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Serum uric acid as a clinically useful nutritional marker and predictor of outcome in maintenance hemodialysis patients

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ABSTRACT

Objective: The importance of serum uric acid (SUA) for the maintenance of a hemodialysis (MHD) population has not been well established. The aim of this study was to determine if SUA levels are associated with nutritional risk and consequently with adverse clinical outcomes in MHD patients.
Methods: This was a 2-y prospective observational study, performed on 261 MHD outpatients (38.7% women) with a mean age of 68.6 ± 13.6 y. We measured prospective all-cause and cardiovascular (CV) hospitalization and mortality, nutritional scores (malnutrition-inflammation score [MIS] and geriatric nutritional risk index (GNRI), handgrip strength (HGS), and short-form 36 (SF36) quality-of-life (QoL) scores.
Results: SUA positively correlated with laboratory nutritional markers (albumin, creatinine), body composition parameters, HGS ($r = 0.26$; $P < 0.001$) and GNRI ($r = 0.34$; $P < 0.001$). SUA negatively correlated with MIS ($r = -0.33$; $P < 0.001$) and interleukin-6 ($r = -0.13$; $P = 0.04$). Patients in the highest SUA tertile had higher total SF-36 scores ($P = 0.04$), higher physical functioning ($P = 0.003$), and role-physical ($P = 0.006$) SF-36 scales. For each 1 mg/dL increase in baseline SUA levels, the first hospitalization hazard ratio (HR) was 0.79 (95% confidence interval [CI], 0.68–0.91) and first CV event HR was 0.60 (95% CI, 0.44–0.82); all-cause death HR was 0.55 (95% CI, 0.43–0.72) and CV death HR was 0.55 (95% CI, 0.35–0.80). Associations between SUA and mortality risk continued to be significant after adjustments for various confounders including MIS and interleukin-6. Cubic spline survival models confirmed the linear trends.
Conclusions: In MHD patients, SUA is a good nutritional marker and associates with body composition, muscle function, inflammation, and health-related QoL, upcoming hospitalizations, as well as independently predicting all-cause and CV death risk.

Introduction

Plasma concentrations of albumin, prealbumin, transferrin, creatinine, cholesterol, and bicarbonate are currently considered the most widely accepted laboratory parameters for diagnosing protein–energy wasting (PEW) and are one of the strongest predictors of adverse outcomes [1,2] in maintenance hemodialysis (MHD) patients [3,4]. The intensive study of the clinical implications of these biomarkers in MHD patients caused the study of uric acid (UA) to remain in the shadows. Consequently, its importance as a marker for the MHD population remains unclear.

Uric acid is the end product of purine breakdown and is linked to gout, a common form of arthritis [5]. High circulating

IB designed, organized, and coordinated the study; managed data entry; contributed to the analysis and interpretation of data; and wrote the manuscript. IS and JS carried out the immunoassays, contributed to the analysis and interpretation of data and wrote the manuscript. AA carried out the nutrition assessment (food-intake analysis, body composition assessment) and contributed to the analysis and interpretation of data and wrote the manuscript. GS, KS, and LF managed data entry, and contributed to the analysis and interpretation of data. ZA contributed to the analysis and interpretation of data and wrote the manuscript. All authors read and approved the final manuscript. The authors have no conflicts of interest to declare.

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concentrations of UA have been shown to be associated with an increased risk for hypertension [6,7], prehypertension [8], peripheral arterial disease [9], diabetes mellitus [10], chronic kidney disease [11], and cardiovascular disease (CVD) in the general population [6,12,13]. Because the kidney eliminates much of the generated UA, hyperuricemia is common in patients with end-stage kidney disease (ESKD) undergoing treatment by both HD [14,15] or peritoneal dialysis (PD) [16]. However, only a few clinical studies tested the association of UA with prognosis in the ESKD population [14–18]. As in the general population, PD patients with higher serum UA (SUA) levels were found to have increased all-cause mortality [16]. However, studies in the HD population showed the reverse. The common denominator of all four studies performed on this topic [14,15,17,18] was that low SUA is a mortality risk factor in HD patients. With regard to higher SUA levels, the data is controversial. Two of the studies [14,15] reported a J-shaped association between UA and mortality in HD patients with a higher mortality risk associated with higher UA levels. Results reported elsewhere were not conclusive about high levels of SUA [18]. The recently reported analysis of the international DOPPS (Dialysis Outcomes and Practice Patterns Study) population [17], found higher UA levels associated with a lower risk for all-cause and CV mortality, supporting the concept of "reverse epidemiology" [19] for the association between UA and survival in HD patients. Additionally, a recent small study reported an inverse association of SUA levels with acute ischemic stroke morbidity in HD patients [20]. To explain the inverse association of UA levels with survival, two of these studies [17,18] suggested that higher UA among HD patients is an indicator of better nutritional status, although they presented only limited evidence to support this claim, showing only associations of UA with laboratory nutritional markers. Positive associations between elevated SUA levels and higher levels of meat consumption [21], higher body mass index (BMI), and fat mass (FM) as parts of metabolic syndrome (MetS) [22] in the general population have been described, which might have led to this assumption. In reviewing the literature, we did not find any information regarding the association between UA and nutritional status in HD patients.

We therefore aimed to investigate the associations between SUA levels and clinical and laboratory surrogates of nutrition and inflammation, muscle function, health-related quality of life, and all-cause and CV morbidity and mortality in MHD patients.

