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

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Abstract

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 have been reported. This study examined 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 and Participants—31 stable maintenance hemodialysis patients from an urban outpatient dialysis unit and 18 people with normal renal function participated.

Predictor—Nutritional status as assigned by Subjective Global Assessment (SGA) score with SGA 7 indicating normal nutritional status, SGA 5 – 6 mild malnutrition, and SGA 3 – 4 moderate malnutrition.

Outcomes and Measurements—The primary outcome was olfactory function as assessed with the University of Pennsylvania Smell Identification Test. Levels of the retained uremic solutes were measured from a predialysis serum sample. Demographic data as well as lab values for nutritional status, adequacy of dialysis, and inflammation were collected.

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

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

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

Keywords

malnutrition; uremia; anorexia; olfaction; C-reactive protein; monomethylamine; ethylamine; indoxyl sulfate; P-cresol sulfates

INTRODUCTION

Malnutrition affects up to 75% of patients with end stage renal disease (ESRD). Malnutrition begins as renal function declines and patients with chronic kidney disease (CKD) are known to have a progressive decline in both protein and total caloric intake as GFR declines.^{1,2} Once patients reach ESRD the presence of malnutrition increases the risk of death and in elderly dialysis patients the rate of deaths 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 remains limited.

Multiple factors may contribute to the development of malnutrition in ESRD patients. These include poor oral hygiene, gastrointestinal complications of co-morbid diseases, abnormally elevated levels of inflammatory cytokines, alterations in tryptophan and serotonin levels, alterations in leptin and ghrelin levels, and elevated levels of uremic toxins such as indoles and middle molecules.^{5–11} Alterations in taste and smell have also been 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. Among elderly people in the general population poor odor perception is associated with lower nutrient intake.¹⁹ Research into olfactory function in ESRD is limited.^{13–18} Few correlations of olfactory function and nutritional status have been reported. Of significant interest is the finding that odor perception is either the same or worse immediately after hemodialysis but fully restored to that of normal controls after renal transplantation.^{15–17} This finding suggests that reduced olfactory function in ESRD is due to 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 as these are small molecules that are not cleared with current dialysis technology due either to sequestration in intracellular compartments or to extensive protein binding. Biologically plausible mechanisms linking some retained uremic molecules and uremic anorexia are known. The aliphatic methylamines are elevated in uremia.^{20,21} Clearance studies of monomethylamine are consistent with the presence of an intracellular sequestered pool.²² Simenhoff et al. demonstrated that the substances contributing to the fishy odor of “uremic breath” are dimethylamine and trimethylamine.²³ Pirisino et al. demonstrated that mice receiving an intracerebroventricular dose of monomethylamine become hypophagic.²⁴

P-cresol sulfate and indican are small aromatic molecules that are elevated in uremia and not efficiently cleared during routine hemodialysis due to avid protein binding.²⁵ Bammens et al. demonstrated in 175 dialysis patients that higher free P-cresol sulfate levels were correlated with higher mortality, impaired nutritional status by SGA score, and a higher malnutrition – inflammation score.²⁶

