Relationship of Impaired Olfactory Function in ESRD to Malnutrition and Retained Uremic Molecules

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Background: Olfactory function is impaired in patients with end-stage renal disease (ESRD) and may contribute to uremic anorexia. Only limited correlations of olfactory function and nutritional status were reported. This study examines the relationship of impaired olfactory function to malnutrition and levels of the retained uremic solutes monomethylamine, ethylamine, indoxyl sulfate, and P-cresol sulfate.

Study Design: Cross-sectional observational study.

Setting & Participants: 31 stable maintenance hemodialysis patients from an urban outpatient dialysis unit and 18 people with normal renal function participated.

Predictor: Nutritional status assigned by using Subjective Global Assessment (SGA) score; SGA score of 7 indicates normal nutritional status; SGA score of 5 to 6, mild malnutrition; and SGA score of 3 to 4, moderate malnutrition.

Outcomes & Measurements: The primary outcome is olfactory function, assessed using the University of Pennsylvania Smell Identification Test. Levels of retained uremic solutes were measured from a predialysis serum sample. Demographic data and laboratory values for nutritional status, adequacy of dialysis, and inflammation were collected.

Results: Mean smell scores were 34.9 ± 1.4 for controls, 33.5 ± 3.3 for patients with SGA score of 7, 28.3 ± 5.8 for patients with SGA score of 5 to 6, and 27.9 ± 4.4 for patients with SGA score of 3 to 4 ($P <$ 0.001 comparing healthy patients with all patients with ESRD). There was no difference in mean smell scores for healthy controls and patients with SGA score of 7. However, patients with lower smell scores had significantly lower SGA scores ($P = 0.02$) and higher C-reactive protein levels ($P = 0.02$). Neither smell score nor nutritional status was associated with levels of retained uremic solutes.

Limitations: Small sample size, only cross-sectional associations can be described.

Conclusions: Our results suggest an association between poor nutritional status and impaired olfactory function in patients with ESRD. Additional research is needed to discover the uremic toxins mediating these processes.

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INDEX WORDS: Malnutrition; uremia; anorexia; olfaction; C-reactive protein; monomethylamine; ethylamine; indoxyl sulfate; P-cresol sulfate.

Malnutrition affects up to 75% of patients with end-stage renal disease (ESRD). Malnutrition begins as renal function decreases, and patients with chronic kidney disease (CKD) are known to have a progressive decrease in both protein and total caloric intake as glomerular filtration rate decreases.[1,2] When patients reach ESRD, the presence of malnutrition increases the risk of death, and in elderly dialysis patients, the rate of death with cachexia is increasing.[3,4] Despite the high prevalence of malnutrition in the ESRD population, our understanding of the mechanisms underlying the development of uremic anorexia is limited.

Multiple factors may contribute to the development of malnutrition in patients with ESRD. These include poor oral hygiene, gastrointestinal complications of comorbid diseases, abnormally increased levels of inflammatory cytokines, alterations in tryptophan and serotonin levels, alterations in leptin and ghrelin levels, and increased levels of such uremic toxins as indoles and middle molecules.[5-11] Alterations in taste and smell also were identified in uremic patients, but their relationship to malnutrition is unclear.[12-18]

Normal olfaction is required for full appreciation of the smell and taste of food. In elderly people in the general population, poor odor per-

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ception is associated with lower nutrient intake.[19] Research into olfactory function in patients with ESRD is limited.[13-18] Few correlations of olfactory function and nutritional status were reported. Of significant interest is the finding that odor perception is either the same or worse immediately after hemodialysis therapy, but is fully restored to that of healthy controls after renal transplantation.[15-17] This finding suggests that decreased olfactory function in patients with ESRD is caused by uremic toxins not adequately cleared with current dialysis techniques, but fully reversible with complete resolution of the uremic state.