Materials and methods

Patients

This prospective observational study was approved by the Ethics Committee of Assaf Harofeh Medical Center, Zerifin (affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Israel). Inclusion criteria were outpatients who underwent MHD for ≥8 wk, were ≥18 y and signed a local institutional review board–approved consent form. Patients with an anticipated life expectancy <6 mo (e.g., because of a metastatic malignancy) were excluded. Exclusion criteria at the entry of the study were also comorbidity (autoimmune disease or acute infections, or both) and medications (prednisone), as well as patients with amputations or any body deformities. In all, 261 patients undergoing MHD treatment at our outpatient HD clinic and at two satellite HD clinics (from the same region) were included in the study. The patients were recruited between October 2010 and April 2012, and were followed until June 2013 or were censored (kidney transplantation or loss to follow-up). Baseline study measurements (including laboratory parameters) were performed at enrollment. The patients were followed-up regarding survival and hospitalization from the time of enrollment in the study. The median duration of the study was 17 mo (interquartile range 9–24 mo). During this period, 64 patients (24.5%) died (the main causes of death were CVD: 31 of 64 deaths; 48.4% and sepsis: 17 of 64 deaths; 26.6%); 6 patients (2.3%) underwent kidney transplantation, 2 patients (0.8%) changed dialysis modality, and 2 others (0.8%) transferred to other hemodialysis units. The causes of renal failure included diabetic kidney disease (50.6%), hypertension (30.7%), glomerulonephritis (6.1%), autosomal-dominant polycystic kidney disease (3.1%), obstructive uropathy (2.7%), and other diseases or unknown causes (6.9%).

All patients underwent regular dialysis via their vascular access (58.2% of patients had arteriovenous fistula and 15.7% had arteriovenous grafts) for 4 h three times per week. The dialysis efficiency was assessed based on the delivered dose of dialysis (Kt/V urea) using a single-pool urea kinetic model (mean Kt/V was1.32 ± 0.31 in this population). The Kt/V values were calculated using the second-generation Daugirdas' formula as recommended by the Disease Outcomes Quality Initiative guidelines. At the start of the cohort, all study participants performed midweek interdialytic urine collection for measurement of urine output. Urine output was expressed as mL/24 h. Residual renal function (RRF) was defined as measured urine volume >200 mL/d.

Dietary intake

Continuous 3-d dietary histories (including a dialysis day, a weekend day, and a non-dialysis day) were self-completed in a food diary. The methods used for collecting the dietary recalls for patients with chronic kidney disease were the same as recently described elsewhere [23]. Dietary energy and protein intake were calculated and normalized for ideal body weight according to the European Best Practice Guidelines [24]. Ideal weight in the present study was calculated from the Lorentz equations differently for men and women. Dietary intake was calculated using computerized analysis (DOS-based program "MANA," specially adapted for data entry and analysis of food intake records). This program was developed by the Israeli Food and Nutrition Administration based on the Food Intake Analysis System of the U.S. Department of Agriculture [25] and especially adapted to meet the needs of the Israeli population.

Dietary protein intake was also estimated by calculating normalized protein nitrogen appearance (nPNA) from the patient's urea generation rate by using urea kinetics modeling [26]. Single-pool model urea kinetics was used to estimate the nPNA.

Anthropometric measurements and handgrip strength

BMI, triceps skinfold (TSF) thickness, mid arm circumference (MAC), and calculated mid-arm muscle circumference (MAMC) were measured as anthropometric variables. MAMC was estimated as follows:

$$\text{MAMC (cm)} = \text{MAC (cm)} - 0.314 \times \text{TSF (mm)}.$$

All measurements were made after dialysis when the patient was at dry weight (the right upper arm was used whenever possible, with exceptions made for patients in whom dialysis access placement, injury, or stroke precluded measurement). The same trained dietitian performed all anthropometric measurements.

Handgrip strength (HGS) was evaluated in both the dominant and nondominant arms using the Harpenden Handgrip Dynamometer (Yamar, Jackson, MI, USA). HGS was repeated three times and the highest value was noted.

Nutritional scores

The malnutrition-inflammation score (MIS) has been described in detail in several previous studies [27,28].

The geriatric nutritional risk index (GNRI) was calculated from the patient's serum albumin, body weight, and height using the equation developed previously [29] by modifying the nutritional risk index for elderly patients.

Short-form 36 quality-of-life scoring system

The Short-Form 36 (SF36) is a short form of the health-related quality-of-life (QoL) scoring system with only 36 items that includes eight independent scales. It is a well-documented, self-administered questionnaire and has been widely used and validated in MHD patients [30]. The eight scales of SF36 are summarized into two dimensions: Physical health and mental health.

Body composition analysis

Body composition was determined by body impedance analysis (BIA; Nutriguard- M, Data-Input, Frankfurt, Germany). Following the recommendations for clinical application of bioelectrical impedance analysis [31], we performed BIA at ~30 min after dialysis. The BIA electrodes were placed on the nonaccess side of the patient (used also for anthropometric measurements) and the patients were in a supine position for at least 5 min before the measurement. The multifrequency technique (using three frequencies: 5, 50 and 100 kHz) has been used to estimate the total body water (TBW), extracellular water (ECW), FM, and lean body mass (LBM). These estimates were obtained with the NutriPlus software, version 5.1 (Data Input GmbH, Germany).