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

SUBJECTS and METHODS

Subjects

31 hemodialysis patients from a single center and 10 healthy controls participated in the olfactory testing. Patients were recruited from October – December 2006 from an outpatient dialysis unit in the Northeast Bronx. Inclusion criteria were being stable on dialysis for greater than three months, ability to give informed consent, and intact mental status defined by a normal Mini Mental Status Exam (MMSE) score. Exclusion criteria were hospitalization in the prior month, presence of active infection, cancer, cirrhosis, or age greater than 70 as olfactory function declines markedly after age 70.²⁷ Demographic data including age, gender, race, access type, current use of angiotensin converting enzyme inhibitors (ACEI), calcium channel blockers, HMG-CoA reductase inhibitors (statins), medical history of diabetes defined as need for diabetic medications or documented history of diabetes mellitus, coronary artery disease (CAD) defined as history of angina, acute coronary syndrome, or coronary revascularization, hypertension (HTN) defined as need for anti-hypertensive medications or elevated blood pressure on more than two occasions, peripheral vascular disease (PVD) defined as documented poor peripheral circulation, claudication, stasis ulcers, or history of peripheral revascularization or amputation, prior cerebrovascular accident (CVA) defined by clinical history or brain imaging study, smoking status, and time on dialysis was collected by patient interview and chart review. Healthy controls were defined as having a Modification of Diet in Renal Disease (MDRD) Study equation estimated GFR of 60 ml/min/1.73m² or greater based on serum creatinine. All participants gave written informed consent prior to participation. For the hemodialysis patients, blood samples were drawn prior to the initiation of hemodialysis and smell testing was done 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 Subjective Global Assessment. The SGA is a validated technique for the evaluation of malnutrition in ESRD patients.^{28,29} This score takes into consideration elements of history and physical exam to define the degree of malnutrition. The seven point SGA score was used with a score of 7 indicating normal nutritional status, 5 – 6 mild malnutrition, 3 – 4 moderate malnutrition, and 1 – 2 severe malnutrition. The original intent of the study was to include 10 patients in each category. However, with the pre-defined 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 – 6), and 10 patients with moderate malnutrition (SGA score 3 – 4) for a total of 31 subjects with ESRD. SGA determination was done by either of two physician investigators (ACR and SL) prior to administration of the smell test. Other markers of dialysis adequacy and nutritional status including body mass index (BMI), eKt/V, normalized protein catabolic rate (nPCR), 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). CRP was measured as a marker of inflammatory state (Spectra East Labs Rockleigh, NJ).

Olfactory function was tested with the University of Pennsylvania Smell Identification Test (SIT) at the beginning of the dialysis treatment. The SIT involves identification of 40 scratch and sniff odors. The SIT is a forced choice test in which the subject must select one of the possible four answers for each question. The score generated is a discrete numerical score of number of odors identified correctly out of 40. A smell score of 35 – 40 or 34 – 40 is considered normal for women and men in the general population, respectively.³⁰

Retained Uremic Solute Levels

Serum from each subject was stored at -70° centigrade and tested in batches for four small molecules: monomethylamine, ethylamine, indican, and p-cresol sulfate. Monomethylamine and ethylamine levels were measured by chromatography using a Shimadzu Prominence HPLC system that consisted of two LC-20AD pumps, a DGU-20A3 degasser, a SIL-20A auto sampler, and an RF-10AXL fluorescence detector. Separation was accomplished on a Phenomenex Onyx monolithic column (C-8, 150×4.6 mm) using an isocratic elution. The mobile phase consisted of 30% methanol (v/v), 30% acetonitrile (v/v), 20-mmol/L phosphate, and the pH was adjusted to 6.80. The flow rate was 1.0 mL/min. The wavelengths of the fluorescence detector for excitation and emission were $\lambda_{\text{ex}} = 420$ nm, $\lambda_{\text{em}} = 480$ nm, respectively. Determinations were duplicated. Peak area was used for quantification. Indican, and p-cresol sulfate were measured as previously described.²⁵

Statistical Analysis

All data was visually plotted and checked for consistency. Comparison between SGA categories was made using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Smell scores were compared across SGA categories using analysis of variance (ANOVA). Pearson's pair-wise correlations were performed to evaluate correlations between co-variables and smell score. Normality of smell scores was tested using the Shapiro-Wilk test and by visual inspection of a quantile normal plot. Unadjusted and adjusted linear regressions were performed to evaluate the associations between smell score and demographic, clinical, and laboratory data. To create a fully adjusted model, we included all co-variables that were associated with both smell score and SGA category at a p-value <0.3 cut-off. Because this included age, MMSE score, and smoking status, for the fully adjusted model we created a propensity score analysis. We ran a logistic regression to obtain a propensity score of being in the SGA 7 category using age, MMSE score, and smoking status. We then used SGA 7 category and the propensity score in another linear regression model. All analyses were performed using Stata release 9.0 (Stata Corp., College Station, TX).