Retained uremic toxins are of particular interest because these are small molecules that are not cleared with current dialysis technology because of either sequestration in intracellular compartments or extensive protein binding. Biologically plausible mechanisms linking some retained uremic molecules and uremic anorexia are known. Levels of aliphatic methylamines increased in patients with uremia.[20,21] Clearance studies of monomethylamine were consistent with the presence of an intracellular sequestered pool.[22] Simenhoff et al[23] showed that substances contributing to the fishy odor of "uremic breath" are dimethylamine and trimethylamine. Pirisino et al[24] showed that mice receiving an intracerebroventricular dose of monomethylamine became hypophagic.

P-Cresol sulfate and indican are small aromatic molecules with increased levels in patients with uremia that are not efficiently cleared during routine hemodialysis because of avid protein binding.[25] Bammens et al[26] showed in 175 dialysis patients that greater free P-cresol sulfate levels correlated with greater mortality, impaired nutritional status by Subjective Global Assessment (SGA) score, and higher malnutrition-inflammation score.

The purpose of this study is to examine the relationship of impaired olfactory identification to markers of malnutrition in patients with ESRD.

METHODS

Subjects

Thirty-one hemodialysis patients from a single center and 10 healthy controls participated in olfactory testing. Patients were recruited from October to December 2006 from an outpatient dialysis unit in the northeast Bronx. Inclusion criteria were being stable on dialysis therapy for more than 3 months, ability to give informed consent, and intact mental status, defined as a normal Mini-Mental Status Examination (MMSE) score. Exclusion criteria were hospitalization in the prior month, presence of active infection, cancer, cirrhosis, or age older than 70 years because olfactory function decreases markedly after age 70.[27] Demographic data, including age; sex; race; access type; current use of angiotensin-converting enzyme inhibitors, calcium channel blockers, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins); medical history of diabetes defined as need for diabetic medications or documented history of diabetes mellitus; coronary artery disease defined as history of angina, acute coronary syndrome, or coronary revascularization; hypertension defined as need for antihypertensive medications or increased blood pressure on more than 2 occasions; peripheral vascular disease defined as documented poor peripheral circulation, claudication, stasis ulcers, or history of peripheral revascularization or amputation; prior cerebrovascular accident defined as clinical history or brain imaging study; smoking status; and time on dialysis therapy, were collected by means of patient interview and chart review. Healthy controls were defined as having a Modification of Diet in Renal Disease Study equation estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater based on serum creatinine level. All participants gave written informed consent before participation. For hemodialysis patients, blood samples were drawn before the initiation of hemodialysis, and smell testing was performed during the dialysis procedure. The Institutional Review Board of Montefiore Medical Center, the Committee for Clinical Investigations of the Albert Einstein College of Medicine, and Fresenius Medical Care of North America approved this study.

Measurements

Nutritional status was determined using the SGA. The SGA is a validated technique for the evaluation of malnutrition in patients with ESRD.[28,29] This score takes into consideration elements of history and physical examination to define the degree of malnutrition. The 7-point SGA score was used, with a score of 7 indicating normal nutritional status; 5 to 6, mild malnutrition; 3 to 4, moderate malnutrition; and 1 to 2, severe malnutrition. The original intent of the study was to include 10 patients in each category. However, with the predefined exclusion criteria, patients with severe malnutrition could not be recruited. The final patient population included 11 patients with normal nutritional status (SGA score 7), 10 patients with mild malnutrition (SGA score 5 to 6), and 10 patients with moderate malnutrition (SGA score 3 to 4) for a total of 31 subjects with ESRD. SGA determination was performed by either of 2 physician investigators (A.C.R. and S.L.) before administration of the smell test. Other markers of dialysis adequacy and nutritional status, including body mass index (BMI), equilibrated urea amount cleared from plasma divided by distribution volume, normalized protein catabolic rate, creatinine, urea, total cholesterol, and albumin, were measured for the month the patient was enrolled in the study (Spectra East Labs, Rockleigh, NJ; Fresenius Medical Care, Waltham, MA). C-Reactive protein (CRP) was measured as a marker of inflammatory state (Spectra East Labs).