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Serum uric acid and mortality risk among maintenance hemodialysis patients

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Our understanding of the role of serum uric acid in the general population has changed since the 1950s [1]. Hyperuricemia was originally considered to be a consequence of renal insufficiency and associated with a variety of cardiovascular diseases, and several studies suggested that hyperuricemia can cause hypertension, renal insufficiency and metabolic syndrome. However, the role of serum uric acid remains unclear in the maintenance hemodialysis (MHD) patient population.

In the MHD population, traditional cardiovascular risk factors, such as body mass index (BMI), serum cholesterol, and blood pressure were paradoxically associated with better outcomes [2]. This evidence for “reverse epidemiology”, is partly explained by the presence of ‘malnutrition-inflammation complex syndrome’ among the MHD patients. Uremic malnutrition, which is now referred to as “protein-energy wasting” (PEW), leads to low BMI and hypocholesterolemia and is common in dialysis patients. PEW is caused by inadequate nutrient intake, nutrient

loss during dialysis, hyper-catabolism associated with dialysis, metabolic acidosis, and endocrine disorders of uremia. PEW has wide overlap with inflammation and other etiologic factors which can be used as assessment tools; this association between PEW and inflammation is believed to be the main cause of cardiovascular disease.

Recently, the role of uric acid has also been re-evaluated in the context of other traditional and non-traditional risk factors in the MHD population. Several studies have found that serum uric acid concentrations were closely correlated with nutritional parameters, including dietary protein intake as measured by normalized protein catabolic rate (nPCR), BMI, albumin and phosphorus and that low serum uric acid concentrations were associated with higher mortality, especially among patients with lower protein intake as reflected by nPCR [3]. Furthermore, nPCR underestimates protein intake among patients with substantial residual renal function if renal urea clearance is not taken into account; therefore, serum uric acid may be an alternative laboratory marker of nutrition intake, compared to nPCR, when patients have substantial residual renal function. The relationship between low serum uric acid and ‘malnutrition-inflammation complex syndrome’ may be responsible for this newly discovered ‘reverse epidemiology’ phenomenon.

In this issue of *Kidney Research and Clinical Practice*, Kim et al [4] examined the relationship between serum uric acid concentrations with all-cause mortality using a retrospective analysis of the data from 7,333 MHD patients documented in the End-Stage Renal Disease

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(ESRD) Registry of the Korean Society of Nephrology. Serum uric acid concentrations closely correlated with other nutritional markers such as BMI, nPCR, and phosphorus levels. Hyperuricemia was associated with lower all-cause mortality risk in both unadjusted and multivariable adjusted models including BMI, serum albumin and presence of residual renal function. This study provides evidence that supports the role of serum uric acid as a nutritional marker and a reverse mortality predictor (i.e., the higher, the better) in the MHD population.

There are several limitations that restrict the generalization of these findings. First, the included patients that had available serum uric acid data had shorter durations of hemodialysis, better nutritional status, including higher BMI, nPCR, hemoglobin, albumin, phosphorus and cholesterol, and a lower residual renal function, compared to the excluded patients, which might reflect selection bias. Considering the voluntary enrollment of data from different dialysis facilities in South Korea, the effect of information bias could not be ruled out and missing serum uric acid data might be related to unobserved reasons, such as differences in clinical practice patterns across the dialysis facilities, registry entry period, or socioeconomic status. Although the authors observed a consistent result in a sensitivity analysis, including those patients with missing serum uric acid, after adjusting for information bias by using multiple imputations, the missing frequency was somewhat high, therefore selection bias could not be ruled out.

The relationship between high serum uric acid and mortality remains controversial in other studies. One study showed high serum uric acid in hemodialysis patients that correlated with an increased risk for death [5]. Another study found a J-shaped association between serum uric acid and mortality in incident peritoneal and hemodialysis patients [6]. Among the peritoneal dialysis patients, the high uric acid was correlated with higher all-cause mortality [7]. Serum uric acid levels were associated with higher mortality which can be understood in the same context of other cardiovascular risk factors. Many research studies have shown that elevated uric acid levels indicate endotoxin and pro-inflammatory factors, which can accelerate decline in renal function, and even cause *de novo* kidney disease, by activating the renin-angiotensin system and progress to preglomerular vasculopathy [1]. However, it is still unclear whether hyperuricemia

can cause further damage to established and progressed renal disease in dialysis patients.

In comparison, the Dialysis Outcomes and Practice Patterns Study [8] and a prospective observational study among MHD patients [9] reported that higher uric acid levels were associated with lower risk of all-cause mortality and cardiovascular mortality. These conflicting observations may be caused by, at least in part, differences in treatment modality such as hemodialysis versus peritoneal dialysis, high serum uric acid, levels of residual kidney function, and the proportion of patients with 'malnutrition-inflammation complex syndrome' in the study populations. However, the results did not indicate a causal relationship. Therefore, additional studies are needed to examine alternative mechanisms, such as the anti-oxidative property of uric acid [10].

For dialysis patients at risk for malnutrition, the short-term care approach to prioritize patient-centered outcomes can be important, and hence, therapies that can lower serum uric acid levels, including allopurinol, febuxostat, or dietary restrictions may not necessarily confer long-term benefits and can potentially be harmful for patients. Clinical trials are needed to elucidate the paradoxical role of uric acid in MHD patient outcomes, and basic science research, including animal models should continue to examine the underlying biologic mechanisms of uremic conditions.

Conflicts of interest

All authors have no conflicts of interest to declare.

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