RESULTS

Patient Characteristics by SGA Category

Patient characteristics are reported by SGA category in Table 1. The mean age was 50.8 years and the median time on dialysis was 38 months. 42% of the patients were women. The self-identified race of the patients was 58% black, 10% white, 29% Hispanic, and 3% Asian. All patients had a normal MMSE score. The mean age of the controls was 42.6 years. 50% were women. 50% of the controls were white, 30% Hispanic, and 20% Asian. The healthy controls had no reported medical history of HTN, CAD, CVA, or smoking habit. Patients with SGA category 5 – 6 were more likely to take a statin ($p=0.02$). There were no significant differences across categories in age, sex, race, type of access, use of ACEI or calcium channel blockers, presence of comorbid disease conditions, smoking category, MMSE score, or time on dialysis.

Adequacy of Dialysis and Nutritional Markers by SGA Category

The patients enrolled in the study were well dialyzed by current standards with the mean eKt/V for the total population of 1.38 ± 0.2 (Table 2). Within this relatively narrow range, SGA score did not correlate with eKt/V ($p = 0.9$). Higher SGA scores were significantly correlated to high BMI ($p = 0.002$), higher serum albumin ($p=0.02$), and lower percentage of patients having an elevated CRP ($p=0.02$). SGA score was not significantly correlated with nPCR, serum creatinine, serum urea, or serum cholesterol.

Smell Score by SGA Category

Mean smell scores were 34.9 ± 1.4 for normal controls, 33.5 ± 3.3 for SGA score 7 patients, 28.3 ± 5.8 for SGA score 5–6 patients, and 27.9 ± 4.4 for SGA score 3–4 patients (Figure 1). Smell score was normally distributed (Shapiro-Wilk test $p = 0.2$). Smell scores were higher in the normal controls compared to the entire population of ESRD patients ($p < 0.001$). There was no difference in mean smell score for normal controls compared to hemodialysis patients with SGA score of 7. However, significantly higher smell scores were seen in ESRD patients with higher SGA scores ($p = 0.02$) and this association remained significant after adjustment for age. By linear regression adjusted for age, for each 1 unit increase in SGA category, smell score is predicted to increase by 1.37 (95% CI 0.09–2.64, $p = 0.04$). Lower smell scores were also associated with elevated CRP values ($p = 0.02$). There was an association between smell score and mini-mental status exam score ($p = 0.03$). However, all mini-mental status scores were within the range of normal and this association was diminished when adjusted for age. By linear regression adjusted for age, for each 1 unit increase in MMSE score, smell score is predicted to increase by 1.35 (95% CI -0.014 –2.71, $p = 0.05$). In the propensity score analysis adjusted for age, MMSE score, and smoking status, being in the SGA 7 category was associated with a 3.85 point higher smell score compared to those with SGA scores 3–6 (95% CI 0.14–7.56, $p = 0.04$). There was no correlation between smell score and adequacy of dialysis eKt/V, BMI, albumin, nPCR, creatinine, urea, cholesterol, or use of ACEI, calcium channel blockers, or statins.

Retained Uremic Solutes

Serum levels of methylamine, ethylamine, indican, and p-cresol sulfate are significantly higher in patients with ESRD than normal controls (Table 3). Mean pre-hemodialysis levels for the entire population and across SGA categories are given in Table 4. There was no significant difference in these small molecule levels across SGA categories. In addition there was no association between smell scores and retained uremic solute levels.

DISCUSSION

Prior studies have examined odor detection, discrimination, and identification in CKD and ESRD patients (Table 5). Results for alteration in detection threshold have been mixed with Frasnelli and Vreman finding no difference in threshold detection using butanol Sniffin Sticks and pyridine sniff bottles but Griep reporting impaired threshold detection using isoamyl alcohol sniff bottles.^{14,17,18} All prior studies examining odor discrimination and identification, however, have found significant differences in odor discrimination and identification using butanol Sniffin Sticks, Isoamyl alcohol sniff bottles, commercial food flavors, and modified versions of the University of Pennsylvania Smell Identification Test.^{13,15–18} Griep et al. is the only group to report any associations of impaired olfactory function and nutritional state. They reported poor odor perception was associated both with elevated serum urea and higher protein catabolic rate. They found no correlation with BMI or serum albumin levels.¹⁷ Olfactory function worsens or does not improve 30 minutes after completion of a dialysis session,^{15–17} but patients with a renal transplant have normal odor detection.¹⁷

