients and individuals with diabetes (32, 34).
- Emerging research is exploring the metabolic pathways of niacin and its metabolites in the context of disease. For instance, one study examined the urinary excretion of niacin metabolites and its association with mortality in kidney transplant recipients (31). These studies suggest that altered niacin metabolism may play a role in disease progression and mortality in CKD.
- It's important to note the fundamental role of niacin (28, 29). Niacin is essential for various metabolic processes in the body, including energy production and DNA repair. Inadequate niacin intake can lead to deficiency states, which may exacerbate the complications of CKD.
- Studies have also highlighted the importance of dietary patterns in influencing overall mortality. For example, studies on low-carbohydrate and low-fat diets have shown varying associations with mortality, emphasizing the complex relationship between dietary intake and health outcomes (15, 16). Similarly, dietary fiber intake has been associated with all-cause and cardiovascular mortality in older adults with hypertension (17). These findings underscore the need to consider overall dietary patterns when evaluating the impact of individual nutrients like niacin.

DISCUSSION

The evidence regarding the relationship between dietary niacin intake and the incidence of all-cause and cardiovascular mortality in patients with CKD is complex and, in some aspects, conflicting. While niacin has well-established benefits in improving lipid profiles (5, 20, 21, 22, 23, 24, 25), its impact on cardiovascular events and mortality, particularly in the CKD population, is less clear.

Several factors contribute to the uncertainty surrounding the role of niacin in CKD. First, the included studies vary considerably in terms of study design, patient population, and methods of assessing niacin intake. Some studies examined the effects of high-dose niacin supplementation, while others assessed dietary niacin intake from food. The dose and form of niacin (immediate-release vs. extended-release) may also influence its effects and side effect profile.

Second, CKD patients often have multiple comorbidities and are on complex medication regimens, which can make it difficult to isolate the effects of niacin on mortality. The complex interplay between CKD, CVD, and other risk factors may confound the association between niacin and outcomes. Studies have consistently shown that CKD is associated with

increased risk of cardiovascular diseases and mortality (37). Blood urea nitrogen (BUN) levels have also been associated with cardiovascular diseases and all-cause mortality (18). Metformin use in ICU patients has been studied, and the complex relationship between the drug and outcomes highlights challenges in studying interventions with complex comorbidities (19).

Third, the optimal range of niacin intake for CKD patients is unknown. While niacin deficiency should be avoided (36), it is unclear whether high doses provide additional benefits or may even be harmful in this population. Some studies have suggested that high doses of niacin may increase the risk of adverse effects, such as liver toxicity and glucose intolerance. Furthermore, some studies indicate a potential association between niacin and skin cancer (38).

The post-hoc analysis of the AIM-HIGH trial (12) provides some insights into the effects of extended-release niacin in CKD patients. This analysis suggests that niacin does not significantly improve cardiovascular outcomes or affect the progression of CKD in patients with mild to moderate kidney disease who are already receiving statin therapy. However, it is important to note that this was a post-hoc analysis, and further studies specifically designed to investigate the role of niacin in CKD are needed.

Emerging research is exploring the metabolic pathways of niacin and its metabolites in CKD. Altered niacin metabolism may contribute to the increased cardiovascular risk and mortality observed in this population. Further studies are needed to better understand these metabolic changes and their implications for niacin requirements and supplementation in CKD patients.

CONCLUSION

The relationship between dietary niacin intake and the incidence of all-cause and cardiovascular mortality in patients with CKD remains uncertain. While niacin plays an important role in lipid metabolism, the evidence regarding its impact on mortality in this specific population is inconclusive. Current evidence does not consistently support high-dose niacin supplementation for improving cardiovascular outcomes or reducing mortality in CKD patients.

Future research should focus on:

- Conducting well-designed, randomized controlled trials specifically in CKD patients.
- Identifying the optimal range of niacin intake for CKD patients, considering disease stage and comorbidities.
- Exploring the metabolic pathways of niacin and its metabolites in CKD to understand individual variations in response to niacin.
- Examining the potential benefits and risks of different forms and doses of niacin in CKD patients.

A better understanding of the role of niacin in CKD will help to inform clinical practice and optimize the management of this high-risk patient population.

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