Our study is the first to use the University of Pennsylvania Smell Identification Test in its unmodified commercial form to evaluate odor identification in a population of ESRD patients. We found that as a group our ESRD patients had significantly impaired odor identification as compared to normal controls. However, we did not find a difference in olfactory function between the normal controls and the “healthiest” group of ESRD patients with an SGA score indicating normal nutritional status. This difference may be due to the small sample size of our study group or to differences in sensitivity of the SIT test vs. other tests of olfactory function. However, it is also possible that by grouping our ESRD patients by SGA score we are

uncovering a sub-population of ESRD patients that have preserved olfactory function. This is also the first study to demonstrate an association of worse olfactory function with higher CRP levels. This suggests that the pathologic changes underlying the malnutrition inflammation complex may also contribute to impaired olfactory function in ESRD patients.

The significance of the observed association of smell score and MMSE is uncertain. The strength of the association diminished with correction for age and all patients had a MMSE score in the normal range. Although it is known that lower GFR and ESRD are associated with cognitive defects,^{31,32} and diminished olfactory function is an early finding in Parkinson's, Alzheimer's, and other neurodegenerative disorders,³³ it is unlikely that the subtle differences found in this study are due to cognitive decline.

Full enjoyment and appreciation of food flavors requires both an intact olfactory and gustatory system. Taste buds perceive the basic tastes of salty, sweet, sour, and bitter while olfactory receptors can distinguish thousands of odorants. The neurologic pathways and higher processing centers are distinct.³⁴ It is estimated that olfaction is responsible for 75% of the interpretation of flavor.³⁵ This is of relevance when patients report alterations in taste as the underlying problem may actually be due to an olfactory disturbance. ESRD patients are known to have impaired taste sensation^{12,14} but confusion of taste and smell perception in objective clinical studies is unlikely as formal chemosensory testing isolates the sense in question through exposure to aerosolized odorants for smell or the direct application of taste solutions or electrical stimuli to the tongue for taste.³⁵

Multiple medications have reported alterations in sense of smell as side effects including three drug classes frequently used in ESRD patients: ACEI, calcium channel blockers, and statins. Interpreting the effect of medications as causal to chemosensory disturbance is difficult however, as there is lack of uniformity in reporting such side effects, little data on mechanisms, and few reports using standardized measurements of olfactory function.³⁶ One small study using quantitative measurement tools for both taste and smell assessment (including the SIT) found no differences in patients taking either captopril, lisinopril, or no ACEI.³⁷ 84% of our study patients were taking at least one medication in these categories. Patients with SGA 5 – 6 score were more likely to be taking a statin but there was no trend with malnutrition as statin use was similar in SGA 7 and SGA 3 – 4 patients. In addition there was no association between use of any of these medications and smell score. Thus it is unlikely that medication use accounts for the measured differences in smell scores in this study.

Despite previous work suggesting biologically plausible links between these molecules and malnutrition, we found no association between monomethylamine, ethylamine, total P-cresol sulfate, or indican and poor nutritional status defined by SGA category or impaired olfactory function. Our results differ somewhat from Bammens et al.²⁶ in that we found no relation of p-cresol sulfate to nutritional score. The studies differ in that ours was cross sectional and of smaller size. Also their assay was of free p-cresol and ours the total predominant sulfated form. Our finding of no relationship of indican to malnutrition is consistent with a randomized double blind placebo controlled study of 12 weeks treatment with an oral sorbent which binds indican in CKD patients that found no improvement in subjective or objective indicators of malnutrition including anorexia, serum albumin, prealbumin, or BUN levels.³⁸ Thus the results of our small study suggest that while these retention molecules may be uremic toxins, they may not be mediating their toxicity through malnutrition or alterations in olfactory function. Further research will be needed to discover the uremic toxins that contribute to malnutrition and alterations in olfactory function.

Although the small uremic molecules tested in this study did not correlate with impaired olfactory function, it is possible that as yet unidentified uremic toxins are responsible. Effects

of a uremic toxin on olfactory function could include disruption due to abnormal levels in an attempt to use the olfactory epithelium as a means of excretion as has been suggested for metabolites of toluene and xylene including hippuric acid,³⁹ changes in excitatory thresholds as have been demonstrated for serotonin and leptin,^{40,41} or neuromodulation of the olfactory message. Perhaps the most intriguing possibilities relate to the unique feature of vertebrate olfactory systems that the olfactory neurons are regenerated and replaced from stem cells for the life of the organism. Thus any toxin that either slows new cell growth or migration or increases cell death would be expected to impair olfactory function. Tumor necrosis factor alpha has been demonstrated to induce apoptosis in rat olfactory epithelium in vitro.⁴² Maintenance of redox homeostasis is essential for normal function and health of the olfactory epithelium and olfactory bulb. Toxins such as diethyldithiocarbamate (DDTC) and drugs such as propylthiouracil are known to interfere with antioxidant enzyme activity in the olfactory bulb and mucosa resulting in degeneration of the structures and impaired olfaction. Withdrawal of the toxin or drug results in regeneration over a four to six week period.^{43,44} These findings suggest a pathologic basis for our findings of a link between elevated CRP as a marker of oxidant stress and impaired olfactory identification in our patients and also provide a possible explanation of the observed time delay in recovery of olfactory function after renal transplant but not after a single hemodialysis session. To our knowledge, there are no published studies describing the structure of the olfactory epithelium or bulb in uremic animal models or humans.

There are several limitations to this study. The study population is small and only a single measurement of olfactory function was made. Prospective observations overtime would allow for a more robust association with malnutrition as well as allow correlation to outcomes such as worsening malnutrition, hospitalization rate, and mortality. In addition the only measurement of malnutrition used was the SGA. While this is validated in the ESRD population, additional determinants of nutritional status such as bio-impedance analysis of fat free body mass could have strengthened the findings especially as this is an obese and overweight patient population. The majority of the patients in this study were black and Hispanic from a socioeconomically disadvantaged urban area. This may limit the generalizability of our findings to white, Asian, or more affluent patients.

Our results confirm that smell identification is impaired in ESRD patients as a group. In addition, we have shown that impaired smell identification is not found in ESRD patients with a normal nutritional status but is impaired in patients with worse nutritional status and higher CRP levels. This suggests that the Smell Identification Test could potentially be used to identify a group of “healthier” ESRD patients. Prospective, longitudinal research would be required to determine if a normal smell score identifies ESRD patients with better outcomes of morbidity and mortality. We believe that the limited existing data on olfactory function in CKD and ESRD patients and prior work demonstrating the reversibility of the defect after transplantation and resolution of the “uremic milieu,” suggests that the link between olfactory dysfunction and uremic malnutrition is complex. Simple tests of olfactory function may provide a useful surrogate end point during the search for the uremic toxins mediating malnutrition.

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Figure 1. Smell Score by SGA Nutrition Category

Mean smell scores were 34.9 ± 1.4 for controls, 33.5 ± 3.3 for SGA 7 patients, 28.3 ± 5.8 for SGA 5 – 6 patients, and 27.9 ± 4.4 for SGA 3 – 4 patients ($p < 0.001$ comparing normal to all ESRD). There was no difference in mean smell score for normal controls and SGA 7 patients. Patients with lower smell scores had significantly lower SGA scores ($p = 0.02$).

Table 1

Patient Characteristics

	Total Population N (%)	SGA 7 N (%)	SGA 5–6 N (%)	SGA 3–4 N (%)	p value [*]
Sex female	13 (42)	6 (55)	5 (50)	2 (20)	0.2
Age mean $\pm$ SD	50.8 $\pm$ 11.2	47.1 $\pm$ 8.7	51.4 $\pm$ 13.2	54.4 $\pm$ 11.4	0.3
Race	1 (3)	0 (0)	1 (10)	0 (0)	0.5
Asian	18 (58)	8 (73)	4 (40)	6 (60)	
Black	9 (29)	3 (27)	3 (30)	3 (30)	
Hispanic	3 (10)	0 (0)	2 (20)	1 (10)	
White					
Access	13 (42)	5 (46)	6 (60)	2 (20)	0.3
AVF	8 (26)	3 (27)	1 (10)	4 (40)	
AVG	10 (32)	3 (27)	3 (30)	4 (40)	
catheter					
Diabetes	16 (52)	5 (46)	7 (70)	4 (40)	0.4
CAD	7 (23)	2 (18)	3 (30)	2 (20)	0.8
HTN	30 (97)	11 (100)	9 (90)	10 (100)	0.3
PVD	10 (32)	1 (9)	4 (40)	5 (50)	0.1
CVA	6 (19)	2 (18)	3 (30)	1 (10)	0.5
Smoker	8 (26)	2 (18)	1 (10)	5 (50)	0.3
current	7 (22)	2 (18)	3 (30)	2 (20)	
prior	16 (52)	7 (64)	6 (60)	3 (30)	
never					
ACEI use	19 (61)	8 (73)	6 (60)	5 (50)	0.6
CCB use	20 (65)	7 (64)	8 (80)	5 (50)	0.4
Statin use	11 (35)	2 (18)	7 (70)	2 (20)	0.02
MMSE score mean $\pm$ SD	28.7 $\pm$ 1.4	29.3 $\pm$ 0.9	28.2 $\pm$ 1.6	28.5 $\pm$ 1.4	0.2
Median (IQR) Months on Dialysis	38 (19–92)	42 (14–98)	37.5 (16.5–52.5)	28 (26–93)	0.8

^{*} p value obtained from chi-square test or Kruskal-Wallis across all SGA categories

Abbreviations: arteriovenous fistula (AVF), arteriovenous graft (AVG), coronary artery disease (CAD), hypertension (HTN), peripheral vascular disease (PVD), cerebrovascular accident (CVA), angiotensin converting enzyme inhibitor (ACEI), calcium channel blocker (CCB), mini-mental status exam (MMSE), interquartile range (IQR)

Table 2
Nutritional Markers (mean $\pm$ SD) in Dialysis Patients by SGA Category

	Total Population N = 31	SGA 7 N = 11	SGA 5 - 6 N = 10	SGA 3 - 4 N = 10	p value*
BMI (kg/m ²)	27.3 $\pm$ 6.5	30.8 $\pm$ 5.1	29.3 $\pm$ 6.9	21.5 $\pm$ 2.8	0.002
eKt/V	1.38 $\pm$ 0.2	1.39 $\pm$ 0.18	1.4 $\pm$ 0.22	1.37 $\pm$ 0.21	0.9
nPCR	0.86 $\pm$ 0.2	0.94 $\pm$ 0.24	0.88 $\pm$ 0.15	0.77 $\pm$ 0.18	0.1
Creatinine mg/dl	11.1 $\pm$ 2.8	12.4 $\pm$ 3.1	10.1 $\pm$ 1.7	10.6 $\pm$ 3.1	0.1
Urea mg/dl	64.0 $\pm$ 16.2	68.8 $\pm$ 14	64.6 $\pm$ 13.9	58.2 $\pm$ 19.8	0.2
Albumin mg/dl	3.9 $\pm$ 0.3	4.1 $\pm$ 0.2	3.9 $\pm$ 0.3	3.7 $\pm$ 0.3	0.02
Cholesterol mg/dl	145 $\pm$ 35	159 $\pm$ 43	152 $\pm$ 33	126 $\pm$ 18	0.09
CRP % < 5.0mg/l	77 %	100 %	80 %	50 %	0.02

* p value obtained from ANOVA across all SGA categories

To convert creatinine in mg/dl to mol/l, multiple by 88.4; urea nitrogen in mg/dl to mmol/l, multiple by 0.357; albumin in mg/dl to g/l multiple by 10; cholesterol in mg/dl to mmol/l multiple by 0.025.

Abbreviations: body mass index (BMI), normalized protein catabolic rate (nPCR), C-reactive protein (CRP)

Table 3Retained Uremic Solute Levels (mean $\pm$ SD) in Healthy Controls vs. ESRD patients

	Healthy Controls	ESRD patients N = 31	p value
Monomethylamine ug/l	N = 10 30.9 $\pm$ 6.1	84.2 $\pm$ 20.8	<0.001
Ethylamine ug/l	N = 10 25.8 $\pm$ 5.8	69.0 $\pm$ 10.2	<0.001
Indican mg/dl	N = 4 0.10 $\pm$ 0.04	2.73 $\pm$ 1.33	0.002
Total P-cresol sulfate mg/dl	N = 4 0.38 $\pm$ 0.33	3.77 $\pm$ 1.87	0.004

Table 4
Retained Uremic Solute Levels (mean $\pm$ SD) in Dialysis Patients by SGA Category

	Total Population N = 31	SGA 7 N = 11	SGA 5-6 N = 10	SGA 3-4 N = 10	p value [*]
Monomethylamine ug/l	84.2 $\pm$ 20.8	76.4 $\pm$ 16.1	97.8 $\pm$ 24.9	79.2 $\pm$ 15.1	0.05
Ethylamine ug/l	69.0 $\pm$ 10.2	67.9 $\pm$ 6.7	74.0 $\pm$ 11.7	65.3 $\pm$ 11.0	0.2
Indican mg/dl	2.73 $\pm$ 1.33	2.44 $\pm$ 1.25	3.48 $\pm$ 1.38	2.30 $\pm$ 1.14	0.2
Total P cresol sulfate mg/dl	3.77 $\pm$ 1.87	4.09 $\pm$ 2.34	3.90 $\pm$ 1.72	3.28 $\pm$ 1.48	0.6

^{*} p value obtained from ANOVA across all SGA categories

Table 5

Summary of Smell Studies in patients with ESRD, CKD, or renal transplant

Study	Subjects	Odor test	Results	Correlations with nutritional markers
Frasnelli et al. Olfactory function in chronic renal failure. Am J Rhinol 16: 275-79, 2002	HD - 49 CKD - 15 Controls - 15	butanol Sniffin sticks Detection threshold Odor discrimination Odor identification	Elevated detection threshold (p=0.46) Reduced discrimination (p = 0.001) Deficient identification (p<0.001)	None reported
Griep et al. Odour perception in chronic renal disease. Nephrol Dial Transplant 12: 2093-98, 1997	HD - 38 PD - 16 CKD - 19 TXN - 28 Controls - 101	Isoamyl alcohol sniff bottles Detection threshold	Elevated detection threshold in HD (p=0.002) and CAPD (p=0.001) No change in detection immediately after HD (p=0.14) TXN had normal thresholds vs. controls (p=0.81)	Poor odor detection correlated with high urea and high PCR NO correlation with BMI or serum albumin
Corwin. Olfactory identification in HD: acute and chronic effects on discrimination and response bias. Neuropsychologica 27: 513-22, 1989	HD - 14 Controls - 15	Modified U Penn SIT yes/no forced choice paradigm Odor identification	Deficient identification (p=0.003) Identification worsens 30 minutes after HD (p=0.0004)	None reported
Conrad et al. Olfaction and HD: Baseline and acute treatment decrements. Nephron 47: 115-8, 1987	HD - 15 Controls - 10	Modified U Penn SIT yes/no forced choice paradigm Odor identification	Deficient identification (p<0.001) Identification worsens 30 minutes after HD (p<0.001)	None reported
Vreman et al. Taste, smell and zinc metabolism in patients with chronic renal failure. Nephron 26: 163-70, 1980	HD - 26 CKD - 7 Controls - 48	Pyridine sniff bottles Detection threshold	Detection threshold declined with age in all groups, no significant difference among groups	None reported
Schiffman et al. Reduced olfactory discrimination in patients on chronic HD. Physiol Behav 21: 239-42, 1978	HD - 11 Controls - 16	14 commercial food flavors multidimensional scaling procedure Odor discrimination	Reduced discrimination (p<0.001) HD patients rated 13/14 odors as more unpleasant than controls (p<0.01)	None reported

Abbreviations: hemodialysis (HD), chronic kidney disease (CKD), peritoneal dialysis (PD), renal transplant (TXN), protein catabolic rate (PCR), body mass index (BMI)